Is it time to consider teleophthalmology as a game-changer in the management of diabetic retinopathy?

É hora de se considerar a teleoftalmologia como um agente de mudança no manejo da retinopatia diabética?

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ABSTRACT

Currently the "pandemic" of diabetes mellitus is noted. The incidence and prevalence of diabetes and diabetic retinopathy, the most common microvascular complications of diabetes, are exponentially growing due to increased life expectancy in many parts of the world. The increasing number of people suffering from diabetic retinopathy not only highlights medical issues, but also an economic burden, representing a medical and social challenge. It is extremely important to identify a disease as soon as possible and successfully treat it. Technological progress results in developing Artificial Intelligence systems capable of detecting diabetic retinopathy. Current screening will be cost effectively based on the use of advanced digital technologies, in particular teleretinal screening systems. At present, we may consider teleophthalmology and Artificial Intelligence with automatic analysis of fundus photos as a Millennium-minded impactful tool for increasing discoverability and manageability of diabetic retinopathy, especially in filling the gap of inaccessibility to hard-to-reach areas, which enforces highly professionally effective time- and cost-saving care everywhere to provide the best possible care for the patients.

RESUMO

Atualmente, observa-se a "pandemia" do diabetes mellitus. A incidência e a prevalência do diabetes e da retinopatia diabética, as complicações microvasculares mais comuns do diabetes, estão crescendo exponencialmente devido ao aumento da expectativa de vida em muitas partes do mundo. O número cada vez maior de pessoas que sofrem de retinopatia diabética não apenas destaca problemas médicos, mas também um ônus econômico, representando um desafio médico e social. É extremamente importante identificar uma doença o mais rápido possível e tratá-la com sucesso. O progresso tecnológico resulta no desenvolvimento de sistemas de Inteligência Artificial capazes de detectar a retinopatia diabética. A triagem atual será econômica com base no uso de tecnologias digitais avançadas, em especial os sistemas de triagem telerretiniana. No momento, podemos considerar a teleoftalmologia e a Inteligência Artificial com análise automática de fotos de fundo de olho como uma ferramenta de impacto do milênio para aumentar a capacidade de descoberta e de manejo da retinopatia diabética, especialmente para preencher a lacuna da inacessibilidade a áreas de difícil acesso, o que impõe um atendimento altamente profissional e eficaz, com economia de tempo e de custos, em todos os lugares, para oferecer o melhor atendimento possível aos pacientes.

INTRODUCTION

Diabetes is "a pandemic of unprecedented magnitude".[1] The incidence and prevalence of diabetes and diabetic retinopathy (DR), as the most common microvascular complication of diabetes,[2] is exponentially growing due to increased life expectancy in many parts of the world. According to The International Diabetes Federation, currently 537 million adults (10.5% of the world's adult population) have diabetes, reflecting a 16% increase comparing to findings in 2019,[3] estimated to rise to 783.2 (12.2%) million by 2045.[4] DR is the most challenging cause of visual impairment and blindness worldwide.[5]

The forecast for the year 2045 indicates that the number of patients with DR will increase more than 50%, reaching 160.5 million with an alarming surge of vision-threatening diabetic retinopathy (VTDR) prevalence by 57.0% to 44.82 million from 2020 to 2045.[6] It must be taken into consideration that these "pandemic" numbers will cause a medical and social challenge with an economic burden, which underscores the significance of screening[7]), providing a window of opportunity for the prevention of vision loss due to DR.

Current screening will be cost effectively based on the use of teleophthalmology- telemedicine in ophthalmology, specifically "asynchronous type of telemedicine with the 'store-and-forward' approach where investigations are captured and uploaded onto cloud servers, and can be analyzed by artificial intelligence (AI) algorithms, to determine diagnosis and management".[8] The term "artificial intelligence" (AI), which means machines capable of performing tasks that typically require human intelligence, was introduced by John McCarthy in 1956.[9,10] Machine learning (ML), as the ability of giving a computer program the skill to learn from examples without being explicitly trained to do so, have shown promising results in image evaluation starting from 1950,[11] but it is worth noting that early imperfect hardware restricts its clinical use for medical image analysis. A lot has changed since then.[12] In 2012, Deep Learning (DL), which is a subset of ML aimed at making decisions using specific algorithm-neural networks through automatically extracted useful pieces of information, was really introduced to the world.[13,14] Technological progress results in developing AI systems capable of detecting DR.

The objective of this review is to evaluate the evidence and discuss the rationale behind the recent suggestions on the role of telemedicine in the management of DR worldwide. based on the currently available findings.

METHODS

For this review, a literature search was conducted using PubMed®/Medline® and Google Scholar for studies published up to November 2022 inclusive. The following keywords were used in various combinations: "diabetic retinopathy", "teleophthalmology", "artificial intelligence", "machine learning", "deep learning". Articles with high or medium clinical relevance, including also manually searched from the references, were selected for this review.

RESULTS

We found that studies have demonstrated the suitability of AI in the management of DR.

In 1996, Gardner et al.[15] presented the use of an artificial neural network in DR detection based on the recognition of vessels, exudates, and hemorrhages with rates 91.7%, 93.1%, and 73.8% respectively, reaching 88% sensitivity and 83.5% specificity, as compared to a trained ophthalmologist. Researchers concluded that "The system could be used as an aid to the screening of diabetic patients for retinopathy", acting as a starting point for new researchers to work on the development of ML systems for DR detection.

A significant amount of validation works that apply AI to medical image analysis in DR were conducted since then.[16-37] Table 1 summarizes recent studies.

Table 1. Summary of Deep Learning algorithms performance in diabetic retinopathy grading

Author	Diagnosis	Sensitivity (%)	Specificity (%)
Abramoff et al.[19]	mtmDR	87.2	90.7
Rajalakshmi et al.[21]	Any DR VTDR	95.8 99.1	80.2 80.4
Keel et al.[22]	Referable (≥ pre-proliferative DR)	92.2	93.7
Gulshan et al.[24]	mtmDR	88.9-92.1	92.2-95.2
Bellemo et al.[25]	mtmDR VTDR	92 99	89 97
Ruamviboonsuk et al.[26]	mtmDR	97	96
Natarajan et al.[27]	mtmDR	100	88.4
Bhuiyan et al.[28]	mtmDR	92.3	94.8
González-Gonzalo et al.[29]	mtmDR	92	92.1
Scheetz et al.[30]	mtmDR	96.9	87.7
Heydon et al.[31]	mtmDR	95.7	54
Lee et al.[32]	mtmDR	80.47	81.28
Ipp et al.[33]	mtmDR VTDR	96 97	88 90.1
Lim et al.[34]	mtmDR	96.5-97	86-88

mtmDR: more-than-mild diabetic retinopathy; DR: diabetic retinopathy; VTDR: vision-threatening diabetic retinopathy.

In 2016, Abràmoff et al.[16] continued refinement of diagnostic algorithm incorporating a DL component and evaluated its performance on 874 subjects. The images have been graded as no DR in case of no DR or mild DR without diabetic macular edema (DME), and referable DR. Referable DR was diagnosed as moderate non-proliferative DR, severe non-proliferative DR, proliferative DR, and/or DME; vision-threatening DR was defined as severe non-proliferative DR, proliferative DR, and/or DME. It was shown that proposed enhanced algorithm was capable of detecting referable DR with 96.8% sensitivity and 87.0% specificity. The authors reported that no cases of severe non-proliferative DR, proliferative DR, and/or DME were missed.

Further assessment and validation of DL algorithm in DR and DME detection based on 128,175 retinal images were conducted by Gulshan et al.[17] It has been reported that tested algorithm achieved a high sensitivity and specificity in grading referable DR. Despite this, however, the authors of the study concluded that it requires further scientific investigation in clinical settings.

Another study initiated by Ting et al.[18] was focused on assessing DL system capability of detecting not only referable DR, but also VTDR, and at the same time eye diseases, as an age-related macular degeneration and glaucoma in patients with diabetes. This was a large scale study based on the analysis of 112,648 retinal images from multiethnic populations, which have evidenced a high sensitivity (90.5%) and specificity (91.6%) for identifying referable DR, and 100% and 91.1% for VTDR, respectively. The similar efficacy were reported for other eye comorbidities. Based on these findings it was also highlighted that it is necessary to have a system verification at healthcare settings.

It is noteworthy that Lee et al.[32] have validated seven DR screening algorithms based on 311,604 images evidencing wide fluctuations in sensitivity. The authors emphasized a need for meticulous testing of all algorithms before clinical implementation. The latest validation retrospective study conducted by Zhang et al.[37] underscored that developed automatic DL system for referable DR detection is suitable for real-word screening.

However, despite multiple credible studies, only in 2018 the Food and Drug Administration (FDA) approved the first autonomous AI-enabled medical device for the detection of DR-Digital Diagnostics' IDx-DR system,[38] connected to the Topcon NW400 non-mydriatic fundus camera and allowing to detect more-than-mild DR (mtmDR) at primary healthcare setting without the eye specialist's image grading.[19] Diagnostic study in a cohort of 819 participants have evidenced 87.2% sensitivity, 90.7% specificity, with 96.1% imageability rate after enrichment correction.

For the first time, the IDx-DR system was prospectively evaluated in 310 youth (5-21 years old) patients with DR.[39] It has been reported that there is 85.7% sensitivity and 79.3% specificity in detection of mtmDR. The latest retrospective validity and reliability study based on the IDx-DR system[40] has shown 100% sensitivity (95% of confidence interval [95%CI] 90.8-100%) and 89.2% specificity (95%CI 87.0-91.1%) for referable DR, at the same time indicating gradeability decrease with ageing.

To date, the second FDA approved fully autonomous for mtmDR detection and the first for mtmDR and VTDR, commercially available system is the EyeArt system (Eyenuk, Inc).[33,41] According to a prospective multicenter cross-sectional study[33] the EyeArt system's version 2.1.0 has shown 96% sensitivity, 88% specificity, and 97% imageability for detecting eyes with mtmDR, and for the first time for VTDR -95.1 and 89.0% respectively in nondilated cases. Despite this, however, the study authors reported that imageability increased after dilation in cases of ungradable results, reaching 97.4%. It should be emphasized that the system used is reliable in detecting, not only mtmDR, but also of VTDR, as was stated by researchers.

Another prospective study in three English diabetes screening programs based on the same software[31] evidenced 98.3% sensitivity for mild-to-moderate non-proliferative retinopathy with referable maculopathy, 100% for moderate-to-severe non-proliferative retinopathy and 100% for proliferative retinopathy respectively. Further supportive data for this notion were obtained by Lim et al.,[34] where it was shown higher sensitivity of the EyeArt system comparing to general ophthalmologists or retina specialists in prospective, pivotal, multicenter trial conducted from April 2017 to May 2018. In contrast to the IDx-DR system, the EyeArt system could detect not only mtmDR, but also VTDR simultaneously.

DISCUSSION

Currently AI-based DR screening systems have been evaluated in multiple prospective studies with patients of different races and ethnicities (Table 2). The results obtained earlier by Kanagasingam et al.[42] in evaluating AI-based grading system in a primary care office in Australia with a small sample size revealed a high false-positive rate with a positive-predictive value of 12%, accordingly from 17 patients with severe DR, and 15 patients were false positives. In contrast, in another study from Australia,[30] also with a small sample size, high sensitivity (96.9%) and specificity (87.7%) were reported with a positive experience feedback from the patients and healthcare workers. These results supported the studies previously conducted by Gulshan et al.,[24] Bellemo et al.,[25] Sosale et al.[43] Another prospective study in three English diabetes screening programs was described above.[31] The latest largest prospective interventional cohort study was conducted by Ruamviboonsuk et al.[44] at nine primary care units in Thailand. This study adds more to the body of knowledge demonstrating DL capability of diagnosing DR similar to retina specialists. In another new prospective, multicenter study[45] in China, a high efficacy of referable DR detection was shown, except for maculopathy. The recent randomized trial[46] evidenced that patients with diabetes, who underwent AI-based screening, sought treatment faster comparing to the control group.

Table 2. Summary of prospective studies worldwide on the efficacy of Artificial Intelligence -based screening systems in the management of diabetic retinopathy

Author	Country where the study was conducted	Studied patients	Diagnosis	Sensitivity (%)	Specificity (%)
Abràmoff et al.[19]	United States	819	mtmDR	87.2	
Rajalakshmi et al.[21]	India	296	Any DR VTDR	95.8 99.1	80.2 80.4
Gulshan et al.[24]	India	3,049	mtmDR	88.9	92.2
Bellemo et al.[25]	Africa	1,574	mtmDR VTDR	92 99	89 97
Natarajan et al.[27]	India	213	any DR mtmDR	85.2 100	92 88.4
Scheetz et al.[30]	Australia	236	mtmDR	96.9	87.7
Heydon et al.[31]	England	30,405 images	mtmDR	95.7	54
Ipp et al.[33]	United States	893	mtmDR VTDR	95.5 97	85 90.1
Wolf et al.[39]	United States	310 (5-21 years old)	mtmDR	85.7	79.3
Kanagasingam et al.[42]	Australia	193	DR/no DR	-	92
Sosale et al.[43]	India	900	mtmDR	93	92.5
Ruamviboonsuk et al.[44]	Thailand	7,651	VTDR	91.4	95.4

mtmDR: more-than-mild diabetic retinopathy; DR: diabetic retinopathy; VTDR: vision-threatening diabetic retinopathy.

All the reports described above and the findings from other prospective studies[19,21,27,33,39] underscore the potential utility of AI based system in DR screening.

Recent reviews and surveys as those of authors like Fenner et al.,[47] Ting et al.,[48] Asiri et al.,[49] Grzybowski et al.,[50] Stolte et al.,[51] He et al.,[52] Bilal et al.,[53] Williamson,[54] Lalithadevi et al.,[55] Iqbal et al.,[56] Celard et al.[57] and Vujosevic et al.[58] cover a significant amount of works that apply DL to retinal image analysis in order to diagnose DR. A metaanalysis conducted by Wu and coworkers in 2019[59] and 2021[60] evidenced a high efficacy of ML algorithms in DR detection, specifically mtmDR. The authors concluded that "ML-based DR screening algorithms are likely ready for clinical applications". However, it is worth noting that recently Nakayama et al.[61] discussed the utilization of supervised ML algorithms for DR classification and have emphasized a need for the implementation of versatile comprehensive classification with equal referral criteria.

The general consensus is that teleophthalmology based on AI is a viable promising approach to detect DR,[51,53,55,56,60,62-69] and also cost-effective.[70-74] From the literature, it is observed that a few researchers have carried out a review on smartphone-based retinal image analysis concluding that it is a quick and cost-effective tool.[75-78]

Further supportive data for this notion were obtained by Malerbi et al.[79] in the retrospective study that evaluated the capability of semiautomated DR screening with mobile handheld retinal camera to diagnose mtmDR and VTDR after pupil dilation in 824 patients. It has been reported that the system achieved 97.8% sensitivity and 61.4% specificity, maintaining a sufficient quality of images in more than 80% of the cases. The obtained results are promising, and they deserve further scientific investigation.

It is worth noting a prospective, open study initiated by Gobbi et al.[80] at the DR screening clinic of Hospital das Clínicas de Ribeirão Preto, in Brazil in an effort to assess suitability of smartphone-based DR photoscreening in ninety-nine diabetic patients (194 eyes) conducted by undergraduate medicine and nursery students unexperienced in retinal imaging, who simulated real-word screening at primary healthcare level. It has been postulated that specificity tends to be greater than sensitivity, 0.94 and 0.71 respectively detecting any level of DR; 0.99 and 0.76 respectively detecting proliferative DR; 0.94 and 0.72 respectively detecting macular exudates. The researchers concluded that "the smartphone-based device showed promising accuracy in the detection of DR (84.07%), making it a potential tool in the screening and early diagnosis of DR".

There is still room for improvement.[81,82] The development of innovative approaches continues.[83-93] The recent one presented by Zhang et al.[83] is based on Deep Graph Correlation Network for grading. Researchers postulated that it has an accuracy near to retinal specialists and more than trained graders. Further improvements are presented by Canayaz,[84] Hu et al.,[85] Datta et al.,[86] Hassan et al.,[87] Venkaiahppalaswamy et al.[88] The efforts have been made to develop the hybrid DL system with a segmentation of optic disc and blood vessels.[88] It has been reported that the system achieved 94% accuracy with capability of detecting early DR. Further research directed to detect retinal vessels were continued by Jiang et al.[89] and Arsalan et al.[90]. According to developers[90], the technology named pool-less residual segmentation network (PLRS-Net) showed to be promising in terms of detecting retinal vessels abnormalities in DR and hypertensive retinopathy. Researchers have found that it has a high accuracy, sensitivity, and specificity, achieving 96.82%, 82.69%, 98.17% respectively and stated that "These accuracies show exceptional segmentation performance of the proposed method compared to state-of-the-art approaches for automatic vessel detection for diagnosis purposes".

Tokuda et al.[91] have selected retinal hemorrhage as a marker for DL-based retinal image analysis in DR. The authors evaluated 70 fundus images of 70 patients categorizing DR as a mild-or-worse non-proliferative DR and moderate-or-worse non-proliferative DR. As was mentioned by investigators, the study has several limitations: hemorrhage is a nonspecific sign, which could accompany other retinal diseases, such as retinal vein occlusions, retinal vasculitis, age-related macular degeneration; signs other than hemorrhage, such as microaneurysms, exudates, and cotton-wool spots could be present in different stages of DR. The algorithm is analyzing single-field 45-degree photographs centered at the fovea. Ischemic proliferative DR is also noneligible for proposed algorithm. The cohort in this study was too small to evidence any benefit. Despite this, however, the study's authors concluded that this approach "could be used to diagnose DR requiring ophthalmologist intervention".

The limitations of the included reports were that, except for prospectively conducted studies,[19,21,24,25,27,30,31,33,39,42-45] other studies evaluating ML capability in DR diagnosis were validated by retrospective data, and also double-blind randomized multicenter studies were unavailable.

Further, the limitation of this review is the lack of comparability due to different algorithms and grading systems used, commonly separating only referable DR from non-referable, which hinders the generalization of data.

Foreseen future research should be aimed at the development of portable, fast, tech-friendly ML-based DR screening system capable of detecting all stages of DR, starting from mild, thereby identifying microaneurysms, which possibly would become treatable.

Future innovations are required on versatile algorithms, capable of diagnosing not only DR, but also other eye diseases, such as glaucoma, age-related macular degeneration, cataract, etc., and at the same time to predict cardiovascular[92] and neurodegenerative diseases,[93] in best scenarios at home as a self-testing.

CONCLUSION

The continued assessment and refinement of diagnostic algorithms have the potential to enhance diabetic retinopathy manageability.

A growing body of evidence indicates that machine learning-based diabetic retinopathy screening system is capable of detecting diabetic retinopathy equally or better than professional levels.

Current diabetic retinopathy screening will be cost effectively based on the use of advanced digital technologies, in particular teleretinal screening systems. At present, we may consider teleophthalmology and artificial intelligence with automatic analysis of fundus photos as a Millennium-minded impactful tool for increasing discoverability and manageability of diabetic retinopathy, especially in filling the gap of inaccessibility to hard-to-reach areas, which enforces highly professionally effective time- and cost-saving care everywhere to provide the best possible care for the patients.

REFERENCES

1. Diabetes is a pandemic of unprecedented magnitude' now affecting one in 10 adults worldwide. Diabetes Res Clin Pract 2021;181:109133.
2. Simó-Servat O, Hernández C, Simó R . Diabetic retinopathy in the context of patients with diabetes. Ophthalmic Res. 2019;62(4):21-17.
3. Magliano DJ, Boyko EJ; IDF Diabetes Atlas 10th edition scientific committee. IDF Diabetes Atlas. 10th ed. Brussels: International Diabetes Federation; 2021.
4. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022;183:109119.
5. Sabanayagam C, Banu R, Chee ML, Lee R, Wang YX, Tan G, et al. Incidence and progression of diabetic retinopathy: a systematic review. Lancet Diabetes Endocrinol. 2019;7(2):140-9.
6. Teo ZL, Tham YC, Yu M, Chee ML, Rim TH, Cheung N, et al. Global Prevalence of Diabetic Retinopathy and Projection of Burden through 2045: Systematic Review and Meta-analysis. Ophthalmology. 2021;128(11):1580-91.
7. Quinn N, Jenkins A, Ryan C, Januszewski A, Peto T, Brazionis L. Imaging the eye and its relevance to diabetes care. J Diabetes Investig. 2021;12(6):897-908.
8. Ting DS, Gunasekeran DV, Wickham L, Wong TY. Next generation telemedicine platforms to screen and triage. Br J Ophthalmol. 2020;104(3):299-300.
9. McCarthy J, Minsky ML, Rochester N, Shannon CE. A proposal for the Dartmouth summer research project on artificial intelligence, August 31, 1955. AI Magazine. 2006;27(4):12.
10. Rajaraman V. JohnMcCarthy—Father of artificial intelligence. Resonance. 2014;19(3):198-207.
11. Mintz Y, Brodie R. Introduction to artificial intelligence in medicine. Minim Invasive Ther Allied Technol. 2019;28(2):73-81.
12. Mendo IR, Marques G, de la Torre Díez I, López-Coronado M, Martín-Rodríguez F. Machine learning in medical emergencies: a systematic review and analysis. J Med Syst. 2021;45(10):88.

13. Krizhevsky A, Sutskever I, Hinton GE. Imagenet classification with deep convolutional neural networks. Communications of the ACM. 2017;60(6):84-90.
14. Anwar SM, Majid M, Qayyum A, Awais M, Alnowami M, Khan MK. Medical Image Analysis using Convolutional Neural Networks: A Review. J Med Syst. 2018;42(11):226.
15. Gardner GG, Keating D, Williamson TH, Elliott AT. Automatic detection of diabetic retinopathy using an artificial neural network: a screening tool. Br J Ophthalmol. 1996;80(11):940-44.
16. Abràmoff MD, Lou Y, Erginay A, Clarida W, Amelon R, Folk JC, et al. Improved automated detection of diabetic retinopathy on a publicly available dataset through integration of deep learning. Invest Ophthalmol Vis Sci. 2016 Oct 1;57(13):5200-5206.
17. Gulshan V, Peng L, Coram M, Stumpe MC, Wu D, Narayanaswamy A, et al. Development and Validation of a Deep Learning Algorithm for Detection of Diabetic Retinopathy in Retinal Fundus Photographs. JAMA. 2016;316(22):2402-10.
18. Ting DSW, Cheung CY, Lim G, Tan GSW, Quang ND, Gan A, Hamzah H, et al. Development and validation of a deep learning system for diabetic retinopathy and related eye diseases using retinal images from multiethnic populations with diabetes. JAMA. 2017;318(22):2211-23.
19. Abràmoff MD, Lavin PT, Birch M, Shah N, Folk JC. Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices. NPJ Digit Med. 2018;1:39.
20. van der Heijden AA, Abramoff MD, Verbraak F, van Hecke MV, Liem A, Nijpels G. Validation of automated screening for referable diabetic retinopathy with the IDx-DR device in the Hoorn Diabetes Care System. Acta Ophthalmol. 2018;96(1):63-8.
21. Rajalakshmi R, Subashini R, Anjana RM, Mohan V. Automated diabetic retinopathy detection in smartphone-based fundus photography using artificial intelligence. Eye. 2018;32(6):1138-44.
22. Keel S, Lee PY, Scheetz J, Li Z, Kotowicz MA, MacIsaac RJ, et al. Feasibility and patient acceptability of a novel artificial intelligence-based screening model for diabetic retinopathy at endocrinology outpatient services: a pilot study. Sci Rep. 2018;8(1):4330.
23. Li Z, Keel S, Liu C, He Y, Meng W, Scheetz J, et al. An automated grading system for detection of vision-threatening referable diabetic retinopathy on the basis of color fundus photographs. Diabetes Care. 2018;41(12):2509-16.
24. Gulshan V, Rajan RP, Widner K, Wu D, Wubbels P, Rhodes T, et al. Performance of a Deep-Learning Algorithm vs Manual Grading for Detecting Diabetic Retinopathy in India. JAMA Ophthalmol. 2019;137(9):987-993.
25. Bellemo V, Lim ZW, Lim G, Nguyen QD, Xie Y, Yip MYT, et al. Artificial intelligence using deep learning to screen for referable and vision-threatening diabetic retinopathy in Africa: a clinical validation study. Lancet Digit Health. 2019;1(1):e35-e44.
26. Raumviboonsuk P, Krause J, Chotcomwongse P, Sayres R, Raman R, Widner K, et al. Deep learning versus human graders for classifying diabetic retinopathy severity in a nationwide screening program. NPJ Digit Med. 2019;2:25. Erratum in: NPJ Digit Med. 2019;2:68.
27. Natarajan S, Jain A, Krishnan R, Rogye A, Sivaprasad S. Diagnostic accuracy of community-based diabetic retinopathy screening with an offline artificial intelligence system on a smartphone. JAMA Ophthalmol. 2019;137(10):1182-8
28. Bhuiyan A, Govindaiah A, Deobhakta A, Gupta M, Rosen R, Saleem S, et al. Development and Validation of an Automated Diabetic Retinopathy Screening Tool for Primary Care Setting. Diabetes Care. 2020;43(10):e147-8.
29. González-Gonzalo C, Sánchez-Gutiérrez V, Hernández-Martínez P, Contreras I, Lechanteur YT, Domanian A, et al. Evaluation of a deep learning system for the joint automated detection of diabetic retinopathy and age-related macular degeneration. Acta Ophthalmol. 2020;98(4):368-77.
30. Scheetz J, Koca D, McGuinness M, Holloway E, Tan Z, Zhu Z, et al. Real-world artificial intelligence-based opportunistic screening for diabetic retinopathy in endocrinology and indigenous healthcare settings in Australia. Sci Rep. 2021;11(1):15808.
31. Heydon P, Egan C, Bolter L, Chambers R, Anderson J, Aldington S, et al. Prospective evaluation of an artificial intelligence-enabled algorithm for automated diabetic retinopathy screening of 30 000 patients. Br J Ophthalmol. 2021;105(5):723-8.
32. Lee AY, Yanagihara RT, Lee CS, Blazes M, Jung HC, Chee YE, et al. Multicenter, Head-to-Head, Real-World Validation Study of Seven Automated Artificial Intelligence Diabetic Retinopathy Screening Systems. Diabetes Care. 2021;44(5):1168-75.
33. Ipp E, Liljenquist D, Bode B, Shah VN, Silverstein S, Regillo CD, et al.; EyeArt Study Group. Pivotal evaluation of an artificial intelligence system for autonomous detection of referrable and vision-threatening diabetic retinopathy. JAMA Netw Open. 2021;4(11):e2134254. Erratum in: JAMA Netw Open. 2021;4(12):e2144317.
34. Lim JI, Regillo CD, Sadda SR, Ipp E, Bhaskaranand M, Ramachandra C, et al. Artificial intelligence detection of diabetic retinopathy: subgroup comparison of the eyeart system with ophthalmologists' dilated examinations. Ophthalmol Sci. 2022;3(1):100228.
35. Dai L, Wu L, Li H, Cai C, Wu Q, Kong H, et al. A deep learning system for detecting diabetic retinopathy across the disease spectrum. Nat Commun. 2021;12(1):3242.
36. Nderitu P, Nunez do Rio JM, Webster ML, Mann SS, Hopkins D, Cardoso MJ, et al. Automated image curation in diabetic retinopathy screening using deep learning. Sci Rep. 2022;12(1):11196.
37. Zhang G, Lin JW, Wang J, Ji J, Cen LP, Chen W, et al. Automated multidimensional deep learning platform for referable diabetic retinopathy detection: a multicentre, retrospective study. BMJ Open. 2022;12(7):e060155.
38. US Food and Drug Administration. FDA permits marketing of artificial intelligence-based device to detect certain diabetes-related eye problems. News Release, US Food and Drug Administration; 2018.
39. Wolf RM, Liu TYA, Thomas C, Prichett L, Zimmer-Galler I, Smith K, et al. The SEE Study: safety, efficacy, and equity of implementing autonomous artificial intelligence for diagnosing diabetic retinopathy in youth. Diabetes Care. 2021;44(3):781-7.
40. Mehra AA, Softing A, Guner MK, Hodge DO, Barkmeier AJ. Diabetic retinopathy telemedicine outcomes with artificial intelligence-based image analysis, reflex dilation, and image overread. Am J Ophthalmol. 2022;244:125-32.
41. Bhaskaranand M, Ramachandra C, Bhat S, Cuadros J, Nittala MG, Sadda SR, et al. The Value of Automated Diabetic Retinopathy Screening with the EyeArt System: A Study of More Than 100,000 Consecutive Encounters from People with Diabetes. Diabetes Technol Ther. 2019;21(11):635-43.
42. Kanagasingam Y, Xiao D, Vignarajan J, Preetham A, Tay-Kearney ML, Mehrotra A. Evaluation of Artificial Intelligence-Based Grading of Diabetic Retinopathy in Primary Care. JAMA Netw Open. 2018;1(5):e182665.
43. Sosale B, Aravind SR, Murthy H, Narayana S, Sharma U, Gowda SGV, et al. Simple, Mobile-based Artificial Intelligence Algorithm in the detection of Diabetic Retinopathy (SMART) study. BMJ Open Diabetes Res Care. 2020;8(1):e000892.
44. Ruamviboonsuk P, Tiwari R, Sayres R, Nganthavee V, Hemarat K, Kongprayoon A, et al. Real-time diabetic retinopathy screening by deep learning in a multisite national screening programme: a prospective interventional cohort study. Lancet Digit Health. 2022;4(4):e235-e244.
45. Yang Y, Pan J, Yuan M, Lai K, Xie H, Ma L, et al. Performance of the AIDRScreening system in detecting diabetic retinopathy in the fundus photographs of Chinese patients: a prospective, multicenter, clinical study. Ann Transl Med. 2022;10(20):1088.
46. Mathenge W, Whitestone N, Nkurikiye J, Patnaik JL, Piyasena P, Uwaliraye P, et al. Impact of Artificial Intelligence Assessment of Diabetic Retinopathy on Referral Service Uptake in a Low-Resource Setting: The RAIDERS Randomized Trial. Ophthalmol Sci. 2022;2(4):100168.
47. Fenner BJ, Wong RLM, Lam WC, Tan GSW, Cheung GCM. Advances in retinal imaging and applications in diabetic retinopathy screening: a review. Ophthalmol Ther. 2018;7(2):333-46.
48. Ting DS, Pasquale LR, Peng L, Campbell JP, Lee AY, Raman R, et al. Artificial intelligence and deep learning in ophthalmology. Br J Ophthalmol. 2019;103(2):167-75.

49. Asiri N, Hussain M, Al Adel F, Alzaidi N. Deep learning based computer-aided diagnosis systems for diabetic retinopathy: A survey. Artif Intell Med. 2019;99:101701.
50. Grzybowski A, Brona P, Lim G, Ruamviboonsuk P, Tan GSW, Abramoff M, et al. Artificial intelligence for diabetic retinopathy screening: a review. Eye (Lond). 2020;34(3):451-460. Erratum in: Eye (Lond). 2019 Dec 10;: PMID: 31488886; PMCID: PMC7055592.
51. Stolte S, Fang R. A survey on medical image analysis in diabetic retinopathy. Med Image Anal. 2020;64:101742.
52. He M, Li Z, Liu C, Shi D, Tan Z. Deployment of artificial intelligence in real-world practice: opportunity and challenge. Asia Pac J Ophthalmol (Phila). 2020;9(4):299-307.
53. Bilal A, Sun G, Mazhar S. Survey on recent developments in automatic detection of diabetic retinopathy. J Fr Ophtalmol. 2021;44(3):420-40.
54. Williamson TH. Artificial intelligence in diabetic retinopathy. Eye (Lond). 2021;35(2):684.
55. Lalithadevi B, Krishnaveni S. Detection of diabetic retinopathy and related retinal disorders using fundus images based on deep learning and image processing techniques: A comprehensive review. Concur Comput Pract Exper 2022; 34(19):e7032.
56. Iqbal S, Khan TM, Naveed K, Naqvi SS, Nawaz SJ. Recent trends and advances in fundus image analysis: A review. Comput Biol Med. 2022;151(Pt A):106277.
57. Celard P, Iglesias EL, Sorribes-Fdez JM, Romero R, Vieira AS, Borrajo L. A survey on deep learning applied to medical images: from simple artificial neural networks to generative models. Neural Comput Appl. 2023;35(3):2291-323.
58. Vujosevic S, Limoli C, Luzi L, Nucci P. Digital innovations for retinal care in diabetic retinopathy. Acta Diabetol. 2022;59(12):1521-30.
59. Wu HQ, Shan YX, Wu H, Zhu DR, Tao HM, Wei HG, et al. Computer aided diabetic retinopathy detection based on ophthalmic photography: a systematic review and Meta-analysis. Int J Ophthalmol. 2019;12(12):1908-16.
60. Wu JH, Liu TYA, Hsu WT, Ho JH, Lee CC. Performance and Limitation of Machine Learning Algorithms for Diabetic Retinopathy Screening: Meta-analysis. J Med Internet Res. 2021 Jul 3;23(7):e23863.
61. Nakayama LF, Ribeiro LZ, Gonçalves MB, Ferraz DA, Dos Santos HNV, Malerbi FK, et al. Diabetic retinopathy classification for supervised machine learning algorithms. Int J Retina Vitreous. 2022;8(1):1.
62. Gunasekeran DV, Ting DSW, Tan GSW, Wong TY. Artificial intelligence for diabetic retinopathy screening, prediction and management. Curr Opin Ophthalmol. 2020;31(5):357-65.
63. Channa R, Wolf R, Abramoff MD. Autonomous Artificial Intelligence in Diabetic Retinopathy: From Algorithm to Clinical Application. J Diabetes Sci Technol. 2021;15(3):695-8.
64. Wang YL, Yang JY, Yang JY, Zhao XY, Chen YX, Yu WH. Progress of artificial intelligence in diabetic retinopathy screening. Diabetes Metab Res Rev. 2021;37(5):e3414.
65. Tan TF, Li Y, Lim JS, Gunasekeran DV, Teo ZL, Ng WY, Ting DS. Metaverse and Virtual Health Care in Ophthalmology: Opportunities and Challenges. Asia Pac J Ophthalmol (Phila). 2022;11(3):237-46.
66. Zafar S, Mahjoub H, Mehta N, Domalpally A, Channa R. Artificial Intelligence Algorithms in Diabetic Retinopathy Screening. Curr Diab Rep. 2022;22(6):267-74.
67. Liu R, Wang X, Wu Q, Dai L, Fang X, Yan T, et al. DeepDRiD: Diabetic Retinopathy-Grading and Image Quality Estimation Challenge. Patterns (N Y). 2022;3(6):100512.
68. Malerbi FK, Melo GB. Feasibility of screening for diabetic retinopathy using artificial intelligence, Brazil. Bull World Health Organ. 2022;100(10):643-647.
69. König M, Seeböck P, Gerendas BS, Mylonas G, Winklhofer R, Dimakopoulou I, et al. Quality assessment of colour fundus and fluorescein angiography images using deep learning. Br J Ophthalmol. 2022 Nov 23:bjophthalmol-2022-321963.
70. Nguyen HV, Tan GS, Tapp RJ, Mital S, Ting DS, Wong HT, et al. Cost-effectiveness of a national telemedicine diabetic retinopathy screening Program in Singapore. Ophthalmology. 2016;123(12):2571-2580.
71. Bellemo V, Lim G, Rim TH, Tan GSW, Cheung CY, Sadda S, et al. Artificial Intelligence Screening for Diabetic Retinopathy: the Real-World Emerging Application. Curr Diab Rep. 2019;19(9):72.
72. Xie Y, Nguyen QD, Hamzah H, Lim G, Bellemo V, Gunasekeran DV, et al. Artificial intelligence for teleophthalmology-based diabetic retinopathy screening in a national programme: an economic analysis modelling study. Lancet Digit Health. 2020;2(5):e240-9.
73. Benet D, Pellicer-Valero OJ. Artificial intelligence: the unstoppable revolution in ophthalmology. Surv Ophthalmol. 2022;67(1):252-270.
74. Chawla S, Chawla A, Chawla R, et al. Trained nurse–operated teleophthalmology screening approach as a cost-effective tool for diabetic retinopathy. Int J Diabetes Dev Countries. 2022; 42:747-50.
75. Vujosevic S, Aldington SJ, Silva P, Hernández C, Scanlon P, Peto T, et al. Screening for diabetic retinopathy: new perspectives and challenges. Lancet Diabetes Endocrinol. 2020;8(4):337-47.
76. Pujari A, Saluja G, Agarwal D, Sinha A, P R A, Kumar A, et al. Clinical Role of Smartphone Fundus Imaging in Diabetic Retinopathy and Other Neuro-retinal Diseases. Curr Eye Res. 2021;46(11):1605-13.
77. Jansen LG, Schultz T, Holz FG, Finger RP, Wintergerst MW. [Smartphone-based fundus imaging: applications and adapters]. Ophthalmologe. 2022 Feb;119(2):112-26. German.
78. Alexopoulos P, Madu C, Wollstein G, Schuman JS. The development and clinical application of innovative optical ophthalmic imaging techniques. Front Med (Lausanne). 2022;9:891369.
79. Malerbi FK, Mendes G, Barboza N, Morales PH, Montargil R, Andrade RE. Diabetic Macular Edema Screened by Handheld Smartphone-based Retinal Camera and Artificial Intelligence. J Med Syst. 2021;46(1):8.
80. Gobbi JD, Braga JP, Lucena MM, Bellanda VC, Frasson MV, Ferraz D, et al. Efficacy of smartphone-based retinal photography by undergraduate students in screening and early diagnosing diabetic retinopathy. Int J Retina Vitreous. 2022;8(1):35.
81. Das D, Biswas SK, Bandyopadhyay S. A critical review on diagnosis of diabetic retinopathy using machine learning and deep learning. Multimed Tools Appl. 2022;81(18):25613-55.
82. Malerbi FK. Artificial intelligence for diabetic retinopathy screening: beyond diagnostic accuracy. Ann Transl Med. 2022;10(20):1080.
83. Zhang G, Sun B, Chen Z, Gao Y, Zhang Z, Li K, et al. Diabetic Retinopathy Grading by Deep Graph Correlation Network on Retinal Images Without Manual Annotations. Front Med (Lausanne). 2022;9:872214.
84. Canayaz M. Classification of diabetic retinopathy with feature selection over deep features using nature-inspired wrapper methods. Applied Soft Comput. 2022; 128:109462.
85. Hu J, Wang H, Wang L, Lu Y. Graph adversarial transfer learning for diabetic retinopathy classification. IEEE Access. 2022; 10:119071-83.
86. Datta P, Das P, Kumar A. Hyper parameter tuning based gradient boosting algorithm for detection of diabetic retinopathy: an analytical review. Bull Electr Eng Inform. 2022;11(2);814-24.
87. Hassan MM, Mollick S, Yasmin F. An unsupervised cluster-based feature grouping model for early diabetes detection. Healthcare Analytics. 2022;2;100112.
88. Venkaiahppalaswamy B, Reddy PP, Batha S. Hybrid deep learning approaches for the detection of diabetic retinopathy using optimized wavelet based model. Biomedical Signal Processing and Control. 2023;79:104146.
89. Jiang Y, Liang J, Cheng T. Bulletin of Electrical Engineering and Informatics MTPA_Unet: Multi-Scale Transformer-Position Attention Retinal Vessel Segmentation Network Joint Transformer and CNN. Sensors. 2022;22(12):4592.
90. Arsalan M, Haider A, Lee YW, Park KR. Detecting retinal vasculature as a key biomarker for deep Learning-based intelligent screening and analysis of diabetic and hypertensive retinopathy. Expert Syst Appl. 2022;200:117009.
91. Tokuda Y, Tabuchi H, Nagasawa T, Tanabe M, Deguchi H, Yoshizumi Y, Ohara Z, Takahashi H. Automatic Diagnosis of Diabetic Retinopathy Stage Focusing Exclusively on Retinal Hemorrhage. Medicina (Kaunas). 2022;58(11):1681.

92. Wong DYL, Lam MC, Ran A, Cheung CY. Artificial intelligence in retinal imaging for cardiovascular disease prediction: current trends and future directions. Curr Opin Ophthalmol. 2022;33(5):440-6.

93. Patil AD, Biousse V, Newman NJ. Artificial intelligence in ophthalmology: an insight into neurodegenerative disease. Curr Opin Ophthalmol. 2022;33(5):432-9.