

Editorial

Artificial Intelligence Systems for Diabetic Retinopathy Screening: Appraisal on the 3rd US FDA Approved Algorithms- AEYE-DS

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Editorial

Artificial Intelligence (AI) has revolutionized the field of healthcare in recent years, and one of its most promising applications is on the interpretation of medical images [1]. In ophthalmology, the first success comes to the screening and diagnosis of Diabetic Retinopathy (DR) [2]. DR is a common complication of Diabetes Mellitus (DM) that affects the eyes, and early detection and treatment is crucial in preventing vision loss, especially over the working populations [3]. The use of AI in DR screening involves analyzing digital fundus images to detect any signs of DR, including microaneurysms, dot and blot haemorrhages, cotton-wool spots, venous beading, intraretinal microvascular anomalies [4]. Currently, there are 3 US FDA approved systems on DR screening, IDx-DR (Digital Diagnostics), EyeArt (Eyenuk, Inc) and AEYE-DS (AEYE Health, Inc) [5-7]. AI has several advantages over traditional screening methods, including usage by non-ophthalmologically trained medical personnel, accessible and stable performance over whatever time and place, increased speed of clinical workflow, these might potentially help to improve outcomes for patients with DM. In the era of rapidly advancing technology, the use of AI in ophthalmology is an exciting development that might transform our future practice [8]. In this appraisal, we focus on the 3rd US FDA approved AI algorithms for DR.

Since the approval of IDx-DR back in 2018, many other systems were compared to IDx-DR for U.S. FDA approval [5]. In 2020, EyeArt was the 2nd AI algorithms approved for DR screening [6]. With promising results demonstrated from the previous two models, in 2022, the 3rd approved systems appeared, it is called AEYE-DS [7]. The FDA approval document mentioned its use with Topcon Model NW400 funduscope camera. Upon literature search on PubMed and MEDLINE, there was no publication concerning AEYE-DS. On PubMed Central search, there was one publication related to AEYE-DS [9]. However, photos were obtained through the portable, handheld fundus camera in that study. That study showed a sensitivity and specificity

of 92.6% and 95.3% respectively. Going onto the EMBASE database search, there was another publication on AEYE-DS [10]. It's a conference abstract submitted to 82nd Scientific Sessions of the American Diabetes Association, ADA 2022, New Orleans, LA, United States. This study also applied the portable hand-held Optomed Aurora for data acquisition, but was not evaluating the sensitivity and specificity of AEYE-DS.

Appraising the clinical performance data over the FDA document, the related clinical trials was NCT04612868, with official title: "Pivotal Prospective Clinical Trial to Demonstrate the Efficacy and Safety of AEYE-DS software device for automated diabetic retinopathy detection from digital fundoscopic images" [11]. The recruitment was completed with 531 participants, and the latest update was results submission to ClinicalTrials.gov on 23rd May 2023. The primary outcome measures were performance of the AEYE-DS software for the detection of more than mild Diabetic Retinopathy (mtmDR) on digital fundoscopic images from patients with known diabetes, time frame of 1 day, in terms of sensitivity and specificity.

Inclusion Criteria:

- Age ≥ 22
- Male or female
- Documented diagnosis of diabetes mellitus, meeting the criteria established by the American Diabetes Association (ADA) and World Health Organization (WHO).
- Understand the study and volunteer to sign the informed consent

Exclusion Criteria:

- Uncorrectable vision loss (e.g., with the use of eyeglasses), blurred vision, or floaters.
- Diagnosed with macular edema, severe non-proliferative retinopathy, proliferative retinopathy, radiation retinopathy, or retinal vein occlusion.
- History of laser treatment of the retina or injections into either eye, or any history of retinal surgery.
- Currently participating in another investigational eye study and actively receiving investigational product for DR or DME.
- Participant has a condition that, in the opinion of the investigator, would preclude participation in the study (e.g., unstable medical status including blood pressure or glycemic control, microphthalmia or previous enucleation).
- Participant is contraindicated for imaging by fundus imaging systems used in the study:
 - Participant is hypersensitive to light
 - Participant recently underwent Photodynamic Therapy (PDT)
 - Participant is taking medication that causes photosensitivity
 - Participant has a history of angle-closure glaucoma or narrow anterior chamber angles

From the FDA document, the demographics of the patients were listed in Table 1. The primary efficacy objective of this study was the sensitivity and specificity of the AEYE-DS device to detect mtmDR on digital funduscopy images, acquired by the Topcon NW400 funduscopy device, based on two macula-centered images (one image from each eye of the patient). With the given data, the 2×2 table was re-created (Table 2). The sensitivity was 92.98% (95% CI 83.00 - 98.05) and specificity was 91.36% (95% CI 88.19 - 93.91%). The 95% CI was re-calculated with the 2×2 table (Table 2). The powered secondary endpoint of the study was the sensitivity and specificity of the AEYE-DS device to detect mtmDR from digital funduscopy images, acquired by the Topcon NW400 funduscopy device, based on four images (one macula centered image and one optic disc centered image per eye). Sensitivity and specificity were 94.74% [97.5% CI: 85.63%; 98.19%] and 88.64% [97.5% CI: 85.18%; 91.38%] respectively. However, no primary data were provided in the document, so re-creation of the 2×2 table was impossible.

After reviewing the FDA data, the performance of AEYE-DS is promising. The advantage of using just two macula-centered images (one image from each eye of the patient) could have saved up some clinical time upon diagnosis. However, if patients suffered from cataract or with vitreous medial opacity, barely relying on single photo may compromise the diagnosis and yielding non-analyzable results [12]. In addition, the age range of included subjects were 21-88, which go against the inclusion criteria of age ≥ 22 [11]. Besides, the proportion of Asian patients were small in the study so the efficacy on Asian DM patients' application requires further studies [7]. Therefore, we look forward to the formal publication of the study over scientific journals for more in-depth understanding of the appraised registered clinical trial and the detailed performance of AEYE-DS, as well as comparison with other AI systems available. Also, we are expecting more real-world performance data publications soon after its FDA approval, hopefully over the Asia-Pacific region.

Study Site	United States	7	Israel	1
Time Point	Start	October 2020	End	November 2021
Gender	Male	47%	Female	53%
DM	Type 1	5%	Type 2	95%
Ethnicity	African-American	29%	White	39%
	Hispanic/ Latino	29%	Others	3%

Table 1: Demographics of the 531 patients.

mtmDR (* 69 non-analyzable) prevalence 12.34%		Ground truth		
		+ve	-ve	Total
AEYE-DS	+ve	53	35	88
	-ve	4	370	374
	Total	57	405	462

Table 2: Results of AEYE-DS compared to ground truth reference standard formed by the reading center diagnostic results, based on two macula-centered images (one image from each eye of the patient).

Keywords: Artificial Intelligence; Algorithms; Diabetic Retinopathy; Diabetes Mellitus; Retina; Ophthalmology

Conflict of Interest

The authors have no conflict of interest to declare.

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