Validation of an autonomous AI-based diagnostic system for holistic maculopathy screening in a routine occupational health checkup context

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Abstract

Purpose: To evaluate the diagnostic ability of an autonomous artificial intelligence (AI) system for holistic maculopathy screening during occupational checkups.

Methods: Retrospective study on a raw dataset of 5,918 images (2,839 individuals) evaluated with non-mydriatic cameras during routine occupational health checkups. Images were obtained by trained technicians using handheld non-mydriatic cameras onsite at the workplace. Three camera models were employed: Optomed Aurora (field of view - FOV 50º, 88% of the dataset), ZEISS VISUSCOUT 100 (FOV 40º, 9%), and Optomed SmartScope M5 (FOV 40º, 3%). Image acquisition took two minutes per patient. Ground truth for each image of the dataset was determined by 2 masked retina specialists, and disagreements were resolved by a 3rd retina specialist. The specific pathologies considered for evaluation were "diabetic retinopathy" (DR), "Age-related macular degeneration" (AMD), "glaucomatous optic neuropathy" (GON), and

"Nevus". Images with maculopathy signs that didn't match the described taxonomy were classified as "Other".

Results: The combination of algorithms to detect any abnormalities had an area under the curve (AUC) of 0.963 with a sensitivity of 0.929 and a specificity of 0.868. The algorithms individually obtained: AMD AUC 0.98 (Sensitivity 0.938; specificity 0.957), DR AUC 0.95 (Sensitivity 0.811; specificity 0.948), GON AUC 0.889 (Sensitivity 0.536 specificity 0.957), Nevus AUC 0.931 (Sensitivity 0.867; specificity 0.907).

Conclusion: Holistic AI approach is comparable to human experts at simultaneous detection of DR, AMD, GON, and Nevus. The integration of pathology-specific algorithms permits higher sensitivities with minimal impact on its specificity. It also reduces the risk of missing incidental findings. Deep learning may facilitate wider screenings of eye diseases.

Introduction

In 2010, 65% of those afflicted by blindness worldwide (32.4 million total) and 76% of those with moderate or severe vision impairment (191 million) had a preventable or treatable cause (Bourne et al. 2013). The causes vary among regions but the trend since 1990 shows a decreased incidence due to cataract or refractive errors while age macular degeneration (AMD), glaucoma and diabetic retinopathy (DR) are on the rise (Bourne et al. 2013). In developed countries, this trend is even more pronounced: AMD is the leading cause of blindness in people aged 75 years and older (Klaver et al. 1998) whereas DR is the most frequent cause of preventable blindness in the working-age population (adults between 20 and 74 years old) (Mohamed, Gillies, and Wong 2007). Future projections do not show any sign of these diseases slowing down either. AMD will affect 288 million people in 2040 (Wong et al. 2014), glaucoma will impact 111.8 million in 2040 (Tham et al. 2014) and 191 million people will suffer DR by 2030 (Ting, Cheung, and Wong 2016). These diseases are treatable with good outcomes if detected early in the course of the disease (Ferris 1993; Lim et al. 2012; Hamilton 2007; Jonas et al. 2017) but they often are not symptomatic until late stages of their development. Thus, it is essential to have good screening systems for a timely diagnosis.

Running screening programs at large scale is costly, being the relatively high fixed costs per equipment the main driver of this cost (Lairson et al. 1992). This is even more noticeable in low density areas, which are underserved by traditional screening approaches performed in primary-care settings (Lee et al. 2008). Additional issues of such programs stem from their limited scope. Primary care physicians, with limited ophthalmological expertise, might often miss abnormalities outside the original screening programme or have lower sensitivity than retinal experts (Farley et al. 2008; Chan et al. 2015). Ophthalmology is also a leading specialty in alternative forms of healthcare delivery. For instance, mobile digital non-mydriatic cameras are getting more affordable and have good specificity and sensitivity for DR (Ahmed et al. 2006;

Massin et al. 2003), which has enabled many screening plans in underserved areas (Levy et al. 2011; Romero-Aroca et al. 2010; Spurling et al. 2010; Beynat et al. 2009). There are also many examples of successful telemedicine screening plans in countries such as Australia, United States, India, Singapur and Spain. (Kumar et al. 2006; n.d.; Sharma et al. 2011; Nguyen et al. 2016; Zapata et al. 2017)

In parallel to the improvements in imaging and digitalization of healthcare, artificial intelligence (AI) based on deep learning (DL) (Lecun, Bengio, and Hinton 2015) represents a breakthrough (Krizhevsky, Sutskever, and Hinton 2012) that has dramatically improved the state-of-the-art in many tasks such as speech recognition, image processing and text generation, among others. In the field of medicine, DL has been most successful in medical imaging analysis, by enabling the creation of Computer-aided diagnosis systems (CADx) with expert-level accuracies. There are many examples in dermatology (Esteva et al. 2017), radiology (Lakhani and Sundaram 2017), gastroenterology (Urban et al. 2018) and ophthalmology (Gulshan et al. 2016; De Fauw et al. 2018). In fact, the first ever FDA[1]-approved autonomous AI is a screening tool for DR (Abràmoff et al. 2018).

While the results of the AI performance presented in many publications are encouraging, there are still questions to be answered regarding their real world application. The vast majority of publications are limited to retrospective studies taken on datasets captured in populations with prior conditions in a hospital setting (Burlina et al. 2017; Brown et al. 2018; Ahn et al. 2018). Also, most publications limit the scope of their algorithm to just one pathology which, while interesting, is not ideal for screening purposes (Chew and Schachat 2015).

This work aims to overcome both limitations, by presenting a retrospective study performed on 2.839 patients evaluated by digital fundus images taken with handheld non-mydriatic cameras, on a routinal checkup performed onsite at work centers. The algorithm evaluated in this study has previously been successful in detecting signs of DR, AMD, glaucoma and nevus, the most common eye pathologies (Zapata et al. 2017). The novelty of our proposal is the combination of multiple pathology-specific algorithms to achieve holistic maculopathy detection. Each algorithm is trained to identify individual diseases and, in conjunction, the final output increases the diagnostic accuracy of the AI system for ocular pathology detection.

Methods

Study population

The dataset consists of 5.918 images from a population of 2.839 individuals, taken between the 9th of January and the 13th of March of 2020. The median age was 43 years old with a standard deviation of 11.52. From the study population, 1786 (63%) were male and 1053 female (37%) (see Table 1 for a detailed breakdown). Participants of this study were enrolled during routine occupational health checkups offered by their employer as medical benefits (Zapata et al. 2020). Participation was

[1]United States Food and Drug Administration

voluntary. All ophthalmologic check-ups were performed by a single provider (Optretina[2], Sant Cugat, Spain). The images were obtained by a trained technician using handheld non-mydriatic cameras on the participating centers office premises, in a room which had been setup with adequate lighting conditions. The camera models employed were Optomed Aurora (FOV[3] 50º, 88% of the dataset), ZEISS VISUSCOUT 100 (FOV 40º, 9% of the dataset) and Optomed SmartScope M5 (FOV 40º, 3% of the dataset). Image acquisition took around two minutes per patient. The raw image dataset was included in the study and no images were discarded due to low-resolution or were modified prior to the analysis.

Digital Fundus Image evaluation

The ground truth of the data was evaluated per eye. For patients with multiple captures, an automated quality filtering was employed to select the highest quality image. Afterwards, each image was graded by 2 specialists (intragrader variability kappa of 0.86 and 0.79 respectively) in a 2-tiered approach (see Figure 1). In case of discrepancies, a 3rd retinal specialist reviewed the image (intragrader variability kappa of 0.83). The first step of the labelling process was to classify the image as "normal" or "abnormal", considering the latter as any digital fundus image showing pathological signs. Abnormal images were further subclassified per pathology. The specific pathologies considered for evaluation were *DR* [defined as more than mild DR, as per the 2019 revision of the American Academy of Ophtalmology's Preferred Practice Pattern (Wilkinson et al. 2003; Flaxel et al. 2020)], *AMD* (defined as mild or worse), *Suspicious glaucomatous optic neuropathy (GON) was defined by a cup-to-disc ratio of 0.7 or more in the vertical axis and/or other typical changes caused by glaucoma, such as localized notches or RNFL defects or peripapilar hemorrages. Nevus was defined with clinical parameters as an hyperpigmented lesion beneath the retina*. Images classified as "abnormal" (with possible signs of maculopathy) not matching the described taxonomy were classified as "*Other" in tier 2*.

[2]https://www.optretina.com/en/

[3]Field of view

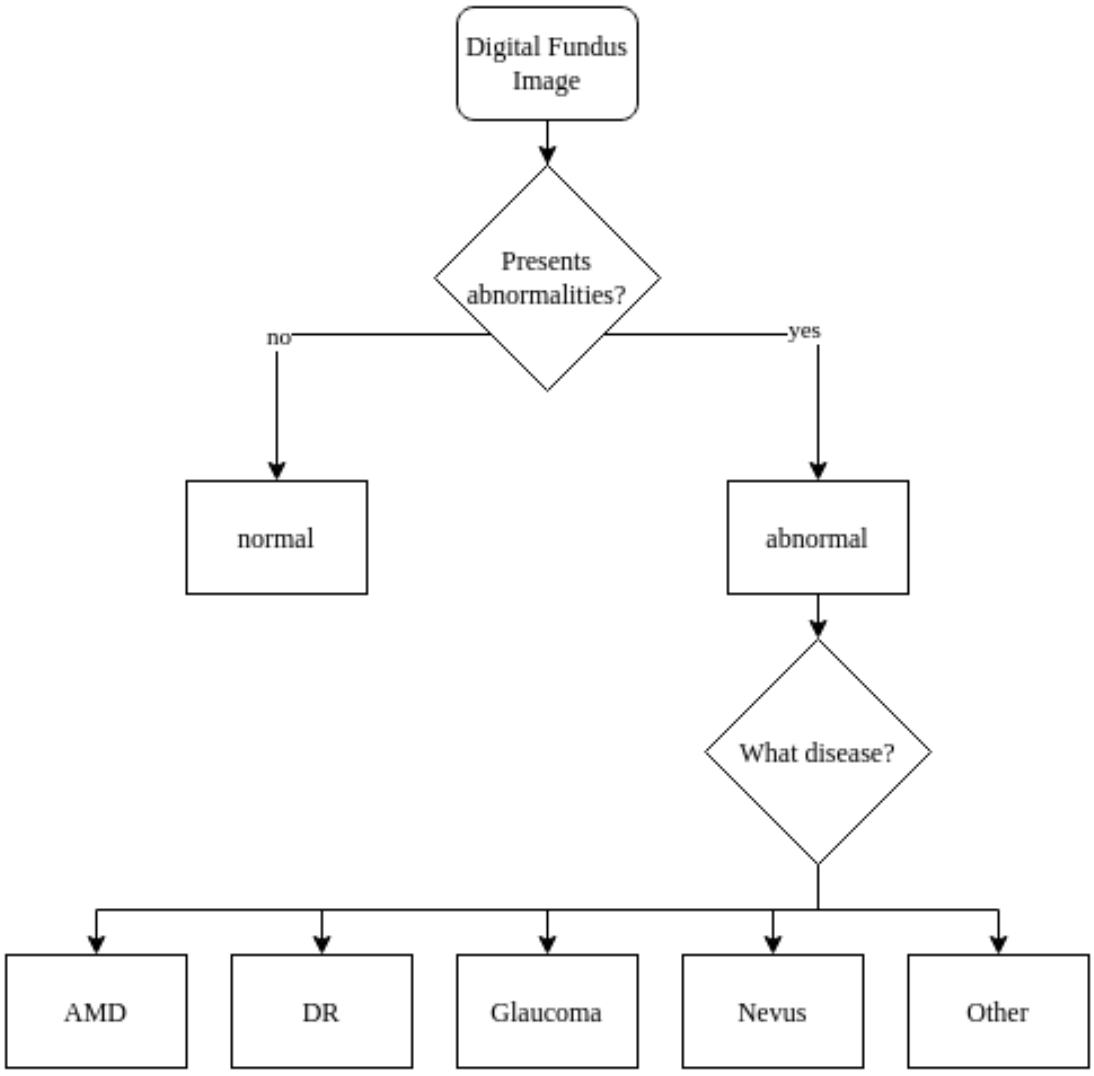

Figure 1: Flowchart depicting the 2-tiered approach followed by all specialists to label the dataset. The ground truth was agreed by at least 2 graders.

Dataset enrichment

We aim to assess the effectiveness of our automated screening algorithm on a wide range of population. Because of the sampling bias of the initial population (working-age participants, mostly without known prior pathologies) the prevalence for AMD and DR was far below that reported in the literature for the general population (Wong et al. 2014; Yau et al. 2012). To balance the data, we enriched the dataset with 384 AMD and 150 DR pathological images, to match the prevalence in the general population of our environment (Romero-Aroca, P) (Spanish Eyes epidemiological). AMD images were obtained from Optretina's image bank (the sample was randomly selected from a cohort of 2212 AMD cases screened from January 2013 to May 2020) (Zapata et al 2017). DR images were randomly selected from a series of positive cases detected in the Institut Català de la Salut (ICS) screening program for diabetics

(Barcelona, Spain). In both cases, the enriched images were labelled by two expert retinal specialists, following the procedure detailed in Figure 1. The dataset details are shown in Table 1.

Table 1: Split of the original and enriched datasets used to train and validate the AI-based algorithms for each pathology. M / F refers to the male / female participant, and LE / RE refers to the left / right eye, respectively.

dataset	n participants (M / F)	age median (std) [range]	n eyes (LE / RE)	n images	abnormal (%)	AMD (%)	DR (%)	Glaucoma (%)	Nevus (%)	Other (%)
Study validation										
original	2839 (1786 M / 1053 F)	43 (11.52) [5-87]	5483 (2747 LE / 2736 RE)	5918	321 (5.42%)	14 (0.23%)	0 (0%)	107 (1.81%)	110 (1.86%)	90 (1.5%)
enriched	3337 (1999 M / 1338 F)	46 (15.22) [5-96]	6009 (3013 LE / 2996 RE)	6452	855 (13.25%)	398 (6.17%)	150 (2.32%)	107 (1.66%)	110 (1.7%)	90 (1.4%)
Algorithm training										
AMD[4]	- (982 M / 1526 F)	75 (11.52) [5-98]	- (1761 LE / 1945 RE)	7218	-	4859 (67.31%)	-	-	-	-
DR[5]	71455 (26691 M / 19296 F)	66 (11.42) [11-99]	116501 (60947 LE / 55554 RE)	139813	-	-	14376 (10.28%)	-	-	-
Glaucoma	1206 (619 M / 587 F)	54 (15.58) [5-96]	1738 (794 LE / 944	2366	-	-	-	1168 (49.37%)	-	-

[4] The total number of participants and the total number of eyes for the AMD training dataset was not available, since the non-pathological images were not assigned to a patient. The reported numbers (M/F, LE/RE, age) are from the pathological cases, which were referenced to a patient.

[5] The sex split and age median only accounts for 65% of the dataset. One of the image sources for this dataset did not include sex nor age information per patient.

			RE)							
Nevus	18750 (8.215 M / 10535 F)	42 (11.64) [5-96]	29352 (15633 LE / 13719 RE)	30054	-	-	-	-	4470 (14.87%)	-
Abnormality	31877 (13843 M / 18034 F)	49 (17.33) [5-99]	52791 (27846 LE / 24945 RE)	53194	17433 (32.77%)	-	-	-	-	-

Statistical analysis

The primary outcome of the analysis is the diagnostic accuracy of the AI system, defined by its sensitivity and specificity, versus the ground truth. Since the AI system performs a holistic screening as well as pathology specific diagnostic, we calculated the sensitivity and specificity for both. The operating threshold was fixed before the analysis and was not adjusted during the tests. The secondary outcomes are the receiver operating characteristic (ROC) curves and their Area under-the-curve (AUC). All reported 95% CI were obtained by performing a non-parametric bootstrap (1000 samples, with replacement).

Study success was defined as reaching a predefined threshold of sensitivity and specificity on our holistic general screening algorithm. The hypotheses of interest were

$$H_0 : p < p_0 \, vs \, H_A : p \geq p_0 \; (1)$$

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where p is the sensitivity or specificity of the AI system. The predefined sensitivity and specificity thresholds were $p_0 = 0.75$ and $p_0 = 0.775$ respectively, benchmark defined by the FDA in their first-approved AI diagnostic system (Abràmoff et al. 2018). A one-sided 2.5% Type I error binomial test was performed for both null hypotheses.

For the sample size calculation, we estimated a prevalence of retinal abnormalities in an occupational health checkup context of 7,8% with a 95% confidence interval, as per our previous study (Zapata et al. 2020). With these figures, the total number of participants needed was 2784. Additionally, we also confirmed (Bujang and Adnan 2016) that the sample size of our enriched dataset was large enough to ensure 80% statistical power ($\beta = .2$) on our sensitivity and specificity metrics, given the reported null hypothesis and the levels of pathological prevalence.

Proposed Approach

The screening algorithm is a combination of five independently trained neural networks. Four of these neural networks target specific pathologies (AMD, DR, Glaucoma and Nevus), while the fifth one has been trained as an outlier detector, with a training dataset containing images from the aforementioned pathologies as well as other undetermined maculopathies (see Figure 2). Each image evaluated by the system is processed independently by each of the five neural networks and, at a second step, their response is combined in a single output. If an algorithm detects signs of any of the individual pathologies, the screened image is classified as "Abnormal". A complete diagram of the AI system architecture is presented in Figure 2.

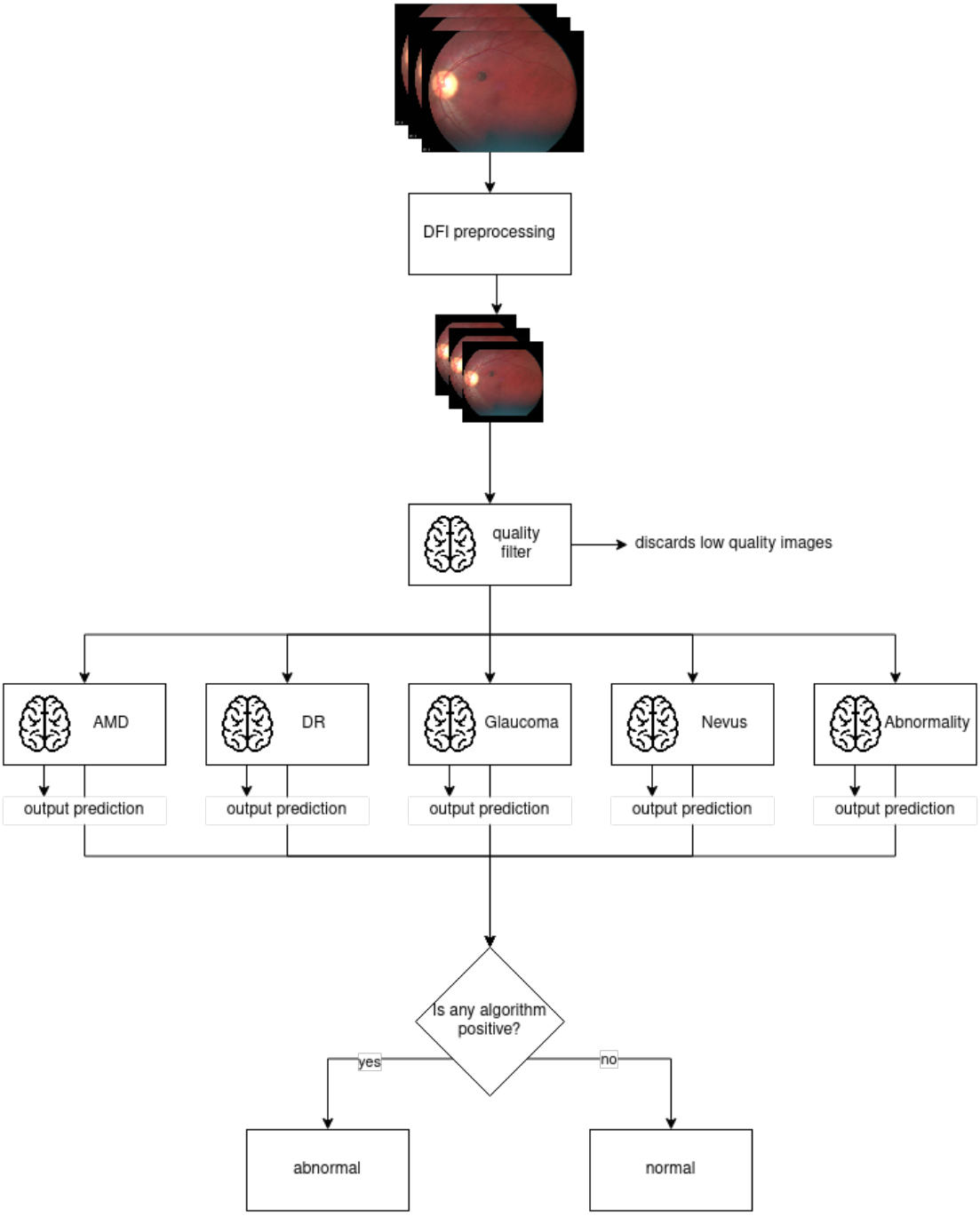

Figure 2: Algorithm execution flowchart. The predictions are performed at the image level.

The "AMD" algorithm uses a custom neural network architecture (Zapata et al. 2020), using RGB images of 512x512 pixels. The "DR" algorithm uses an InceptionV3 architecture (Szegedy et al. 2016) with inputs of 512x512. "Glaucoma" uses a ResNet50 (Wu, Zhong, and Liu 2017) with inputs of 224x224. "Nevus" detection employs an InceptionV3 at 299x299 and the "Abnormal" images detector another InceptionV3 at 299x299. All algorithms have been trained end to end with manually

annotated images by retinal experts. Table 1 contains detailed information regarding the composition and size of each training dataset.

Code and Data availablity

The AI system described in this study is copyrighted by Optretina S.L. and consequently, the underlying source code is not available. The data could be provided upon reasonable request by contacting the corresponding author.

Ethical considerations

Optretina is a company supervised by the ethics committee of the Vall d'Hebron Hospital in Barcelona, who approved this clinical trial (Study code PR(OPT)370/2019). Patient's informed consent was exempted because of the restrospective nature of the study, using fully anonymized retinal images.

Results

The ensembled abnormality algorithm correctly identified 92% of the analyzable images annotated as "Abnormal" (776/843). The performance of individual disease algorithms is herein described: 99% of AMD images were correctly identified (385/386), 100% of DR images were correctly classified (150/150), 71% of Glaucoma images were correctly identified (71%, 74/103), 90% of Nevus images were correctly identified (92/102) and 73% of undetermined maculopathies were correctly classified (75/102). Insufficient quality of the images was observed in 0.23% of the cases (15/6452), that could not be graded. Of these, 80% were labeled as abnormal by our graders (12/15).

The single NN (neural network) abnormality algorithm correctly detected 82% (691/843) of the analyzable images. The percentage of images correctly classified disclosed by pathologies was: 98.8% of AMD images (382/386), 94.6% of DR images (142/150), 45.6% of Glaucoma images (47/103), 49% of Nevus images (50/102) and 49% of other maculopathies images (50/102).

The AMD algorithm correctly detected 90% of AMD images (350/386). False positive rates were 62.6% of DR images (94/150), 6.7% of Glaucoma images (7/103), 0% of Nevus images (0/102) and 22.5% of other maculopathies images (23/102).

The DR algorithm correctly detected 68.6% DR images (103/150). False positive rates were 4.1% of AMD images (16/386), 0% of Glaucoma images (0/103), 0.9% of Nevus images (1/102) and 11.7% of other maculopathies images (12/102).

The Glaucoma algorithm correctly detected 58.2% of Glaucoma images (60/103). False positive rates were 10.6% of AMD images (41/386), 12.6% of DR images (19/150), 2.9% of 102 Nevus images (3/102) and 8.8% of other maculopathies images (9/102).

The Nevus algorithm correctly detected 88.2% of the Nevus specific images (90/102). False positive rates were 88% of AMD images (340/386), 100% of DR images

(150/150), 2.9% of Glaucoma images (3/103) and 63.7% of other maculopathies images (65/102).

Table 2: Summary of sensitivity, specificity and AUC aggregated and per individual algorithm.

Algorithm	Sensitivity (95% CI) [p value]	Specificity (95% CI) [p value]
Ensembled Algorithm:		
Abnormality	0.929 (0.910, 0.946) [<.001][6]	0.868 (0.858, 0.877) [<.001][7]
Single NN Algorithms:		
Abnormality	0.834 (0.806, 0.859)	0.934 (0.927, 0.940)
AMD	0.938 (0.916, 0.963)	0.957 (0.952, 0.962)
DR	0.811 (0.753, 0.881)	0.948 (0.941, 0.954)
Glaucoma	0.536 (0.431, 0.631)	0.957 (0.952, 0.962)
Nevus	0.867 (0.807, 0.940)	0.907 (0.901, 0.915)

The sensitivity and specificity obtained from all algorithms are summarized in Table 2. The threshold for each individual CNN was not adjusted to boost the sensitivity or specificity operating point. Sensitivity and specificity were calculated per eye, using the best quality image if multiple were available. Discarding eye duplicates had little effect in the metrics in our study cohort (sensitivity: 0.9210 duplicates vs 0.9288 no-duplicates; specificity: 0.8760 duplicates vs 0.8685 no duplicates). Enforcing high quality standards in the preprocessing pipeline, the effect is more noticeable (sensitivity: 0.9288 any quality vs 0.9262 high quality; specificity: 0.8685 any quality vs 0.8919 high quality). The dataset, as classified by the automatic quality algorithm, consisted of 53.4% high quality images (n=3444), 43.6% of acceptable quality images (n=2809) and 3.0% of low quality images (n=196).

To represent the best operation points we plotted the ROC curve for the ensembled and individual models in Figure 3. Additionally, we also computed the AUC of the ensembled (0.963) and the single NN version (0.948).

[6] p-value for sensitivity on the ensembled abnormality algorithm was computed using a one-sided tailed binomial test using a sensitivity of $p=0.75$ as the null hypothesis.

[7] p-value for specificity on the ensembled abnormality algorithm was computed using a one-sided tailed binomial test using a sensitivity of $p=0.775$ as the null hypothesis.

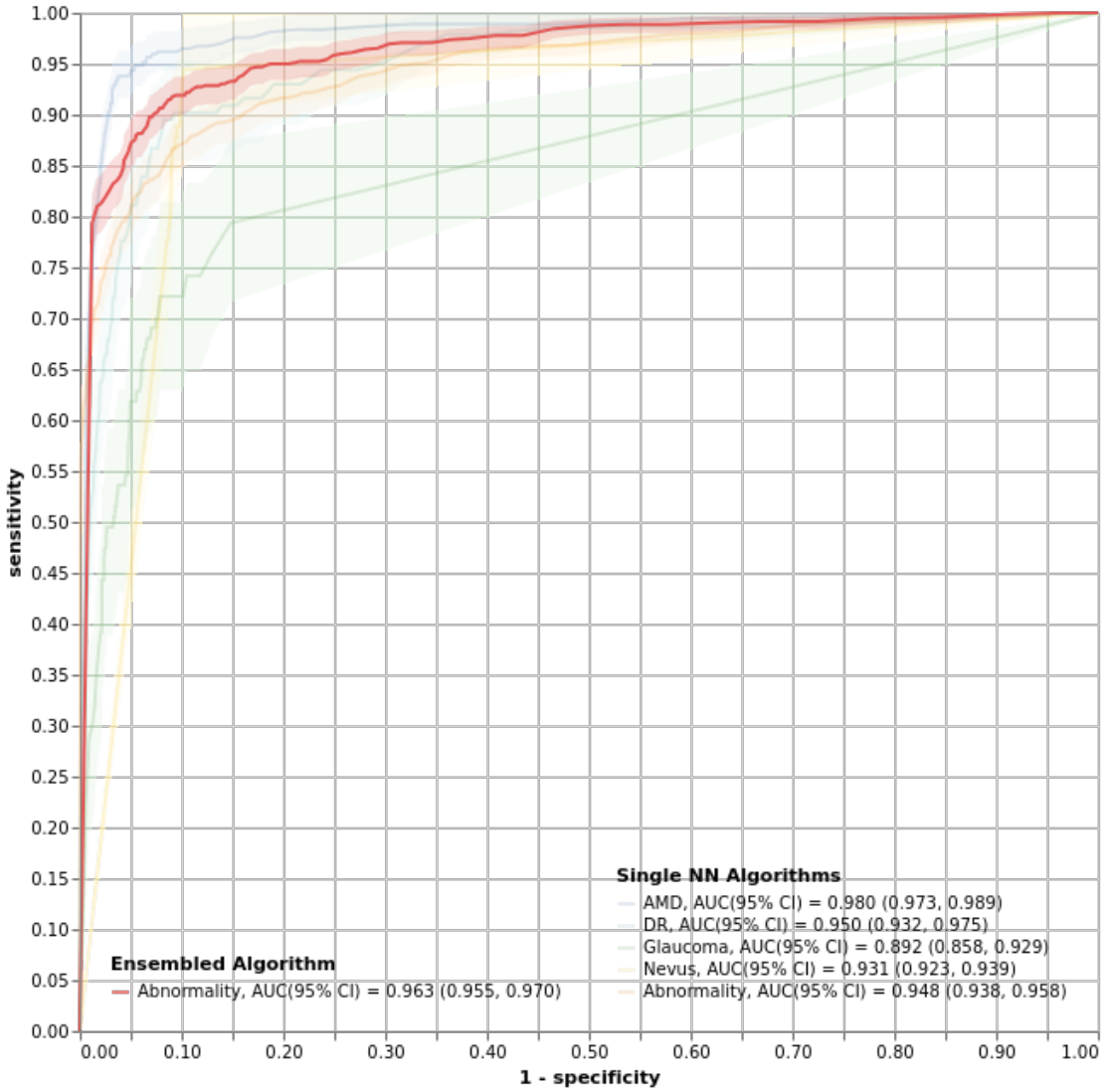

Figure 3: Receiver operating curve for the ensembled and individual algorithms.

Discussion

The proposed study has exceeded the expectations of the holistic solution proposed for screening the central retina's diseases. The reported diagnostic accuracy levels are similar to other algorithms already available on the market and higher than those required by the FDA for approval (Abràmoff et al. 2018). However, the proposed system present the additional benefit that several pathologies are simultaneously screened, with those that cause greater visual loss in industrialized countries among them. These are also the main causes of preventable, non-reversible blindness, which are experiencing more growth in the world (Adelson et al. 2020).

It is widely demonstrated that early detection of these diseases (mainly AMD, DR, and glaucoma) and their early treatment, if necessary, can prevent visual loss in a very high percentage of patients (Chew et al. 2014; Ferris 1994; Phu et al. 2020). Simultaneous screening for multiple pathologies of the retina has previously been contemplated in some publications, both associated with human reading and artificial intelligence, mainly combining the detection of AMD and DR (Chan et al. 2015; González-Gonzalo et al. 2019), and also glaucoma (Ting et al. 2017). To date, all artificial intelligence studies using fundus images in this area have been carried out only in existing databases, with no clinical validation studies performed prospectively.

Currently, screening programs in most countries focuses on DR, probably for cost-effectiveness reasons. Our study population is relatively young, and a priori, healthy, despite previous studies that report alterations in fundus images in almost 8% of cases in this type of population (Zapata et al. 2020). Although usually these alterations do not represent serious or urgent cases, any pathology in this population, young and working, can have significant socio-economic repercussions. The incorporation of artificial intelligence and the simultaneous screening of several diseases can make these early detection systems more cost-effective. Despite the fact that the objective of this study is not an economic evaluation, the use of automatic detection software can reduce previously reported costs, lower than 10 euros per patient. (Zapata et al. 2020).

One of the most important causes of loss of effectiveness of AI is related to the quality of the images (Schmidt-Erfurth et al. 2018). In our series, we have had 3% of fundus photographs of low quality, a figure significantly lower than other published series such as Abramoff et al (Abramoff et al) (above 8%) or Liu et al. (16%) (Liu et al. 2020). We would like to note that our numbers are obtained on real conditions, with portable cameras and, generally, under certainly strict timeframes. This difference can be due to different reasons. While portable cameras traditionally tended to be of lower quality than desktop cameras, the technical advances in recent years have improved the quality of the images, and current cameras like Aurora are of equivalent quality. Moreover, screening has been carried out in relatively young people, in which ocular media opacities are much less common and tend to have more dilated pupils in scotopic conditions.

One of the most interesting points is the study of comorbidities; to date, it is also one of the limits set by AI. With this type of approach, lesions can be detected by independent algorithms that combine together in a holistic diagnostic. This results in a more robust system, less likely to miss incidental findings, with higher overall sensitivity while only penalizing slightly on specificity. The use of AI for DR screening is already being implemented successfully in some countries. However, pathology-specific approach carries the risk of ignoring other possible findings, since the neural networks employed are not designed for it. We do believe that it would be beneficial if those IA systems are combined and set up with a more holistic approach, to minimize the risk of ignoring that incidental findings.

The combination of multiple algorithms also makes it easier to deploy improvements on the system. We can tackle algorithms per pathology and any improvements in the individual models will benefit in the final output. We have already achieved gains in multiple retrainings of the DR algorithm, and we believe that the AMD and Glaucoma algorithms could be similarly improved in the near future.

This study's limits are those determined by carrying out a retrospective study, those related to the population studied (in this case, younger and with a lower rate of pathology than the general population), and the limits derived from the pathology studied. To compensate for possible biases, the database has been enriched with a presence similar to the population of age-related macular degeneration and DR. It would be convenient, in the future, to introduce other highly prevalent pathologies in the population, such as the presence of epiretinal membranes or macular signs associated with high myopia. Another area that we want to study further is in the image capture workflow, to offer not only an automated way of screening, but a better screening workflow with hybrid systems. We believe that by integrating the image acquisition process with an online platform for automated data collection it's possible to instrument the whole process and guide the technician through, with the additional benefit that the images are automatically assigned to the right patient and checked for adequate quality prior to running any subsequent diagnostic analysis.

In conclusion, the use of an autonomous AI-based diagnostic system based on fundus images for holistic maculopathy screening in a routine occupational health checkup context seems effective, with high levels of sensitivity and specificity that improves further those achieved by specific algorithms. The application of these systems could allow more extensive screening programs with greater detection of pathology in working-age patients.

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