

Evaluation of a system for automatic detection of diabetic retinopathy from color fundus photographs in a large population of patients with diabetes.

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ABSTRACT

Objective: evaluate the performance of a system for automated detection of diabetic retinopathy in digital retinal photographs, built from published algorithms, on a large, representative, screening population.

Research design and methods: Retrospective analysis of 10,000 consecutive patient visits = exams (4 retinal photographs, two left and two right) from 5,692 unique patients from the EyeCheck diabetic retinopathy screening project imaged with three types of cameras at ten centers. *Inclusion criteria:* no previous diagnosis of diabetic retinopathy, no previous visit to ophthalmologist for dilated eye exam, both eyes photographed. One of three retinal specialists evaluated each exam as unacceptable quality, no referable retinopathy, or referable retinopathy. The system selected exams with sufficient image quality, on those, determined presence or absence of referable retinopathy. Outcome measures: area under ROC curve (AROC), 'number needed to miss one case' (NNM), type of false negative.

Results: Total AROC was 0.84, NNM was 80 at a sensitivity of 0.84 and a specificity of 0.64. At this point, 7689/10000 exams had sufficient image quality, 4648/7689 (60%) were true negatives, 59/7689 (0.8%) false negatives, 319/7689 (4%) true positives, and 2581/7689 (33%) false positives. 27% of false negatives contained large hemorrhages and/or neovascularizations.

Conclusion: automated detection of diabetic retinopathy using published algorithms cannot yet be recommended for clinical practice. However, performance is such that evaluation on validated, publicly available datasets should be pursued. If algorithms can be improved, such a system may in the future lead to improved prevention of blindness and visual loss in patients with diabetes.

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Diabetic retinopathy blinds approximately 25,000 patients with diabetes annually in the United States alone, and is the main cause of blindness in the U.S. and Europe working age populations (1). Almost fifty percent of the 18 million patients with diabetes in the U.S do not undergo any form of regular documented dilated eye exam (Centers for Disease Control, <http://www.cdc.gov/diabetes/statistics/preventive/tX.htm>, accessed July 2007). This is in spite of overwhelming scientific evidence that this, if combined with appropriate management, can prevent up to 95% of cases of visual loss and blindness (2-9), and also in spite of guidelines by the American Diabetes Association and the American Academy of Ophthalmology, that advise an annual dilated eye exam for most patients with diabetes (10). Digital photography of the retina examined by ophthalmologists or other qualified readers has been shown to have sensitivity and specificity comparable to or better than indirect ophthalmoscopy by an ophthalmologist (11,12), and has been proposed as an approach to make the dilated eye exam available to underserved populations that do not receive regular exams by ophthalmologists. If all of these populations were to be served with digital imaging, the number of retinal images to be evaluated annually is 32 million (approximately 50% of patients with diabetes and at least two photographs per eye) (12,13).

Over the last few years, we, and others, have developed and published computer algorithms that can aid the ophthalmologist with the evaluation of digital fundus photographs for early forms of diabetic retinopathy in a community (screening) population(14-21,21-26). Our studies on small number of patients show that such algorithms have the capacity to perform comparably to retinal specialists and

outperform most other published algorithms on limited tasks:

- correct localization of the optic disc in 999/1000 retinal images (27),
- segmentation of retinal vessels at an accuracy of 94.2% in 20 retinal images(28),
- detection of hemorrhages, microaneurysms and vascular abnormalities with sensitivity 100% and specificity 87% in 100 retinal images(29),
- detection and separation of exudates, cotton-wool spots and drusen with a lesion sensitivity of 95% and specificity of 88% in 300 retinal images(30),
- detection of retinal images with insufficient image quality with an accuracy of 97.4% in 1000 retinal images (31).

Though these algorithms were targeted to these narrowly focused tasks, they can potentially be combined into a complete system for the detection of diabetic retinopathy in a screening setting, meaning in a population in which the incidence of newly diagnosed diabetic retinopathy is less than 30% (13,32-34). No studies have examined the performance of a combined system, built from published algorithms, for the detection of diabetic retinopathy on a large group of patients from a true screening population, i.e. with a high proportion, of up to 90%, of normal appearing fundi and a low proportion, of up to 30%, of fundoscopically detectable diabetic retinopathy. Typical screening projects consist of multiple sites, often employ multiple types of digital fundus-cameras, with camera-operators with varying levels of experience, resulting in retinal images that exhibit considerable variation in size, resolution and image quality.

The gold standard for the evaluation of diabetic retinopathy is 7-field stereo fundus photography read by trained readers in accordance with the ETDRS standard (35),

and ideally, the performance of a complete system would be compared to the evaluation of ETDRS stereo slides taken from the same patients on the same day. However, the expense of such a study with 7-field stereo photography by trained photographers and evaluation by ETDRS readers on a sufficiently large number of patients can only be warranted if preliminary studies show that such a research effort may be worthwhile.

The EyeCheck project for online diabetic retinopathy detection in the Netherlands employs so-called 'non-mydriatic' fundus cameras. Over 20,000 exams have been performed to date, with 2 photos per eye, on patients not known to have diabetic retinopathy and read by a single ophthalmologist (out of three participating ophthalmologists) according to a strict protocol: prevalence of referable diabetic retinopathy ranges between 5-10% in this population (32).

The present study was designed as a preliminary study to determine how well the performance of a combination of published algorithms for automated detection of diabetic retinopathy holds up in comparison to the clinical evaluation of a single retinal specialist on the same 10,000 retinal exams, consisting of 40,000 retinal images obtained with a variety of different retinal cameras from the EyeCheck project.

METHODS

Subjects. In this retrospective study, we selected 10,000 consecutive patient visits from 5692 unique patients. These visits consisted of four retinal photographs – two left, two right eye - as well as textual information about age, HbA1C, gender, and presence of risk factors, over the period 2003-2005, to the EyeCheck project which has been described elsewhere (32). Patients are photographed annually in community health centers according to an imaging protocol described below. The study protocol was

approved by the institutional review board of the University of Iowa. Because of the retrospective nature of the study and because full anonymity was maintained throughout the study, informed consent was judged not to be necessary by the IRB.

In-, exclusion criteria. Patients were included if they had a diagnosis of diabetes according to WHO criteria, and were of age 18 and over. Patients were excluded if they had had a diagnosis of diabetic retinopathy, had had a previous visit to an ophthalmologist for a dilated retinal eye exam, had had only one eye photographed, had less than two photographs per eye, or no demographic data available. Once a patient is evaluated as having referable retinopathy, he or she cannot be re-photographed. Thus, the exams were always of patients either up until then known not to have referable diabetic retinopathy based on a previous exam, or until then not known to have diabetic retinopathy.

Imaging protocol. Patients were photographed with 'non-mydriatic' digital retinal cameras by trained technicians, at ten different sites, employing either the Topcon NW 100, the Topcon NW 200 (Topcon, Tokyo, Japan) or the Canon CR5-45NM (Canon, Tokyo, Japan) 'non-mydriatic' cameras. Across sites, four different camera settings were used: (A) 640x480=0.3 Megapixels (Mp) and 45° field of view; (B) 768x576 = 0.4 Mp and 35°; (C) 1792x1184 = 2.1 Mp and 35°; (D) 2048x1536 = 3.1 Mp and 35°; all images were JPEG compressed at the minimal compression setting available. For each exam, four images were acquired, two of each eye, one centered on the fovea and one centered on the optic disc. The exam, date of birth, duration of diabetes and HbA1C status were transmitted over the internet to the website (www.eyecheck.nl), and evaluated by a single out of three ophthalmologists based on the International Clinical Diabetic Retinopathy Disease Severity Scale, as either no referable retinopathy or referable

retinopathy, as well as for sufficient image quality (36). This evaluation was documented online, and was immediately available to the primary care physician and patient at the community health center. Patients were recommended for follow-up for imaging for one year or two years, depending on risk factors not available for this study. For this study, from each exam the following were available: the anonymized retinal images, the age of the patient when the photographs were taken, an anonymized sequential unique site id, an anonymized unique patient id, and an aggregate human expert evaluation of the four images in each exam:

- unacceptable quality
- *no referable retinopathy* or no apparent diabetic retinopathy
- *referable retinopathy*: at least mild non-proliferative retinopathy

System of computer algorithms for evaluation of retinal images for diabetic retinopathy. After automatic cropping of the black border, all retinal images were automatically resampled to 640x640pixels. Then, the following sequence of image operations was performed on each image:

- Automatic determination of the probability that the image has a sufficient quality for evaluation, based on the presence of particular image structures with a particular spatial distribution, as described previously (31). After preliminary testing, the threshold for insufficient image quality was set so that approximately 80% of exams judged by the human expert to have unacceptable quality were rejected, while 20% of exams judged by the human expert to have acceptable image quality were rejected by the system as having unacceptable quality.
- Automatic segmentation of the vessels using pixel feature classification as we have described previously, resulting in a vessel probability image, which is

necessary to exclude false positive 'red lesions' (28,37).

- Automatic detection and masking of the optic disc using a method that determines where blood vessels converge, as we have described previously (27).
- Automatic detection of 'red lesions': microaneurysms, hemorrhages or vascular abnormalities, using feature classification, as we have described previously, resulting in a red lesion probability map (29)
- Automatic detection of 'bright lesions': exudates, cotton-wool spots and drusen, using pixel feature classification, resulting in a combined probability map for exudates, cotton-wools spots and drusen (the differentiation between drusen and the other two is not used by the combined system we present here) as described previously (30)

We have used these machine learning algorithms as is, in other words, no retraining of the algorithms was performed for this study. The total runtime of the complete system for a single image on a standard Windows PC was 7 minutes, and one exam thus took $4 \times 7 = 28$ minutes. To quickly evaluate the complete set of 10,000 exams we implemented our system on a cluster of 30 PCs with an automatic job distribution system.

Outcome parameters and data analysis. Several features such as the number and probability of the lesions in all four images of an exam as detected by the red and bright lesion detection algorithms were used to create the per-exam retinopathy probability. Each of the four images, from both eyes, were therefore considered independently. Combined with the output of the image level image quality algorithm, two probabilities were thus created at the exam level, namely the probability that an exam has sufficient quality for evaluation and the probability that that exam shows referable retinopathy. The image quality threshold is a number that

determines when an image is ungradable. By varying the thresholds for red and bright lesion, the sensitivity and specificity of the system compared to the clinician's reading can be made to vary. Sensitivity and specificity of the complete system relative to the clinical evaluation are calculated at each threshold setting. These sensitivity/specificity pairs are used to create Receiver Operator Characteristic (ROC) curves, showing the sensitivity and specificity at various thresholds. The area under the ROC curve is regarded as a comprehensive measure of system performance: an area of 1.0 has sensitivity = specificity = 1 and represents perfect detection, while an area of 0.5 is the performance of a system that essentially performs a coin-toss on average. From the ROC curve, the 'optimal threshold' is the subjective point at which we deemed sensitivity and sensitivity to be optimal for a screening setting.

In addition we defined the Number Needed to Miss (NNM) = $\frac{1}{\left(\frac{\text{false negatives}}{\text{all negatives}}\right)}$ as

the number of normal exams after which, on average, one case of referable retinopathy will be missed, for a specific threshold setting. The effect of camera type and administration of pharmacologic dilation, if any, on system performance was evaluated by determining the sensitivity and specificity of the algorithm, at the optimal threshold.

RESULTS

Descriptive. Of the 5692 patients included, 3107 patients had one exam, 1601 patients had two exams, and 986 patients had three or more exams over the time period. All included patients had two photographs of each eye taken (see inclusion criteria). The average age of these 5692 patients at the time of their first exam was 61.8 years (± 1 standard deviation 12.81 years). 3833 (49.85%) patients were male, and 3856

(50.15%) were female. 9017/10000 exams (90%) were evaluated by an ophthalmologist as having no apparent retinopathy, 498 (4.98%) exams were evaluated by an ophthalmologist as having at least minimal non-proliferative retinopathy, and 485 (4.85%) exams were evaluated as having insufficient image quality on one or more images.

The system detected 2311/10,000 exams as not having sufficient quality, and 7689/10,000 exams were determined by the system to have sufficient image quality for all images in the exam. These 7689 exams were from 4739 unique patients. Average age for these 4739 patients was 59.9 (± 11.7) years. Of these 7689 exams with system determined sufficient image quality on all four images, 7229 (94%) were evaluated by the human expert as having no referable retinopathy, 378 (4.92%) as having referable retinopathy, and 81 (1.05%) as having insufficient image quality on one or more images. As mentioned in the Methods, the quality threshold for the automatic system was set so that 80% of the 9515 exams that were thought by humans to have sufficient quality were allowed to pass.

We performed a limited estimate of the reading by the single human expert on these 7689 exams, by selecting a random set of 500 exams from these. The exams in this set were read independently by three masked retinal specialists. Compared to the original reading, their sensitivity/specificity pairs (referable retinopathy or not) were 0.85/0.89, 0.73/0.89, and 0.62/0.84.

If the human expert was taken as the reference standard or 'truth', the area under the Receiver Operator Characteristic Curve was 0.84 for all 7689 sufficient image quality exams, 0.85 for all 4739 patients on their first visit, and 0.84 for those 1701 patients with a second visit, see Figure 1. The optimal threshold had a sensitivity of 0.84 and a specificity of 0.64. At this point, 4648/7689

(60%) exams were correctly identified by the system as having no referable retinopathy, 59/7689 (0.8%) exams did have referable retinopathy but were missed by the system, 319/7689 (4%) exams were correctly identified as having referable retinopathy, see Figure 2A, B for an example, and 2581/7689 (33%) exams were false positives, i.e. the system estimated them as having diabetic retinopathy while the human expert did not. The 'number needed to falsely miss one case' (NNM) of referable diabetic retinopathy, at this point, was 80, meaning that for every 80 exams, one case of referable retinopathy is missed at this chosen, 'optimal' threshold. See Figure 2C for an example of such a false negative, missed exam.

If the sensitivity of the system was increased, by adjusting the threshold, the NNM could be increased up to a maximum of 127, at which point the system had a (very low) specificity of 0.22.

We performed a preliminary, qualitative analysis of a sample of 87 false negative exams obtained at a specific point in the ROC curve to understand where the system was failing and the potential for improvement. Of these 87 false negative exams, 24/87 (27%) contained large hemorrhages and/or neovascularizations of the disc or elsewhere, 23 contained one or a few small hemorrhages, 18 contained exudates or cottonwool spots only, and 22 exams contained other lesions that the system was not designed to detect, including nevi and retinal scars, that were not deemed to be diabetic retinopathy by a second expert.

The effect of camera type and pharmacologic dilation on system performance at the optimal threshold was as follows: in the subgroup that was pharmacologically dilated, sensitivity / specificity were 0.76 / 0.39, while in the group that was not pharmacologically dilated, these were 0.80 / 0.43 respectively. Across camera types, they were camera (A)

0.86/0.22, (B) 0.88/0.56 (C) 0.79/0.83, (D) 0.78/0.73 respectively.

DISCUSSION

To our knowledge, this is the first time that an automated diabetic retinopathy screening system, based exclusively on previously published algorithms, has been tested on an unselected set of exams of this size obtained from a representative diabetes population. The data used in this study was collected over a three year period and represents real, unselected, screening data obtained in a diabetic retinopathy screening program. The area under the curve of 0.85 on the first visit, and an optimal sensitivity of 0.84 and specificity of 0.64, show the potential of such a system. That the system is relatively stable is shown by the fact that the area under the curve for the second visit is 0.84. The limited validation on a sample of 500 exams shows that the original single human expert reading corresponds quite closely to the independent readings by three masked retinal specialists. However, because independent expert readings on the full dataset are not available, it is impossible to determine how the system compares to human readers on this aspect.

However, the system cannot yet be recommended for clinical practice because the number needed to screen to miss one case (NNM) of diabetic retinopathy was 80 at the optimal threshold and was never higher than 127. Another more important reason is that of the 87 false negatives at the optimal threshold, approximately were 25% isolated neovascularizations or large hemorrhages *not* accompanied by any other lesion such as exudates or microaneurysms – while such isolated lesions still require urgent referral to an ophthalmologist. Therefore there is a compelling need for algorithm improvement, including for better detection of neovascularizations, for which no specific algorithm has yet been published. In

comparison with these results, Usher, et al., previously tested a complete system on a set of 733 patients, with a high prevalence of diabetic retinopathy of 38%, and found a maximum sensitivity of 95.1% and a specificity of 46.3% (38). Larsen et al., tested a previously commercially available system on 100 patients, 63% of patients with diabetic retinopathy and found a sensitivity of 96.7% and a specificity of 71.4% (39). These smaller test populations, with a higher prevalence of diabetic retinopathy, should not be considered representative of a true, large scale screening population, in which an automated system is expected to be deployed.

The results do show that performance is close enough to that of human experts to warrant additional studies on high quality, validated, datasets such as the ETDRS dataset (40). Additionally the results show that reporting only sensitivity and specificity or area under the ROC curve may not be sufficient to evaluate a system for screening for diabetic retinopathy, as our preliminary analysis of false negatives shows. Finally, the results show that a measured performance comparable to human experts on limited tasks, such as red lesion detections, does not translate directly to comparable results on much larger, unselected datasets. This caveat, to our knowledge, also applies to all other published diabetic retinopathy lesion detection algorithms. There is a large difference between the rate of exams with images of insufficient quality in this study (4.85%) and in most previous studies, including our own study, where we reported a rate of 12% of ‘ungradeable photographs’ (32). The EyeCheck population is a partially closed population, and not a cohort. Patients, once photographed, remain in the population until they either fail to show up for their repeat exam or are referred because of insufficient image quality or referable abnormalities including diabetic retinopathy. Thus, over time, patients with

initially insufficient image quality leave the population, while patients in the population accrue insufficient image quality much more slowly, for example, from cataract formation. Patients that had pre-existing abnormalities leave the population at their first exam, while the accrual of diabetic retinopathy is much slower. On the other hand, new screening sites are added almost monthly, so there is a continuous influx of new patients. We expect that the observed change in rates of insufficient quality exams reflects the above balance. There seemed to be a slight effect that increasing camera resolution resulted in improved system performance: this subject merits additional study.

There are several important limitations with this study. Most importantly, the estimate by the system was compared to a single reading by a human expert, and because of the nature of the study, could not be compared to the gold standard, 7 field stereo photography read by experts (40). It is therefore impossible to state whether the performance of the system would have been different if compared to the gold standard.

The automated system is also slow, taking 28’ per patient (4 images). This was a non-optimized version running in debug mode, and meanwhile, we have more than halved this time. For screening projects that are online, response time can be increased simply by running the system on multiple PC’s. However, for real time diagnosis directly in the camera – an option we currently see as less attractive - this is likely to still be too long.

In summary, this study indicates that automated detection of diabetic retinopathy using a combination of published algorithms cannot yet be recommended for clinical practice, based on this test on a true population of patients screened for diabetic retinopathy. On the other hand, the performance is such that evaluation on validated, publicly available datasets should

be pursued. Individual algorithms for lesion detection, as well as the manner in which lesion detection algorithms are combined merit additional research before they can be

considered for automated detection of diabetic retinopathy in patients with diabetes, where they may aid in the prevention of blindness and visual loss in these patients.

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FIGURE LEGENDS

Figure 1. Receiver operator characteristics (ROC) curve for algorithm versus human expert on 4739 first visits (left graph), and 1701 second visits (right graph). Vertical axis, sensitivity of the system at different thresholds, horizontally, corresponding 1-specificity. Area under the curve is 0.85 (first visit) and 0.84 (second visit).

Figure 2. Example of one image from an exam (A) where both expert and automated system agree on the presence referable retinopathy. (B) shows where the automated system detected exudates and cotton wool spots (shades of red and purple) and hemorrhages (shades of yellow-green) and the location of the optic disc (white circle). C. Example of false negative exam showing evidence of diabetic retinopathy, (large hemorrhage attached to artery, indicated with white arrow), detected by the human expert, but missed by the system.

FIGURE 1

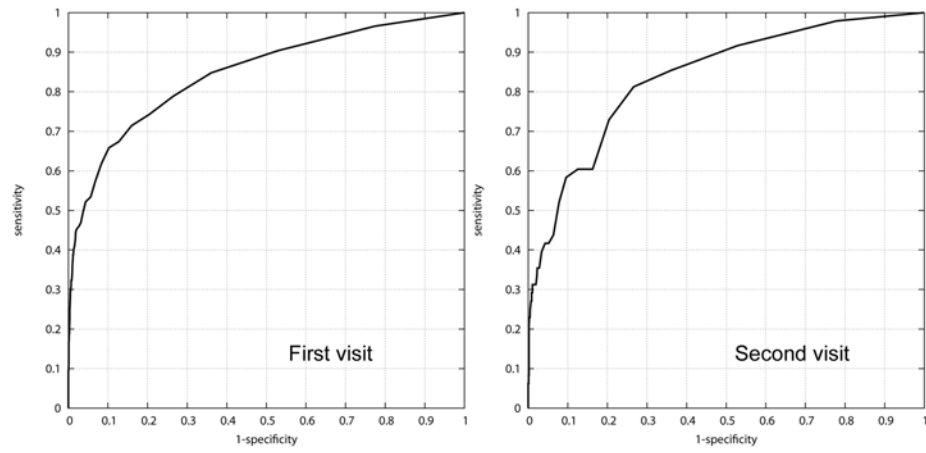


FIGURE 2

