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Original article

Evaluation of automated fundus photograph analysis algorithms for detecting microaneurysms, haemorrhages and exudates, and of a computer-assisted diagnostic system for grading diabetic retinopathy

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Abstract

Aims. – This study aimed to evaluate automated fundus photograph analysis algorithms for the detection of primary lesions and a computer-assisted diagnostic system for grading diabetic retinopathy (DR) and the risk of macular edema (ME).

Methods. – Two prospective analyses were conducted on fundus images from diabetic patients. Automated detection of microaneurysms and exudates was applied to two small image databases on which these lesions were manually marked. A computer-assisted diagnostic system for the detection and grading of DR and the risk of ME was then developed and evaluated, using a large database containing both normal and pathological images, and compared with manual grading.

Results. – The algorithm for the automated detection of microaneurysms demonstrated a sensitivity of 88.5%, with an average number of 2.13 false positives per image. The pixel-based evaluation of the algorithm for automated detection of exudates had a sensitivity of 92.8% and a positive predictive value of 92.4%. Combined automated grading of DR and risk of ME was performed on 761 images from a large database. For DR detection, the sensitivity and specificity of the algorithm were 83.9% and 72.7%, respectively, and, for detection of the risk of ME, the sensitivity and specificity were 72.8% and 70.8%, respectively.

Conclusion. – This study shows that previously published algorithms for computer-aided diagnosis is a reliable alternative to time-consuming manual analysis of fundus photographs when screening for DR. The use of this system would allow considerable timesavings for physicians and, therefore, alleviate the time spent on a mass-screening programme.

Keywords: Diabetic retinopathy; Macular edema; Fundus photography; Screening; Automated image analysis

Résumé

Évaluation d'algorithmes d'analyse automatique de photographies du fond d'œil pour la détection des microanévrismes, des hémorragies et des exsudats et d'un système de diagnostic assisté par ordinateur pour la classification de la rétinopathie diabétique.

Objectifs. – Évaluer des algorithmes d'analyse automatique de photographies du fond d'œil pour la détection de lésions élémentaires de la rétinopathie diabétique. Évaluer un système de diagnostic assisté par ordinateur permettant de classer le stade de rétinopathie diabétique et le risque d'œdème maculaire.

Méthodes. – Deux analyses prospectives de photographies du fond d'œil de patients diabétiques ont été effectuées. La détection automatique des microanévrismes et des exsudats a été appliquée sur deux petites bases d'images sur lesquelles ces lésions ont été marquées manuellement. Le système de diagnostic assisté par ordinateur permettant la classification de la rétinopathie diabétique et du risque d'œdème maculaire a ensuite été développé et testé sur une large base de données contenant à la fois des images normales et pathologiques, puis comparé à la détection manuelle.

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Résultats. – L'algorithme de détection automatique des microanévrismes, évalué sur 94 images, a révélé une sensibilité de 88,5 % avec un nombre moyen de 2,13 faux-positifs par image. L'évaluation de l'algorithme de détection automatique des exsudats, menée sur 30 images, a montré une sensibilité de 92,8 % et une valeur prédictive positive de 92,4 %. La détermination du stade de rétinopathie diabétique et du risque d'œdème maculaire a été effectuée sur 761 images provenant d'une large base de données. La sensibilité et la spécificité de l'algorithme de détection de la rétinopathie diabétique étaient respectivement de 83,9 % et 72,7 %. Pour la détection de l'œdème maculaire, une sensibilité de 72,8 % et une spécificité de 70,8 % ont été trouvées.

Conclusion. – Notre étude montre que les algorithmes de détection automatique de la rétinopathie diabétique précédemment publiés représentent une alternative fiable à l'analyse manuelle de photographies du fond d'œil pour le dépistage de la rétinopathie diabétique et de l'œdème maculaire. Leur utilisation en pratique clinique permettrait une épargne de temps considérable pour les praticiens et allègerait ainsi le dépistage de masse.

Mots clés : Rétinopathie diabétique ; Œdème maculaire ; Photographies du fond d'œil ; Dépistage ; Analyse automatique d'image

1. Introduction

The complications of diabetic retinopathy (DR) remain the most common cause of blindness among adults aged greater than 65 years in the developed countries [1–4]. Although early detection and laser treatment of DR have proved effective in preventing visual loss [5,6], many diabetic patients are not treated in time because of inadequacies of the currently available screening programmes [7,8]. As 75% of the blindness due to diabetes is known to be preventable, instituting an efficient screening programme for the detection of at-risk patients at a stage when they can still be effectively treated is now a recognised urgent worldwide priority. In an effort to detect DR at an early stage, international and national guidelines recommend annual fundus examination for all diabetic patients [9–11]. In 2005, health professionals from a number of European countries met in Liverpool in the UK, where a declaration was drawn up stating that, by 2010, all European countries should have systematic programmes in place for screening 80% of the diabetic population. In France, the Haute Autorité de santé (HAS) [12] issued guidelines recommending annual fundus screening of diabetic patients using colour fundus photography. This technique was approved as a standard reference because of its high sensitivity in detecting retinal lesions [13–15].

To improve DR screening in France, where several studies have shown that less than 40% of diabetic patients undergo an annual fundus examination [7,8], several programmes have been proposed. One that has proved to be feasible and valid for DR detection is the telemedical screening network system OPHDIAT©, supported by the French Ministry of Health. This programme consists of taking non-mydriatic fundus photographs that are tele-transmitted to a reading centre where they are then graded by independent ophthalmologists [16]. This separation of fundus picture-taking from their reading was approved by the HAS in 2007. In other countries, there are technicians who are qualified to grade fundus photographs but, in France, this is performed by ophthalmologists. However, because of the increasing prevalence of diabetes among the French population [17] and the predicted decrease in the number of ophthalmologists in France over the next 10 years, the interpretation of fundus photographs is expected to become a huge burden, making the development of automated fundus imaging analysis algorithms necessary.

Over the past 10 years, the Centre of Mathematical Morphology (CMM) at the Paris school of Mines, in collaboration with the Lariboisière Hospital ophthalmology department, has been developing algorithms for automated fundus colour-image analysis. These algorithms are able to detect the main retinal elements, such as the vessels [18,19], optic disk [18,19] and macula [18], and certain characteristic features of DR, such as microaneurysms (μA) [18,20], hard exudates [18,21] and haemorrhages. They have also been used to develop a new computer-assisted diagnostic system for the detection and grading of DR and the risk of macular edema (ME).

Therefore, the purpose of the present study was to evaluate the results obtained using the μA and exudate detection algorithms, and using the computer-assisted diagnostic system.

2. Patients and methods

2.1. Databases and manual annotation

Two small databases comprising high-quality images were acquired after pupil dilation by the Lariboisière ophthalmology department, using a Sony 3CCD colour video camera attached to a Topcon TRC 50 IA retinograph, with a resolution of 640 × 480 pixels. These images were used to develop and evaluate algorithms for the detection of μA and exudates. The database for μA was divided into a learning set of 21 images and an evaluation set of 94. To obtain a 'gold' standard, the μA were manually marked by three independent expert ophthalmologists, who were also asked to discuss their results to reach a consensus for every candidate, including those they had not personally marked. Candidates for whom a consensus could not be reached were not included in the final statistical analyses. All 21 images in the learning set and 68/94 images in the evaluation set contained at least one μA, but neither set contained images with greater than 20 μA, as it has been observed that the graders' accuracy decreases when images include greater than 15–20 μA. An example of manual marking is shown in Fig. 1, in which the μA accepted by the three graders are shown in black, while the others are shown in green. The algorithm for exudate detection was evaluated on a database that included 30 images not used for algorithm development: 15 of these images contained no exudates while, in the other 15, the exudates were graded manually. Unlike μA, there are few doubtful cases in the manual detection of exudates. Therefore, a gold-standard reference

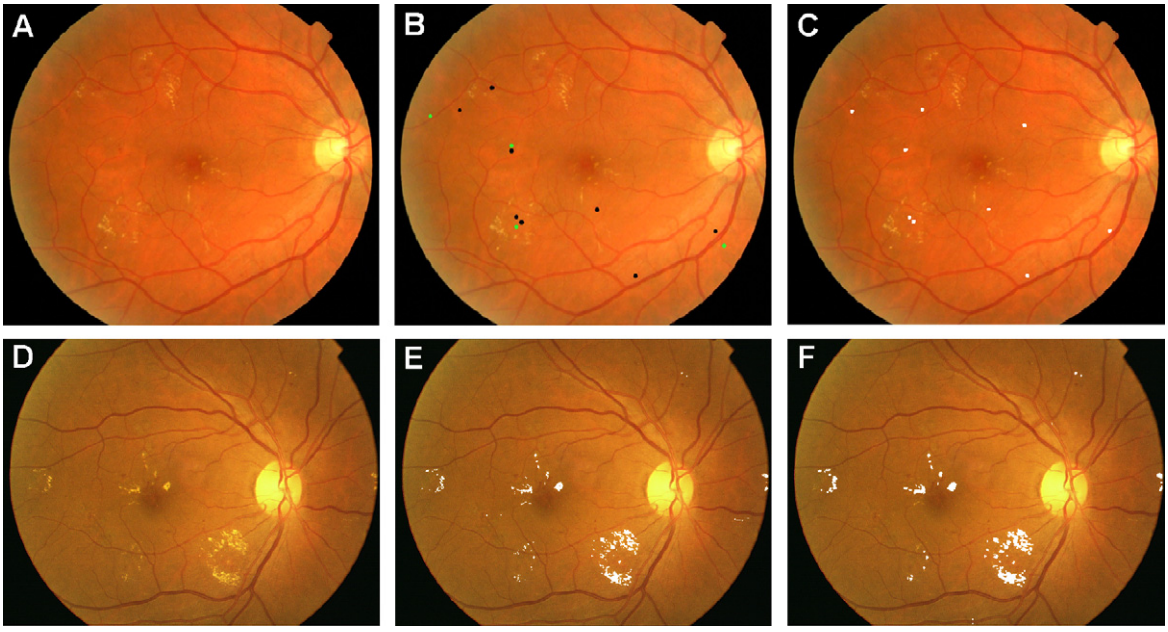

Fig. 1. (Upper) colour fundus photographs before (A) and after (B) manual microaneurysm marking. The confirmed microaneurysms are marked in black and the doubtful ones in green. Automatically detected microaneurysms are shown in white on image C. (Lower) colour fundus photographs before (D) and after (E) manual exudates were marked in white. Automatically detected exudates are shown in white on image F.

was built up from the images marked by only one ophthalmologist.

The *méthodes d'évaluation de systèmes de segmentation et d'indexation dédiées à l'ophtalmologie rétinienne* (MESSIDOR); methods of evaluation of systems of classification and indexing dedicated to retinal ophthalmology) is a large database of retinal images that was created to evaluate a new computer-assisted diagnostic system developed for the detection and grading of DR as well as estimation of the risk of ME. The huge number of colour images of the posterior pole of the fundus included in the MESSIDOR database was acquired using a Topcon TRC NW6 non-mydriatic camera (Topcon, Rotterdam, The Netherlands) with a 45-degree field of view. The images were captured with eight bits per colour plane at 1440 × 960, 2240 × 1488 or 2304 × 1536 pixels. Three images (one central and two peripheral) of the same fundus were included in the database, although only the central images were annotated. Of these images, 406 were acquired by the ophthalmology department of Brest Hospital without pupil dilation, and 962 were from the ophthalmology department of Lariboisière Hospital (Paris) and St-Étienne Hospital with pupil dilation, using one drop of 10% tropicamide. As the algorithms for μA and exudate detection were developed from images with pupil dilation, only the latter 962 central images were used, divided into two groups:

- a learning set, comprising 201 images, that was used to test and improve the available algorithms, develop and test the new computer-assisted diagnostic system, and validate the evaluation of the results for detection and grading;
- an evaluation set, comprising 761 images, that was used to evaluate the results produced by the computer-assisted diagnostic system for grading the stage of DR and the risk of ME.

Every image in both sets was manually marked by a retina specialist according to the following two criteria:

- the stage of DR, using criteria shown in Table 1, with grade 0 = no DR, grade 1 = mild DR, grade 2 = moderate DR and grade 3 = severe DR (as, so far, no current algorithm has been developed for the detection of neovascularisation, this criterion was not included);
- the risk of ME, based on the severity of ME according to exudate location in relation to the centre of the macula (Table 1), with grade 0 = no risk of ME, grade 1 = mild risk of ME and grade 2 = severe risk of ME.

The study adhered to the tenets of the Helsinki declaration. To ensure maximum protection of patients' privacy, any information that might have allowed a patient's identity to be determined was removed and, as far as the authors are aware, none of the study images can be used, either alone or in combination, to identify any patient. Also, the present study was conducted

Table 1
Criteria used for grading diabetic retinopathy (DR) and macular edema.

DR stage	
Grade 0 (no DR)	$\mu A = 0$ and $H = 0$
Grade 1 (mild)	$1 \leq \mu A \leq 5$ and $H = 0$
Grade 2 (moderate)	$5 < \mu A < 15$ or $0 < H \leq 5$
Grade 3 (severe)	$\mu A \geq 15$ or $H > 5$
Risk for macular edema	
Grade 0	No visible exudates
Grade 1 (mild)	Shortest distance between macula and hard exudates > 1 optic-disk diameter
Grade 2 (severe)	Shortest distance between macula and hard exudates ≤ 1 optic-disk diameter

μA: microaneurysms; H: haemorrhage.

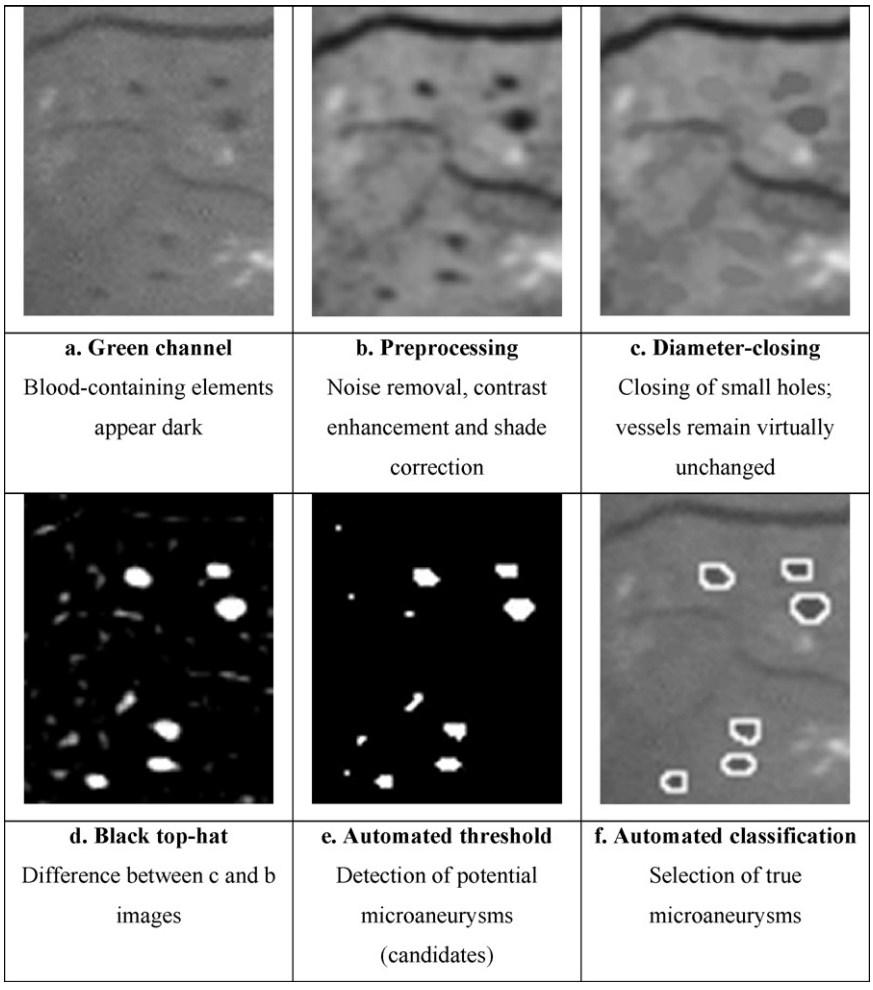

Fig. 2. Main aspects of the algorithm used for the automated detection of microaneurysms.

in accordance with the French law on computerised information and civil liberties (Commission nationale informatique et Libertés [CNIL]).

2.2. *Study algorithms and automated classification*

All of the algorithms for the automated detection of the main retinal elements [22] and the characteristic lesions were developed by the CMM in collaboration with the Lariboisière Hospital ophthalmology department. As a good example of the application of image processing in the detection of retinal lesions on colour fundus photographs, the algorithm for μA detection is described here, the main aspects of which are shown in Fig. 2. The automated algorithm works on the green channel of the colour image, which was selected because it provides maximum contrast for elements that contain blood. μA are defined as small isolated areas with a diameter $\boldsymbol{\lambda} < 125$ μm (about nine pixels in an image of 640 × 480 pixels; Fig. 2a). The algorithm has five main steps. The preprocessing step (Fig. 2b) filters the image, enhances the contrast and performs a shading correction to compensate for the non-uniform illumination across the image. The diameter-closing step is a mathematical morphological transformation that fills in all the black dots with diameters smaller than λ. After such transformation, the grey-scale value of the filled-in dots is higher than in the enhanced image, while the vessels and other elements remain virtually unchanged (Fig. 2c). The black top-hat [23] step (Fig. 2d) uses size and shape criteria to extract black components contrasted against the background, and is the result of the difference between the images obtained by the diameter closing and pre-processing steps. The automated threshold step identifies any elements in the black top-hat image that are possible μA candidates (Fig. 2e) and, finally, the classification step uses properties calculated for these candidates to identify them as either true μA or false positives, using a *k*-nearest neighbours (*k*-NN) classifier [24,25], based on the learning set in the small database (details of the method are not included here, as it is a standard method of classification). The classifier acts like a human grader by taking into account features such as size, contrast, circularity, grey-scale level and colour. The true μA selected by this process are shown in Fig. 2f.

However, the quality of the images still greatly affects the results, so the presence of laser scars, large lesions or interrupted small vessels can lead to false-positive findings, while the lack

of adequate contrast or focus can generate false negatives. An example of automated marking is shown in Fig. 1.

2.3. Computer-assisted diagnostic system for grading DR and ME risk

All algorithms developed for fundus colour-image analysis by the CMM and Lariboisière eye department were integrated into the computer-assisted diagnostic system. For each image, the software had to perform four tasks:

- detection of the vessel tree and evaluation of its area; as vessel visibility is a good criterion of focus quality and media transparency, this feature is also used to classify the images as either gradable or ungradable;
- detection and measurement of the numbers of μA and haemorrhages, which are then used for automated grading of the DR stage;
- detection of the macula;
- detection of exudates, and evaluation of the shortest distance between them and the macula, the value of which is used to grade the risk of ME.

The combination of all four results is then used to assess the severity of DR, according to the rules shown in Table 1.

2.4. Evaluation of algorithms and the computer-assisted diagnostic system

The small database was used to evaluate μA and exudate detection algorithms by comparing, for μA, the automatically detected and manually marked lesions and, for exudates, the automatically detected and manually marked pixels. Evaluation consisted of determining, for μA, the number of lesions that were true positives (TP), false positives (FP) and false negatives (FN) and, for exudates, the number of pixels that were similarly TP, FP and FN.

The DR stage and risk of ME obtained with the computer-assisted diagnostic system were compared with those obtained from the large evaluation database by manual grading. For further analyses of sensitivity, specificity and positive predictive values, the images were classified into two groups: for DR, grade 0 images were classified as 'normal', and grades 1–3 as 'abnormal'; for the risk of ME, grade 0 images were classified as 'normal', and grades 1–2 as 'abnormal'. The statistical relevance of using such a binary system was determined by the algorithm's sensitivity, specificity and positive predictive value, using manual grading as the gold standard.

3. Results

3.1. Evaluation of the algorithm for automated detection of microaneurysms

In all, 115 images were manually marked for μA, 21 of which were used for the learning set. The evaluation set consisted of 94 images, of which 68 contained at least 1 μA. Also, there were exudates in 29 images, haemorrhages in 27 and no signs of DR in 26. The mean number of μA was four per image. This set of 94 images also contained 373 μA marked manually. Sensitivity was 88.47%, with 2.13 FP per image. Specificity, according to the formula $\frac{TN}{TN+FP}$, could not be determined because the number of true negatives (TN) makes no sense in this context. Also, the positive predictive value, according to the formula $\frac{TP}{TP+FP}$, is not relevant for comparisons of different algorithms applied to different datasets, as the number of TP is limited by the number of μA present, whereas the number of FP is only due to artifacts. This means that the positive predictive value tends to be low if the absolute number of μA is low. Therefore, the best way to use the average number of FP per image is as a secondary criterion.

Table 2
Results of the computer-assisted diagnostic system for diabetic retinopathy (DR) detection in the evaluation set of the large database.

Automated detection	Manual detection (gold standard)		
	Normal (*n*)	Abnormal (*n*)	Total (*n*)
Normal	224	71	295
Abnormal	84	370	454
Unclassified	8	4	12
Total	316	445	761

3.2. Evaluation of the algorithm for automated exudate detection

This algorithm was evaluated on 30 images that were not used in the development of the algorithm. Fifteen of these images contained exudates, which were manually outlined by one ophthalmologist and used for the statistical evaluation. The images outlined by hand and marked automatically were compared pixel by pixel, with one pixel of tolerance either way. By this means, a mean sensitivity of 92.8% and a positive predictive value of 92.4% were obtained. Again, specificity could not be used as a quality criterion, as the number of TN pixels tends to be high compared with the number of FP, leading to a specificity that is invariably close to 100%.

3.3. Evaluation of the computer-assisted diagnostic system

The evaluation set contained 761 colour images of 761 eyes. Of these, 316 were classified manually as 'normal' (grade 0) and 445 as 'abnormal' (grade > 0). For DR, the comparison between automated and manual classification is shown in Table 2. The computer-assisted diagnostic system was able to classify 749 of the 761 images (98.4%) with a sensitivity of 83.9%, a specificity of 72.7% and a positive predictive value of 81.5%. The grading results are shown in Table 3. The sensitivity, specificity and positive predictive values for the detection of the moderate-to-severe grades of DR were 91.8%, 75.7% and 81.5%, respectively.

To evaluate the risk of ME, 581 images classified manually as 'normal' and 180 as 'abnormal' were assessed. The comparison between automated and manual classification is shown in Table 4. All of the images were gradable by the algorithm, with

Table 3
Results of the computer-assisted system for grading diabetic retinopathy in the evaluation set of the large database.

Automated detection	Manual grading (gold standard)				
	Normal (grade 0; *n*)	Mild (grade 1; *n*)	Moderate (grade 2; *n*)	Severe (grade 3; *n*)	Total (*n*)
Normal (grade 0)	224	38	27	6	295
Mild (grade 1)	51	35	36	3	125
Moderate (grade 2)	27	20	58	30	135
Severe (grade 3)	6	4	29	155	194
Unclassified	8	1	2	1	12
Total	316	98	152	195	761

Table 4
Results of the computer-assisted diagnostic system for detecting the risk of macular edema (ME) in the evaluation set of the large database.

Automated detection	Manual detection (gold standard)		
	Normal (*n*)	Abnormal (*n*)	Total (*n*)
Normal	412	49	461
Abnormal	169	131	300
Total	581	180	761

a sensitivity and specificity of 72.8% and 70.8%, respectively. The grading results are shown in Table 5.

4. Discussion

The development and evaluation of algorithms for the automated detection of DR involved three steps: first, the development and evaluation of algorithms for automated detection of the main DR characteristics, such as the presence of μA and hard exudates; second, the evaluation of the ability of these algorithms to discriminate between the presence and absence of DR in a sample of selected images; and, third, the evaluation of these algorithms in a large, unselected set of examinations representative of a screened diabetic population.

Compared with the recent findings by Quellec et al. [26], μA detection by the present algorithms exhibited slightly lower sensitivity (88.1% vs 89.6%), but also a lower average of FP results per image (2.1 vs 2.5). The present study also involved a greater number of images (94 vs 32). For exudate detection, Sopharak et al. [27] reported a sensitivity of 80% and a positive predictive value of 68.6%, whereas our present algorithm results were 92.8% and 92.4%, respectively. Other studies have reported lower sensitivity [22,28]. As for the detection of ME risk, we found a sensitivity of 72.7% and a specificity of 70.9% in our 761 patients, rates that are below those for the recent evaluation of automated grading for ME reported by Nayak et al. [29] in 350 subjects. In that study, Nayak et al. used the algorithm developed by our team [21] and obtained a sensitivity of greater than 95% and a specificity of 100%. The difference between their results and the present study findings may be explained by the fact that Nayak et al. only took into account exudates located near the macula whereas, in our study, those lying at the periphery were also considered. The latter are often more difficult to detect because of the variable illumination across a fundus image and the presence of other features, such as optic disk, that have similar colour and contrast properties.

For DR grading — the classification of images for 761 eyes as either normal or abnormal — we found a sensitivity of 83.9% and a specificity of 72.7%, results that are consistent with those of several previous reports on the use of different approaches to automated grading of DR, but involving a smaller number of images [24,25]. Recently, Larsen et al. [30] tested a commercially available system based on the detection of 'red dots', and reported a sensitivity of 96.7% and a specificity of 71.4% for 200 eyes, while Bouhaimed et al. [31], using the same software, found a 94.8% sensitivity and 52.8% specificity for 192 eyes. Finally, Usher et al. [32], using an artificial neural network, found a maximum sensitivity of 95.1% and a specificity of 46.3% in a series of 773 patients. All of these studies, as with the present one, were performed with a sample of selected gradable photographs with a high DR prevalence. Although such a prevalence is not representative of a screened population, it allowed the investigators to evaluate the ability of these algorithms to discriminate between the presence and absence of DR.

From a clinical point of view, the objective of developing such algorithms is to ensure, when screening for DR, a safe and competent alternative to analysis of fundus photographs by ophthalmologists, and to address the issue of determining the likelihood that a patient's condition is normal and not requiring further investigation by human operators. This would save

Table 5
Results of the computer-assisted system for grading the risk of macular edema (ME) in the evaluation set of the large database.

Automated detection	Manual grading (gold standard)			
	Normal (grade 0; *n*)	Mild (grade 1; *n*)	Severe (grade 2; *n*)	Total (*n*)
Normal (grade 0)	412	25	24	461
Mild (grade 1)	158	22	16	196
Severe (grade 2)	11	10	83	104
Total	581	57	123	761

physicians time because, by excluding normal images, it would reduce the burden of manual analysis by about 70%, as normal fundi predominate in DR-screened populations. However, to be able to exclude normal images, algorithms must have both high specificity and high sensitivity to avoid misdiagnosis of potentially sight-threatening retinopathy. The present study algorithms appear to be well balanced for sensitivity and specificity in the detection of all forms of DR compared with previous studies [30–32]. UK guidelines for diabetes recommend a minimum of 80% sensitivity and 95% specificity for the detection of sight-threatening DR [32] but, in the opinion of the present authors, a sensitivity greater than 80% and a specificity greater than 70% appear to be acceptable for the early stages of DR whereas, for later stages (greater than mild non-proliferative DR), sensitivity should be greater than 90% and specificity greater than 70%. This suggests that the present study's sensitivity of 91.8% for the detection of moderate-to-severe forms of DR is acceptable.

Nevertheless, the ultimate goal of a computer-assisted diagnostic system is to go beyond binary classification of normal/abnormal images and DR grades, and to restrict manual grading to only those images that have a certain degree of abnormality. This would mean that patients would only need to be referred to an ophthalmologist if they presented with moderate non-proliferative DR or worse, or with ME, or if their fundus photographs were ungradable. At present, however, the major limitation of computer-assisted grading is the lack of reliable methods for the robust detection of neovascularisation. A few studies using automated grading of different retinopathy stages have been published [25,30,33,34], but further evaluation of such grading is still required.

Automated computer-assisted DR detection in a large screened population has been evaluated in only a few studies. Abramoff et al. [35], who evaluated an automated DR screening system based exclusively on previously published algorithms, found a sensitivity of 84% and a specificity of 64% for 7689 screened patients [36]. They concluded that automated grading software could not yet be recommended for clinical practice, as 27% of their FN involved severe forms of DR or neovascularisation. Another large cohort was the series by Philip et al. [37], who evaluated an automated form of DR grading based on image quality assessment and μA detection, testing 14,406 images from 6722 consecutive patients participating in a screening programme. Their reported high sensitivity (90.5%) for the detection of technical failure and any form of retinopathy, and a specificity of 67.4%, allowed a grading reduction of 60%.

In conclusion, the results of the computer-assisted diagnostic system tested in the present study show a good compromise between sensitivity and specificity, and highlight the important role of automated detection in screening for DR. The next step is to integrate such a system into the multicentre OPHDIAT© telemedical network developed for DR screening in France.

Conflict of interest

No potential conflicts of interest relevant to this article have been reported.

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