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


Service d'ophtalmologie, hôpital Lariboisière, Assistance publique–hôpitaux de Paris, université Denis-Diderot Paris-7, 2, rue Ambroise-Paré, 75010 Paris, France
Mines ParisTech, centre de morphologie mathématique (CMM), mathématiques et systèmes, 35, rue Saint-Honoré, 77305 Fontainebleau cedex, France
Université Hospital Bellevue, service d'ophtalmologie, Saint-Étienne, France

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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 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.

* Corresponding author. Service d’ophtalmologie, hôpital Lariboisière, 2, rue Ambroise-Paré, 75475 Paris cedex 10, France.
E-mail address: p.massin@lrb.aphp.fr (P. Massin).

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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 allégerait ainsi le dépistage de masse.

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

### 1. Introduction

Les complications diabétiques (DR) restent l’une des causes les plus fréquentes de la cécité parmi les adultes de 45 ans et plus dans de nombreux pays [1–4]. Même si l’identification et le traitement par laser de la DR ont prouvé leur efficacité en termes de prévention de la perte de vision [5,6], de nombreux diabétiques ne sont pas traités à temps à cause de l’absence de programmes de dépistage [7,8]. La détection manuelle de la DR est souvent considérée comme un moyen de prévention de la cécité chez les diabétiques, mais elle impose une surcharge sur les ophthalmologistes. La quantité de photographs qui doivent être analysées par un ophthalmologiste est importante, ce qui est un facteur qui a contribué au développement de l’automatisation.

D’après les estimations de l’Autorité de santé (HAS) [12], il est prévisible que le nombre d’ophthalmologistes en France augmente de 10 % par an en France, ce qui va de pair avec une augmentation de la demande de dépistage. Les programmes de dépistage de la DR ont été mis en place par le HAS en 2007 [13–15].

Depuis la publication de nos travaux précédents [13–15], de nombreux algorithmes de détection automatique de la DR ont été développés. Ils se distinguent par leurs performances et leurs applications. Cependant, de nombreux défis restent à relever, en particulier en termes de spécificité et de sensibilité. Les recherches sur l’automatisation de la DR se poursuivent dans le monde entier. Les algorithmes de détection automatique de la DR ont été développés par différentes équipes, notamment par l’équipe de Dupas et al. [16,17].

Les défis actuels de l’automatisation de la DR sont multiples et nécessitent une approche multidisciplinaire. Les algorithmes de détection automatique de la DR ont montré des performances différentes en termes de spécificité et de sensibilité. En France, de nombreux centres de dépistage de la DR utilisent des algorithmes automatisés pour l’analyse de la photographie du fond d’œil. Cependant, la validation des algorithmes automatisés est une étape cruciale pour garantir leur efficacité et leur fiabilité.

L’objectif de cet article est de présenter les résultats d’un projet de validation de l’algorithme automatisé de détection de la DR, développé par l’équipe de Dupas et al. [16,17]. Le protocole de validation a été effectué en partenariat avec le Centre de Mathématique et Morphologie (CMM) de l’École des Mines de Paris, dans le cadre de la collaboration entre l’hôpital Lariboisière et l’institut ophthalmo-logique (CMM). Le protocole de validation a été effectué sur une base de données de photographies du fond d’œil provenant de patients diabétiques.

### 2. Patients and methods

#### 2.1. Databases and manual annotation

Deux petits échantillons comprenant des images de haute qualité ont été utilisés pour la validation de l’algorithme automatisé de détection de la DR. Ces échantillons ont été acquis après dilatation du pupille par le département ophthalmologique de l’hôpital Lariboisière, en utilisant une caméra couleur Sony 3CCD connectée à un microscopie de l’œil Topcon TRC 50 IA. Les images étaient résolues à 640 × 480 pixels. Les images ont été utilisées pour développer et tester les algorithmes de détection de la DR.

Pour la validation, une base de données de photographies du fond d’œil provenant de patients diabétiques a été utilisée. Cette base de données a été utilisée pour le développement et la validation de l’algorithme de détection de la DR. Les images de la base de données ont été annotées manuellement par des ophthalmologistes experts. Ce processus a permis de générer une base de données d’apprentissage et de test pour l’algorithme automatisé de détection de la DR.

Le protocole de validation comprend une étape de validation par deux experts ophthalmologistes. Les images ont été annotées manuellement par deux ophthalmologistes experts, puis l’algorithme automatisé de détection de la DR a été testé sur ces images. Les résultats obtenus ont été comparés aux annotations manuelles pour évaluer la performance de l’algorithme automatisé.

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.
The \textit{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 microaneurysms 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>
<thead>
<tr>
<th>Criteria used for grading diabetic retinopathy (DR) and macular edema.</th>
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<tbody>
<tr>
<td><strong>DR stage</strong></td>
</tr>
<tr>
<td>Grade 0 (no DR)</td>
</tr>
<tr>
<td>Grade 1 (mild)</td>
</tr>
<tr>
<td>Grade 2 (moderate)</td>
</tr>
<tr>
<td>Grade 3 (severe)</td>
</tr>
<tr>
<td><strong>Risk for macular edema</strong></td>
</tr>
<tr>
<td>Grade 0</td>
</tr>
<tr>
<td>Grade 1 (mild)</td>
</tr>
<tr>
<td>Grade 2 (severe)</td>
</tr>
</tbody>
</table>

\( \mu_A \): microaneurysms; \( H \): haemorrhage.
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 $\lambda < 125 \mu$m (about nine pixels in an image of $640 \times 480$ 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 $\lambda$. 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...
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.

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.

<table>
<thead>
<tr>
<th>Automated detection</th>
<th>Manual grading (gold standard)</th>
<th>Total (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (grade 0; n)</td>
<td>224</td>
<td>295</td>
</tr>
<tr>
<td>Mild (grade 1; n)</td>
<td>51</td>
<td>125</td>
</tr>
<tr>
<td>Moderate (grade 2; n)</td>
<td>27</td>
<td>135</td>
</tr>
<tr>
<td>Severe (grade 3; n)</td>
<td>6</td>
<td>194</td>
</tr>
<tr>
<td>Unclassified</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>316</td>
<td>761</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Automated detection</th>
<th>Manual detection (gold standard)</th>
<th>Total (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>412</td>
<td>461</td>
</tr>
<tr>
<td>Abnormal</td>
<td>169</td>
<td>300</td>
</tr>
<tr>
<td>Total</td>
<td>581</td>
<td>761</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Automated detection</th>
<th>Manual grading (gold standard)</th>
<th>Total (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (grade 0; n)</td>
<td>412</td>
<td>461</td>
</tr>
<tr>
<td>Mild (grade 1; n)</td>
<td>158</td>
<td>196</td>
</tr>
<tr>
<td>Severe (grade 2; n)</td>
<td>11</td>
<td>104</td>
</tr>
<tr>
<td>Total</td>
<td>581</td>
<td>761</td>
</tr>
</tbody>
</table>

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
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 DR. 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.

Acknowledgements

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Conflict of interest

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


