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Web-Based Screening for Diabetic Retinopathy in a Primary Care Population: The EyeCheck Project

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ABSTRACT

The objective of this study was to evaluate the feasibility of ATA category 2 Web-based screening for diabetic retinopathy in a primary care population in the Netherlands. A total of 1,676 patients in a primary care setting, with diabetes, without known diabetic retinopathy, and without previous screening by an ophthalmologist, were included between January 1 and December 31, 2003. Patients underwent a brief questionnaire and two field retinal photography. Photographs were independently read by two ophthalmologists. Outcome measures were gradability of the photographs, need for pharmacologic pupil dilation, assessment as suspect for presence of diabetic retinopathy, of neovascularization and of diabetic retinopathy, and agreement between graders.

Of the population studied, 11.3% of patients required pupil dilation, average transmission time of images was 73 sec, 12.0% of patients had ungradable photographs, 10.4% of the patients with gradable photographs were assessed as "suspect for diabetic retinopathy," and 2.0% were assessed to need urgent referral. Red lesions were present in 3.5% and bright lesions were present in 1.6% of all gradable patients. Neovascularization of the disk was found in one patient. Type 1 patients had much higher rates of "suspect for diabetic retinopathy" (34.5%) than type 2 patients (9.4%). Interrater agreement κ was 0.93.

Web-based screening, using open source technology and uncompressed images, is feasible in a primary care setting, with a high rate of inter-rater agreement. Dilate-as-needed may be a sensible approach for retinal photography. The high incidence of "suspect for diabetic retinopathy" in type 1 diabetes patients illustrates that web-based diabetic retinopathy screening programs for these patients may detect diabetic retinopathy that would otherwise have gone undetected.

INTRODUCTION

DIABETIC RETINOPATHY is the most important cause of blindness in the working population in the United States and in the European Union.[1] Through early diagnosis and timely treatment, vision loss and blindness can largely be prevented.[2–5] For a variety of reasons, only 50% of patients with diabetes are screened according to the guidelines and protocols of their respective countries.[6,7] Digital retinal color fundus photography has been shown to have sensitivity and specificity comparable to indirect ophthalmoscopy by an ophthalmologist.[8,9] Computer-assisted diagnosis of lesions in such photographs is on the horizon.[10–12]

In 2000, the EyeCheck project was started in the Netherlands to try and solve such problems. It offers online screening for diabetic retinopathy over the Internet, nationwide, to any

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primary care physician in the Netherlands. It conforms to the American Telemedicine Association Recommendations Category 2 for Diabetic Retinopathy Telediagnosis Systems.[13,14] The purpose of the present study was to examine the impact of Web-based screening for diabetic retinopathy on a large primary care population by determining demographic and clinical characteristics over a single year, 2003.

MATERIALS AND METHODS

The setting for this retrospective study was a primary care population in family care physicians' offices or family physician laboratories. A physician or nurse trained to be able to diagnose and treat side effects of pharmacologic dilation drops was required to be present.

The inclusion criteria included diagnosis of diabetes at least one month previously, with the patient being interviewed and photographed at a primary care physician center for the EyeCheck project, with data submitted between January 1 and December 31, 2003.

Exclusion criteria included known diabetic retinopathy, previous inferior quality retinal photographs, and previous visit to an ophthalmologist for screening.

All patients gave informed consent after explanation at the end-user's site. No personalized health information was accessible to the researchers, and they only had access to aggregate data for the purpose of this study. The study followed the tenets of the Declaration of Helsinki.

Technology applied

Web technology: The methodology of the EyeCheck project was based on an online Web server system. This system was built using the Java programming language, from open source components exclusively, including image processing, data security, and data storage.[15] Data security was provided by state-of-the-art, 512-bit Secure Socket Layer (SSL) version 3.0 technology integrated into Java 2.[16,17] Patient data was transmitted and stored using an Extended Markup Language (XML)–Hospital Language 7 (HL7) based data dictionary, and images were transmitted and stored uncompressed in the Digital Imaging and Communications in Medicine (DICOM) ophthalmology supplement 81 standard, in an open source Standard Query Language (SQL) database.[18] The system conforms to the American Telemedicine Association Recommendations Category 2 for Diabetic Retinopathy Telediagnosis Systems.[13,19] The EyeCheck project was initiated in 2000.

The system is fully Web-based, with online tools for configuration. All patient data and images are stored on a need-to-know basis, so that only those individuals that are allowed to access specific items of a submission are able to do so. For example, a "grader" is not allowed access to date of birth, street, city, telephone, or insurance status information. For this study, only aggregate information could be accessed, and access to any personal health information was not possible. The terminology for EyeCheck includes the terms "end-user site," "grader," and "submission." An "end-user site" is the location where patients with diabetes are examined, a "grader" is the person who in the Netherlands is required to be an ophthalmologist, to assess whether or not a patient's photographs are suspect for diabetic retinopathy, and a "submission" is the combination of patient data and retinal images.

Screening protocol: The protocol includes a brief Web-based questionnaire, measurement of visual acuity, and four retinal photographs, one disk centered and one fovea centered, for each eye. Fundus cameras for the EyeCheck project are required to have at least 768 × 512 32-bit color resolution, and cameras used for this study were the Topcon NW100 (Topcon Europe, Rotterdam, the Netherlands) and Canon CR5-45NM (Canon, Kanagawa, Japan) nonmydriatic color fundus cameras set to 45° field of view. Pharmacologic pupil dilation (Tropicamide 0.5% solution) was left to the discretion of the end-user, that is, a test image is taken and if deemed of sufficient quality (see below), no dilating drops are administered. The answers to the questionnaire together with the retinal photographs are then transmitted over the Internet and stored as a "submission."

Table 1. Descriptive Statistics

	Mean	*95% Confidence interval*
Age (years)	60.4	59.8–61.0
Gender (male)	44.9%	42.5–47.3%
Type 1	3.1%	2.0–4.2%
Type 2	96.9%	95.8–98.0%
HbA1C	7.0%	6.7–7.3%
Transmission speed (all data)	73 sec	42–268 sec

Image quality

Submissions could be classified as nongradable by either end-user or expert reader (see below). Gradability criteria were available in a manual and were focus of the large vessels, visibility of at least one arteriole or capillary in both the upper and the lower half of the image, evenness of illumination, and absence of artifacts. If at least one image was nongradable, the submission was nongradable.

Reading of retinal images

The retinal photographs are graded using a browser and image processing tools available on the website. The result of the assessment can be either "not suspect," "suspect, not urgent" if a submission (at least one of the four images) is assessed to be suspect for diabetic retinopathy, "suspect, urgent" if a submission is assessed to require urgent referral to an ophthalmologist, or "not gradable," if one or more of the four images is below standard image quality as set forward in the protocol (see above). Additionally, if graders were certain that red lesions, namely, hemorrhages or microaneurysms; bright lesions, namely, exudates or retinal infarcts ("cotton wool spots"); or disk neovascularizations were present, they indicated the presence of these lesions. Graders were masked to each others' grading. If they disagreed, final grading was performed by a third grader who did have access to the two previous grades. After agreement by two or three graders, the grading process was closed, and the result of the assessment became immediately available at the "end-user site" on the Internet, where it can be stored or printed as a letter for the patient and the referring physician. If any suspicion of diabetic retinopathy was found, the patient was required to be referred to an ophthalmologist. Two retinal specialists (MDA, MSA) and one general ophthalmologist were graders in the EyeCheck project for the duration of this study.

Study parameters: Mean and 95% confidence interval [CI] for age, time for data transmission to Web-server in seconds, serum HbA1C; and proportion and 95% proportion confidence interval for: gender, presence or absence of pupil dilation, type 1 or type 2 diabetes. Outcome measures were: proportion and 95% proportion CI of presence of bad quality photographs, white lesions, red lesions, disk neovascularization (which because of its urgent nature is graded separately), retinal nevus, for each grader, "suspect, not urgent" and "suspect, urgent" assessment, and interrater agreement kappa (κ) of this assessment. Ethnicity or race is not allowed to be recorded in the Netherlands.

Statistics

Mean, two rater agreement κ and 95% CIs were determined straightforwardly. Confidence intervals for proportions p of dichotomous variables were estimated using the continuity correction:

$$p = p \pm z\left(\sqrt{\frac{p(1-p)}{N}} + \frac{1}{2N}\right)$$

RESULTS

A total of 1,676 patients were included. Demographic data were consistent with an elderly type 2 diabetes population, see Table 1. Only

Table 2. Diagnostic Results

Images unreadable	12%	11%–14%	% of all
Not suspect for diabetic retinopathy	89.6%	89.3%–89.9%	% of gradable
Suspect for diabetic retinopathy	10.4%	10.2%–10.7%	% of gradable

Table 3. Specific Criteria for Diabetic Retinopathy

≥1 Red lesion present	3.5%	3.2–3.8%	% of gradable
≥1 Bright lesion present	1.6%	1.3–1.9%	% of gradable
Neovascularization of optic disk present	0.07%		% of gradable
Nevus present	0.6%		% of gradable

3.1% of patients (95% CI, 2% − 4.2%) had type 1 diabetes. Average age was 60.4 years (95% CI, 59.8 − 61.0 years), and 44.9% (95% CI, 42.5% − 47.3%) were male. Metabolic control was comparatively good as shown by an average HbA1C of 7.0% (95% CI, 6.7%–7.3%). Pharmacologic pupil dilation was used in 11.3% (95% CI, 9.3%–13.3%) of patients. Transmission time of a submission was 73 seconds (95% CI, 42 s–268 s).

Diagnostic results are summarized in Table 2. The retinal images were found not to be gradable in 12.0% of patients (95% CI, 10.9%–13.1%), and these patients were re-screened, and excluded from further study. Reasons for nongradability included all reasons in the protocol (see Materials and Methods section). Patients with nongradable photographs were somewhat older (65.1 years, 95% CI, 63.4–66.8 years) than patients with gradable photographs (60.1 years, 95% CI, 58.6–62.4 years). There was no difference in gender between these two groups.

Of all patients with gradable photographs, 10.4% (95% CI, 8.9%–11.8%) were assessed to be "suspect for diabetic retinopathy," while all other patients were found to be not suspect. 2.0% of all gradable patients (95% CI, 1.3%–2.8%) were assessed to need urgent referral. Patients assessed as "suspect" were slightly older (65.3 years, 95% CI, 63.9–66.7) than patients not assessed as suspect (60.1 years, 95% CI, 58.6–61.7). The HbA1C of patients assessed as "suspect" had a nonsignificant trend for higher HbA1C (suspect 7.38%, 95% CI, 6.84–7.91, not suspect 6.94%, 95% CI, 6.64–7.25.

An analysis of different lesions is shown in Table 3. Red lesions, including microaneurysms and hemorrhages, were present in 3.5% (95% CI, 3.4%–3.5%) of all gradable patients, while bright lesions, including exudates and cotton-wool spots, were present in 1.6% (95% CI, 1.5%–1.6%) of all gradable patients (Fig. 1A). Only 52% of all patients assessed as "suspect for diabetic retinopathy" had confirmed white or red lesions. Because neovascularization of the disk is an indicator of advanced diabetic retinopathy and need for immediate evaluation by an ophthalmologist, these were analyzed

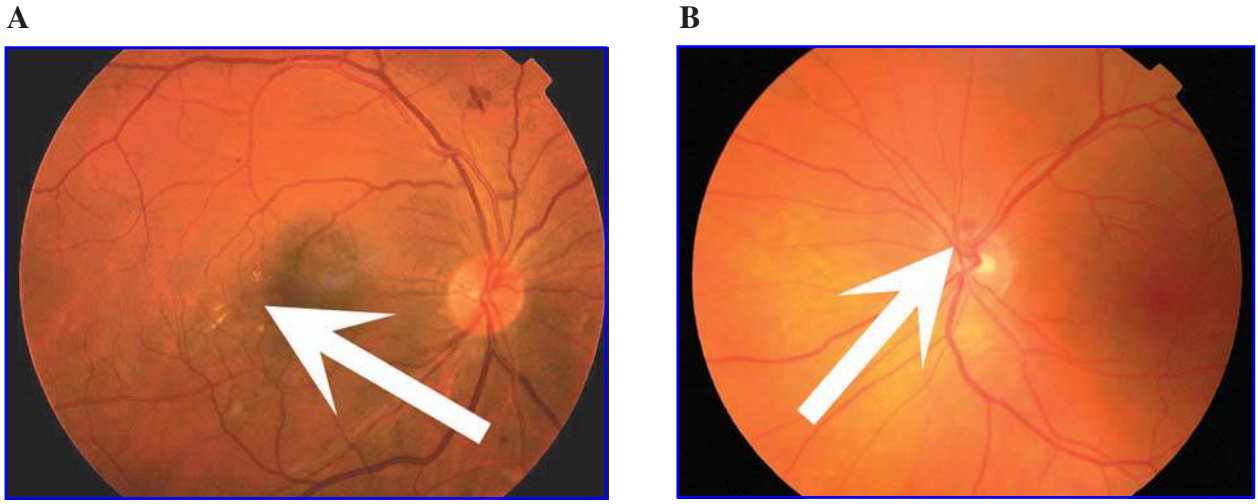

FIG. 1. **(A)** Retinal photograph centered on the macula of the right eye, showing probable exudates (white arrow) and retinal hemorrhages. **(B)** Retinal photograph centered on the disc of the left eye, showing a probable neovascularization over the superior part of the optic disc (white arrow).

Table 4. Subanalysis of Patients Suspected of Diabetic Retinopathy

Type 1, suspect	34.5%	16%–53%	% of all suspect
Type 2, suspect	9.4%	7.5%–11.4%	% of all suspect
Age, suspect	60.1	58.6–61.7	years, of all suspect
Gender, suspect	45.0%	39.2–50.9%	% male, of all suspect

separately, and was found in one gradable patient (0.7%, Fig. 1).

There was no difference in age or gender between patients suspect and nonsuspect for diabetic retinopathy, but type 1 patients were suspect much more often (34.5%, 95% CI, 16%–53%) than type 2 patients (9.4%, 95% CI, 7.5%–11.4%, Table 4). An assessment not related to diabetic retinopathy, retinal nevus, was found in 6 (95% CI, 6%–6%) of gradable patients.

The agreement between graders measured as two observer $\kappa = 0.93$ (85% CI, 0.90–0.96).

DISCUSSION

Our results show that online screening for diabetic retinopathy is feasible, and that low cost open source and open standard technology can be used for this. We have shown that data transmission rates are sufficient for the needs of such projects. We found that less than 20% of patients in this population with diabetes, but without known diabetic retinopathy, required pharmacologic pupil dilation. This means that dilate-as-needed may be a reasonable approach in similar populations, balancing the need for adequate quality photographs versus the cardiovascular risk and the risk of angle closure glaucoma.

We found that the combination of camera resolution, number of photographs, and Web-based grading user interface ensures a high rate of intergrader reliability as evidenced by a $\kappa > 0.93$. This high agreement seems to warrant that grading by two ophthalmologists can be done on an as-needed basis, that is, photographs are only graded by a second ophthalmologist if the grading ophthalmologist thinks that this is necessary.

Our study showed that in this relatively well-regulated population, the proportion of patients assessed as "suspect for diabetic retinopathy," and referred to an ophthalmologist, was approximately 10%, and that the proportion of submissions with insufficient quality was approximately 12%. The decision of whether or not to dilate pharmacologically was at the discretion of the end-user (the operator of the camera), and the reason was not recorded. Anecdotal evidence indicates that the usual reason for pharmacologic dilation was either inability to visualize the fundus or too dark fundus photographs. In almost half (48%) of all patients that were assessed as "suspect for diabetic retinopathy," graders were not certain of the presence of red or bright lesions pathognomic for diabetic retinopathy. Patients "suspect for diabetic retinopathy" were older and had a nonsignificant tendency for higher HbA1C in this study, confirming findings in earlier, less well-controlled, populations.[20]

The results may imply that the workload of ophthalmologists in such populations can be decreased by close to 75%. The results also seem to indicate that the proportion of patients assessed as 'suspect for diabetic retinopathy', may be substantially higher than the number of patients with a true diagnosis of diabetic retinopathy. Just over half of the 'suspect' patients showed any evidence of hemorraghes, microaneurysms, cotton-wool spots, exudates, or neovascularizations. Consequently, the graders may have erred on the safe side and referred a considerable number of patients not because of overt diabetic retinopathy, but because of small retinal irregularities or 'artifacts' where the artifactual nature of a 'lesion' could not be confirmed. In this study, neovascularizations of the disk, a criterion for urgent referral to an ophthalmologist, was rare, occurring in only 0.7% of gradable patients.[21]

The results shows a much higher incidence of assessment as "suspect for diabetic retinopathy" in type 1 diabetes patients (34.5%) compared to type 2 diabetes patients (9.4%) in this

population. This may be related to the fact that only patients without a previous visit to an ophthalmologist were included. A likely explanation is that most patients with type 1 diabetes, who are usually more aware of the importance of screening than type 2 patients, are already undergoing screening. The remaining patients, who for a variety of reasons had not been previously seen by an ophthalmologist, apparently have a much higher likelihood of diabetic retinopathy. This finding together with the low prevalence (3.1%) of type 1 diabetes in this population, clearly illustrates the attractiveness of Web-based screening for this group of patients.

Other studies of Web-based screening have been published.[4,21–22] However, to our knowledge, this is the first large-scale study, using published, open source standardized technology and uncompressed images, on feasibility, the impact of data transmission speed, proportion of nongradable photographs, frequency of pharmacologic pupil dilation, risk factors, and agreement between graders.

A drawback of this study is that it is a retrospective study, and that no independent confirmation of the accuracy, sensitivity, or specificity of the assessments is available. In other words, even though two ophthalmologists had to agree whether the photographs were suspect for diabetic retinopathy, and their inter-rater agreement was high, no ground truth from a reading center was obtained to evaluate their assessment. It cannot be determined from this study whether any diabetic retinopathy present in the photographs was missed by the graders or was present outside the field of view of the two field photographs. Other studies have shown that this risk is relatively small.[8] Additionally, there are indications, as explained above, that the ophthalmologists were overly sensitive.

In summary, this study has shown that large-scale screening for diabetic retinopathy over the Internet is feasible, that the technology can be based on open source technology and open standards, and that it allows a high rate of agreement between ophthalmologists. We are currently studying the relative risk for different risk factors, the effectiveness of computer-aided diagnosis, and the follow-up management by referral ophthalmologists of the patients assessed as suspect, both in Iowa and the Netherlands.[11,12,23] If employed on a larger scale, projects such as EyeCheck, especially if coupled with computer-aided diagnosis, can become a relatively low cost tool to reduce visual loss and blindness in patients with diabetes.

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