

The Sensitivity and Specificity of Nonmydriatic Digital Stereoscopic Retinal Imaging in Detecting Diabetic Retinopathy

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OBJECTIVE — The objective of this study was to determine the sensitivity and specificity of Joslin Vision Network nonmydriatic digital stereoscopic retinal imaging (NMDSRI) as a screening tool in detecting diabetic retinopathy.

RESEARCH DESIGN AND METHODS — We reviewed the records of 244 patients with diabetes who had a dilated funduscopic examination (DFE) and NMDSRI done within 1 year of each other at four locations in the metropolitan Washington, DC, area. The images were transmitted through a local area network to a central reading location where they were graded by a single retinal specialist.

RESULTS — Images of 482 eyes from 243 patients were included in the study. Four images did not transmit, and 35% of the images were not gradable. Of the remaining 311 eyes, there was 86% agreement in the grading between NMDSRI and DFE: 227 eyes with no diabetic retinopathy and 40 eyes with diabetic retinopathy. In 46 eyes (15%) there was a disagreement between gradings made by the two techniques. NMDSRI detected diabetic retinopathy in 35 eyes reported as normal by DFE, and in the remaining 11 eyes, the DFE grade was one grade higher than the NMDSRI grade. Adjudicated nonconcordant examinations were within one grade. In the 76 eyes with diabetic retinopathy, retinal thickness could not be assessed in 17 (21%) eyes. When the NMDSRI result was gradable, the overall sensitivity of NMDSRI was 98% and the specificity was 100% for retinopathy within one grade of the DFE. In the limited number of eyes that had diabetic retinopathy with macular edema (six), agreement with the clinical examination was 100%.

CONCLUSIONS — NMDSRI is a sensitive and specific method for the screening and diagnosis of diabetic retinopathy, which may help improve compliance with the standards of eye care for patients with diabetes.

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D iabetes is the leading cause of new cases of blindness among adults aged 20–74 years with diabetic retinopathy, causing as many as 24,000 new

cases of blindness per year (1). Crude prevalence rates of diabetic retinopathy and vision-threatening retinopathy in adults ≥ 40 years of age are 40.3 and

8.2%, respectively (2). In those with type 1 diabetes, the crude prevalences of any diabetic retinopathy were 74.9 versus 82.3% in black and white individuals, respectively, and of vision-threatening retinopathy were 30.0 versus 32.2%, respectively (3). Because the prevalence of diabetes is projected to increase by 35% worldwide between the years 1995 and 2025 (4), the number of Americans with blindness and significant visual impairment will probably rise as well. The high incidence of visual loss and the fact that even severe diabetic retinopathy may be asymptomatic provide strong support for screening (5). The Diabetic Retinopathy Study (DRS) and the Early Treatment Diabetic Retinopathy Study (ETDRS) showed that early treatment can reduce an individual's risk of severe vision loss by 57% (6,7). Moreover, focal laser photocoagulation for diabetic macular edema can reduce the risk of moderate vision loss by 50% (8).

Patients with diabetes often do not get the recommended screening for retinopathy. Thirty-five percent of the participants in a community-based study did not follow the vision care guidelines (9). Among the 109 Veterans Affairs medical centers, adherence to the annual eye screening recommendation varies from 48 to 93% (mean \pm SD 69.1 \pm 10.3%) (10). Only 54% of the patients with diabetes in the Walter Reed Health Care System receive an annual retinal examination. In general, the barriers to regular eye examinations are multifactorial and include inadequate knowledge about the need for routine eye examinations among patients and providers, lack of convenient transportation for medical appointments, lack of clinic availability, and a shortage of eye care professionals. Use of the Joslin Vision Network (JVN) nonmydriatic digital stereoscopic retinal imaging (NMDSRI) overcomes some of these barriers by offering same-day evaluation in a primary care or endocrinology clinic setting with remote reading by an ophthalmologist. An added benefit is the ability to have real-time review of the retinal images with the patient, enabling patients to become more involved in their own health care. This

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Abbreviations: CSME, clinically significant macular edema; DFE, dilated funduscopic examination; DRS, Diabetic Retinopathy Study; ETDRS, Early Treatment Diabetic Retinopathy Study; JVN, Joslin Vision Network; LAN, local area network; NMDSRI, nonmydriatic digital stereoscopic retinal imaging; NPDR, nonproliferative diabetic retinopathy.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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technology also holds promise for more efficient use of ophthalmic clinic resources for patients with significant pathological conditions.

The American Diabetes Association (11), the American Academy of Ophthalmology (12), and other professional groups recommend that patients with diabetes undergo a dilated funduscopy examination (DFE) with stereoscopic examination of the posterior pole using slit-lamp biomicroscopy. To ensure that the performance of the NMDSRI is comparable with these recommendations, we compared the NMDSRI examination with dilated eye examinations performed by an ophthalmologist or an optometrist. Previous reports have demonstrated that the JVN NMDSRI compares favorably with ETDRS seven standard field photography, but these studies were performed at a single site (13). To our knowledge, no studies have been done to validate this technology using a regional network.

RESEARCH DESIGN AND METHODS

A diabetes disease management program was established in the Walter Reed Health Care System to improve compliance with the process and quality measures established by the Diabetes Quality Improvement Project. As part of this program, patients underwent NMDSRI at the time of their routine diabetes clinic appointment. If they had not had a dilated eye examination within the last 12 months, they either were given an appointment to the ophthalmology or optometry clinic at the time of this visit or encouraged to make an appointment within the next 3 months. We reviewed the charts and the retinal images of 365 consecutive men and women with both type 1 and 2 diabetes, who were seen at one of the four locations of the Walter Reed Health Care System. The outlying clinics are distributed around the Washington, DC, metropolitan area and are within 30 miles of Walter Reed Army Medical Center. Of the 365 patients, 244 (69%) had a dilated retinal eye examination within a year of the NMDSRI examination. There were 133 men and 111 women; all but 5 patients had type 2 diabetes. The age of the patients was 60 ± 11.3 (mean \pm SD) years, and the duration of diabetes was 8.9 ± 6.4 years (range 1 month–24 years). Their HbA_{1c} was 7.53 ± 0.78 . Dilated eye examinations were performed by military or civilian ophthalmologists (87%) or optometrists (13%). The time between the dilated ret-

inal examinations and the nonmydriatic examination was within 3, 3–6, and 6–12 months in 57, 20, and 23% of patients, respectively. The retinal images were obtained by a trained technician at one of the above locations and transmitted through a local area network (LAN) to a retina specialist for determination of the presence or absence of diabetic retinopathy. Five technicians were performing imaging at the four sites over the span of the study. The technicians came from a variety of backgrounds: one was a registered nurse, three were licensed practical nurses, and one was a medical receptionist with no previous medical training. The technicians all underwent 3 days of training at the Joslin Diabetes Center. Diabetic retinopathy was graded using the modified version of the Airlie House classification (14). The retina specialist was unaware of the results of the DFE at the time that the images were read.

Image acquisition system

The image acquisition system used in the study has been described previously (13). In brief, a Topcon TRC-NW5S (two sites) or TRC NW6S (two sites) nonmydriatic stereoscopic digital camera was used to obtain three 45-degree retinal field images. Three nonsimultaneous 45-degree field stereoscopic fundus images were obtained 1) at the optic disc and macula, 2) superotemporal to the optic disc, and 3) nasal to the optic disc. These sites encompass a significant portion of the retina imaged by ETDRS seven standard field stereoscopic retinal photography (14). For each retinal field, a stereoscopic pair of images was acquired by manual horizontal translation of the fundus camera (13). A single external image was obtained for each eye. The digital camera is interfaced to a Sony DXC-970-MD color video camera with 750–horizontal line resolution. The camera system was interfaced with a Dell workstation running Windows 2000 Professional and equipped with a Matrox Meteor II-Multichannel/4 image capture card. Images were typically compressed to 15:1 before sending over the LAN to the Image Reading Center.

Image Reading Center

The specifications for the Image Reading Center have been described previously (13). It is located in the Ophthalmology Clinic of Walter Reed Army Medical Center. The workstation is equipped with a graphics intensive display card (Wildcat

II 5110), which when used in conjunction with stereographic glasses is capable of displaying retinal images in stereo. The system also allows the user to compare simultaneously up to 16 images from a patient, either from a single imaging visit or from previous visits.

One of the authors (T.W.) first reviewed the external image, looking particularly for ocular media clarity, the size of the pupil, the presence or absence of neovascularization of the iris, the presence or absence of lid and periorbital abnormalities, and the presence or absence of cataract. After completing a review of the external photographs, all six images of the fundus from each eye were reviewed, both in color and in red-free mode. A stereo image of each of the three fields was then reviewed by using liquid crystal display shuttered goggles, looking particularly for the presence of retinal thickening, elevated neovascularization, or retinal detachment. To grade the level of retinopathy, the presence or degree of hemorrhages or microaneurysms, venous dilation or venous caliber abnormalities, intraretinal microvascular abnormalities, retinal exudates, cotton wool spots, retinal thickening, retinal detachment, vitreous hemorrhage, or neovascularization of the disc or retina was recorded. Diagnosis of the level of diabetic retinopathy was based on ETDRS guidelines (14). Other retinal lesions, such as nevi, were recorded if present.

Data storage

The Agfa Impax (Basix) storage server is used to house all patient data, study images, and reports. The server allows validation of images for demographic information from our health information system before they are stored. The system has a 600-MHz dual processor, 512 MB of RAM, and a 40-GB hard drive.

Grading of images

We used the modified Airlie House classification for retinal photograph grading (14). We chose five levels of diabetic retinopathy as a means of both broadly categorizing the level of diabetic retinopathy and providing a clinically meaningful assessment that would lead to an appropriate management plan for these patients in a telemedicine arena. These clinical levels of diabetic retinopathy are a result of an integration of the presence and location as well as relative severity of the different lesions. Because retinal thickening was not detected in some of the images, grad-

Table 1—Retinal grades with the nonmydriatic retinal camera versus dilated retinal examination in 313 eyes of patients with diabetes

Nonmydriatic camera examination	Dilated retinal examination					Total
	1.00	2.00	3.00	4.00	5.00	
1.00	227	7	0	0	0	234
2.00	35	38	0	0	0	73
3.00	0	0	1	2	0	3
4.00	0	0	0	0	0	0
5.00	0	0	0	0	1	1
Total	262	45	1	2	1	311

Grade 1.00: no diabetic retinopathy; grade 2.00: mild to moderate nonproliferative diabetic retinopathy; grade 3.00: severe nonproliferative diabetic retinopathy; grade 4.00: very severe nonproliferative diabetic retinopathy; grade 5.00: proliferative diabetic retinopathy.

ing of maculopathy was done separately in patients with any level of diabetic retinopathy. Macular thickening was classified as no thickening, thickening not gradable, macular edema but not clinically significant, or clinically significant macular edema (CSME).

RESULTS— Three stereo retinal fields and an external image were obtained from each of 486 eyes. The images of four eyes in four different patients were not transmitted due to technical difficulties. Therefore, we analyzed 482 eyes from 243 patients and compared the diagnosis of the level of diabetic retinopathy to the diagnosis from the dilated retinal examinations. The mean and median numbers of days between the NMDSRI and DFE were 130 and 84, respectively. There were 171 images (35%) that were judged inadequate to be graded fully. Of the remaining 311 gradable eyes, 227 eyes (73%) had no retinopathy detected on either NMDSRI or DFE. Forty eyes (13%) had retinopathy of the same grade (concordant) detected on both NMDSRI and DFE. Thus, overall there was concordance in 267 eyes (86%). In 44 eyes (14%), there was a disagreement in the diagnosis between the two modalities. The nonmydriatic camera images gave a diagnosis of mild to moderate nonproliferative diabetic retinopathy in 35 eyes, whereas no retinopathy was diagnosed on the dilated eye examination. In two eyes, the diagnosis was severe nonproliferative diabetic retinopathy (NPDR) by NMDSRI and very severe NPDR by DFE (i.e., within one grade). Seven eyes (2%) were read as normal by NMDSRI but had mild to moderate NPDR on dilated ophthalmologic examination (within one grade) (Table 1).

We adjudicated the discrepant readings by two independent readers (L.A. and J.C.). They found that the JVN was correct in all but five eyes. These eyes

were found to have mild nonproliferative retinopathy by DFE but none by NMDSRI. Nevertheless, the adjudicated readings did not cause an increase in the grade discrepancy between the two modalities.

When NMDSRI results were gradable, the overall sensitivity of NMDSRI was 98% and the specificity was 100% for retinopathy within one grade of that indicated by DFE. Specificity was 86% for exact grade concordance. Using the clinical retinal examination as a standard, the false-positive rate was 11% (35 of 311) and the false-negative rate was 2% (7 of 311) (within one grade). We did not find an effect of the delay between imaging and clinical assessment on sensitivity and specificity. Because we plan to use NMDSRI to screen for the presence of diabetic retinopathy, we assessed macular edema separately in all patients who had a diagnosis of any diabetic retinopathy. Of 76 eyes with retinopathy detected on NMDSRI, retinal thickness could not be assessed in 16 eyes (21%). Of the 60 gradable eyes, 6 (10%) had macular edema (not clinically significant) and 1 (1.6%) had CSME. There was 100% concordance in the gradable eyes for macular edema and CSME in this small number of eyes. Of the ungradable eyes, dilated retinal examination showed that there were more eyes with grades 3, 4, and 5 retinopathy (5.8%) than in the gradable eyes (1.60%). The patients with ungradable eyes were significantly older (65 ± 10.6 years) than those with gradable eyes (57 ± 10.6 years). The mean \pm SEM in the percentage of gradable images among the technicians was $66.5 \pm 3.17\%$. There did not seem to be any improvement over time in the ability to obtain a gradable image nor was there any apparent relationship to the educational background of the technician (data not shown).

CONCLUSIONS— Screening is vital to prevent visual loss due to diabetes because diabetic retinopathy is often asymptomatic early in its course. It is also cost-effective for detection and treatment of proliferative diabetic retinopathy and macular edema. Javitt (15) showed that prevention programs aimed at improvement in eye care for diabetic individuals not only would result in substantial federal budgetary savings but also are highly cost-effective health investments for society. Hence, ophthalmologic screening for diabetic individuals may be one of the most cost-effective health interventions that can be offered to these patients.

Schoenfeld et al. (9) found that more than one-third of participants do not follow vision care guidelines. Factors related to nonadherence in this study were younger age, type 2 diabetes, shorter duration of diabetes, last examination performed by an optometrist or other nonophthalmologist, less practical knowledge about diabetes, and no prior formal diabetes education.

A nonmydriatic eye examination at the time of a routine clinic appointment is convenient and can provide the opportunity to involve patients effectively in their care and educate them about their disease. The examination takes about 15–20 min, the flash used to acquire images does not cause discomfort, and the patient's eyes do not need to be dilated. These features help overcome related barriers such as shortage of caregivers, geographic isolation, socioeconomic challenges, and cultural patterns.

We chose to classify the images in five broad categories based on the ETDRS. These categories are more user friendly than those of the ETDRS and are similar to the International Clinical Diabetic Retinopathy Disease Severity Scale. Whereas ETDRS levels of diabetic retinopathy provide a finer granularity, these levels are

not necessary to drive a clinical management plan. Thus, the ETDRS grades are more often used in clinical trials in which more events of diabetic retinopathy advancement in a shorter period of time can be obtained.

In our study, 86% of NMDSRI examinations were concordant with DFE examinations (227 eyes with no diabetic retinopathy and 38 eyes with diabetic retinopathy); as a result, ~72% of the patients with gradable images would not require an ophthalmologic or optometric referral, whereas 28% of patients (patients with the 39 eyes with diabetic retinopathy and those with eyes that had ungradable images) would need to be referred. The 35% rate of ungradable images was similar to that seen by Choremis and Chow (16) and by Higgs et al. (17) but higher than that demonstrated by Gomez-Ulla et al. (18) and Cavallerano et al. (19) (4 and 13%, respectively). The reason for the ungradability was one of three factors: a blurred image (either due to photographer error or the presence of a cataract), shadows in the image (usually from a combination of photographer error and small pupils), or two stereo images that were vertically misaligned (due to photographer error).

The specificity and sensitivity that we found are similar to those in previous reports. Gomez-Ulla et al. (18) found 100% sensitivity and specificity for the presence or absence of retinopathy between the two techniques. However, 6% of the eyes were underclassified on the digital images due to difficulty to differentiate among new vessels, large intraretinal hemorrhages, and intraretinal microvascular abnormalities using a nonstereoscopic camera for their study. Cavallerano et al. (19) demonstrated that the retinal images with the camera agreed exactly with or within one level of diabetic retinopathy in 89.3% of eyes. Only 3% of eyes had a two or more level of retinopathy discrepancy between the digital camera and the retinal examination. In no patient with a digital camera diagnosis of no diabetic retinopathy did a retinal specialist find a diagnosis of greater than mild nonproliferative diabetic retinopathy. In our study, disagreement between the grading made by the nonmydriatic camera examination and the dilated eye examination was seen in 15% of eyes. NMDSRI detected diabetic retinopathy in 36 eyes read as normal by a dilated eye examination. This overgrading can be explained by two major factors: 1) the reader was able to examine the im-

ages with high magnification and without the time constraints present during a clinical examination, and 2) the reader in this study was a retinal specialist, whereas the dilated examinations were performed by optometrists and ophthalmologists with many different levels of expertise.

The level of diabetic retinopathy on the DFE was higher than that on NMDSRI in 12 eyes. Two of the eyes (different patients) were diagnosed with severe NPDR by the nonmydriatic camera and with very severe NPDR by dilated eye examination. Nevertheless, using the classification of the International Classification of Diabetic Retinopathy (20), the grading would be considered identical. The remaining 10 eyes were graded as normal by the nonmydriatic camera versus a diagnosis of mild to moderate NPDR by dilated eye examination. In five eyes there was an interval of 3–12 months between examinations. This time interval between the examinations is a limitation of this study as the retinal findings may change in this interval. Macular edema was graded separately in all patients who had a diagnosis of any level of diabetic retinopathy by NMDSRI. Of these 76 eyes, retinal thickness could not be assessed in 16 eyes (21%). Six of the gradable eyes had macular edema, and one eye had CSME. Albeit this is a small sample, there was 100% agreement in the gradable eyes for macular edema and CSME. However, previous studies have shown that CSME cannot always be excluded with this methodology (18,21–23). Thus, we feel it would be prudent that all patients with any level of diabetic retinopathy still be referred for a DFE until the technology improves. However, in patients with no diabetic retinopathy or in those with previously diagnosed retinopathy that is unchanged over the prior year and who have constant visual acuity, it may be reasonable to have the patient followed by yearly NMDSRI.

In summary, the use of nonmydriatic stereoscopic retinal images as acquired and evaluated in this program and transmitted over a LAN is a sensitive and specific method for detecting diabetic retinopathy. Its simplicity and convenience make this technology ideal for incorporation into a diabetes disease management program, thus allowing improvement in compliance with the standard care for retinopathy screening in diabetic subjects.

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