Assessment of Diabetic Retinopathy Using Nonmydriatic Ultra-Widefield Scanning Laser Ophthalmoscopy (Optomap) Compared With ETDRS 7-Field Stereo Photography

MARCUS KERNT, MD
INDRAWATI HADI
FLORIAN PINTER, MD
FLORIAN SEIDENSTICKER, MD
CHRISTOPH HIRNEISS, MD

CHRISTOS HARITOGLOU, MD
ANSELM KAMPIK, MD
MICHAEL W. ULBIG, MD
ALJOSCHA S. NEUBAUER, MD, MBA

OBJECTIVE—To compare the diagnostic properties of a nonmydriatic 200° ultra-widefield scanning laser ophthalmoscope (SLO) versus mydriatic Early Treatment of Diabetic Retinopathy Study (ETDRS) 7-field photography for diabetic retinopathy (DR) screening.

RESEARCH DESIGN AND METHODS—A consecutive series of 212 eyes of 141 patients with different levels of DR were examined. Grading of DR and clinically significant macular edema (CSME) from mydriatic ETDRS 7-field stereo photography was compared with grading obtained by Optomap Panoramic 200 SLO images. All SLO scans were performed through an undilated pupil, and no additional clinical information was used for evaluation of all images by the two independent, masked, expert graders.

RESULTS—Twenty-two eyes from ETDRS 7-field photography and 12 eyes from Optomap were not gradable by at least one grader because of poor image quality. A total of 144 eyes were analyzed regarding DR level and 155 eyes regarding CSME. For ETDRS 7-field photography, 22 eyes (18 for grader 2) had no or mild DR (ETDRS levels $\leq$ 20) and 117 eyes (111 for grader 2) had no CSME. A highly substantial agreement between both Optomap DR and CSME grading and ETDRS 7-field photography existed with $\kappa = 0.79$ for DR and 0.73 for CSME for grader 1, and $\kappa = 0.77$ (DR) and 0.77 (CSME) for grader 2.

CONCLUSIONS—Determination of CSME and grading of DR level from Optomap Panoramic 200 nonmydriatic images show a positive correlation with mydriatic ETDRS 7-field stereo photography. Both techniques are of sufficient quality to assess DR and CSME. Optomap Panoramic 200 images cover a larger retinal area and therefore may offer additional diagnostic properties.

Diabetes Care 35:2459–2463, 2012

Ocular complications of diabetes, including diabetic retinopathy (DR) and diabetic macular edema, are leading causes of visual impairment in developed countries (1,2). Monitoring of the retina and good metabolic control, as well as early detection of DR, are important because DR may be asymptomatic even in its advanced stages. To avoid visual loss, annual screening of diabetic patients and correct assessment of the DR level is the current gold standard of care in patients with no or mild DR (3). However, especially in areas with poor access to eye care and shortage of retinal specialists, a lack of screening capacity often exists (4). In this context, screening for DR by (digital) retinal photography and telemedicine has emerged as a low-cost alternative to an annual dilated retinal examination (5,6). Although Early Treatment of Diabetic Retinopathy Study (ETDRS) photography and grading is considered the gold standard for photographic evaluation of DR and macular edema in clinical trials until today (7,8), it is time consuming, expensive, and highly dependent on the experience of the examiner. Thus, it is not practical for large screening programs (8). Therefore, various imaging techniques and protocols for DR screening, using up-to-date digital technology and attempting to meet the demands of different settings, have been introduced. These include digital smaller devices (9) or are even based on mobile/smart phone technology (10,11).

Ultra-widefield scanning laser ophthalmoscopy (SLO) is a novel nonmydriatic fundus imaging device (Optomap Panoramic 200; Optos PLC, Scotland, U.K.) that allows nonmydriatic imaging not only for the posterior pole of retina but even extending over the equator (12–14). It covers 180–200° with no need for pupil dilation, which has theoretical advantages over standard photography. Moreover, it is well known that a SLO is less susceptible to media opacities, such as cataract, and to decreases in pupil diameter (15). Therefore the ultra-widefield SLO seems to be a promising technology for DR screening and may provide an alternative. However, there is only limited data regarding the validity of DR assessment using the Optomap ultra-widefield imaging technique. This study compares the diagnostic properties of nonmydriatic Optomap ultra-widefield SLO to ETDRS stereoscopic, mydriatic, 30°, 7-field, color photography for DR screening.

RESEARCH DESIGN AND METHODS

Patients
Consecutive patients were recruited from the outpatient clinic of the Department of Ophthalmology of Ludwig Maximilian

University. Patients were included if they had diabetes (based on World Health Organization criteria) for at least 3 years. Eyes were excluded if there were eye diseases involving the posterior pole other than DR, such as age-related macular degeneration. Media opacities were not exclusion criterion. All patients underwent complete ophthalmological examination including a dilated (1% tropicamide) stereoscopic fundus exam with slit-lamp biomicroscopy (78 D lens) by a retina specialist. As part of the clinical examination, the degree of DR was assessed using the international clinical DR severity scale (16). The presence of clinically significant macular edema (CSME) was evaluated according to the EDTRS scale. Photographic graders were blinded for the clinical exam of the patients and had no access to clinical data. Informed consent was obtained from all participants, and the study conformed to the principles expressed in the Declaration of Helsinki. Institutional Review Board approval was obtained.

Optomap imaging

Optomap imaging was performed without pupil dilation before and independently of the clinical examination. It consisted of taking several images, and the best image per eye was saved for grading. The SLO takes one image in ~0.25 s, thus avoiding motion artifacts. Total scanning time is ~3–5 min, including patient positioning, and was performed by one author (I.H.). The Optomap Panoramic 200 device is a scanning laser ophthalmoscope, (SLO) with two laser wavelengths scanning: a green (532 nm) and a red (633 nm) laser wavelength. The two images are then either viewed separately or superimposed by the software to yield semirealistic color imaging. This device requires a small optical path of only 2 mm, and by a special mirror design, it is able to obtain widefield images of ~180–200° through an undilated pupil. The optical resolution was $3,900 \times 3,072$ pixels, resulting in ~15–21 pixels per degree of arc. Due to the SLO principle, sharp images with high contrast were obtained (15).

ETDRS 7-field stereo color photography

Prior to retinal photography, the patient's pupils were dilated using tropicamide 1% and additional epinephrine 10% drops if required. This was repeated if pupils did not reach at least 6 mm in diameter. Color retinal photographs, with a high-quality retinal digital camera (Zeiss FF450; Carl Zeiss Meditec AG, Jena, Germany), were taken by an ETDRS-certified photographer. A 5.0-megapixel, charge-coupled device (CCD) sensor (Sony 3CCD; Sony, Tokyo, Japan) was used in this study. Focusing and alignment of the image were performed using the ocular tube of the camera in addition to a previewing camera.

Each study eye had 16 digital photographs taken according to the ETDRS protocol: seven nonsimultaneous color stereo field pairs of the retina and one pair of the anterior segment. All images were taken by the same photographer, certified by the University of Wisconsin Fundus Photograph Reading Centre for ETDRS protocol photography, and for each patient, digital photographs were taken in the same format sequence. An example of an Optomap widefield SLO scan with an overlay of an ETDRS-type 7-field composite fundus photograph is shown in Fig. 1.

Grading of images

All retinal images were loaded from the server to a viewing station (equipped with a conventional cathode ray 17" noncalibrated color monitor) via network and assessed with the Optomap viewing software (Optomap U-revu, version 1.0). This software allows basic image manipulations such as changing contrast, brightness, and zooming. It also offers both viewing in the composite color image and the single color laser wavelengths. The images obtained by the different wavelengths were used to better identify and differentiate lesions (especially red-free images) (17). Grading of Optomap images and ETDRS 7-field stereo color photography was performed by two independent graders (M.K. and F.P.) who had not participated in examination of the patients and were masked to all additional information, such as visual acuity, duration of diabetes, or clinical symptoms. The graders, however, could decide not to grade due to poor image quality, which was defined as not covering at least the central 60° and both the macula and optic disc in adequate quality. Nongradable images were reassessed by a third grader (A.S.N.) to reach consensus in gradability. The level of DR was assessed according to the EDTRS. In addition, the presence of CSME was graded according to the ETDRS classification (18).

Statistics

All data were collected in a Microsoft Excel 2000 spreadsheet (Microsoft Corporation,

Figure 1—*Overlay montage of a representative Optomap scan and ETDRS 7-field (mild NPDR). (A high-quality digital representation of this figure is available in the online issue.)*

Redmond, WA) and analyzed using SPSS 19.0 for Windows (SPSS Inc., Chicago, IL). On all tests, $P < 0.05$ was considered significant, and nonparametrical testing was applied where appropriate. DR severity level agreement was cross-tabulated. κ statistics were calculated and assessed based on Landis and Koch (19): <0.20, poor; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; and 0.81–1.00, almost perfect strength of agreement. Unweighted κ was used to avoid potential bias by weighting. Eyes with photographs classified as nongradable (level 90) were excluded. For assessing agreement based on different "thresholds," we used ETDRS severity levels ranging from level 15/20 to high-risk proliferative DR (PDR) (level 71/75). Severity level agreement was cross-tabulated, and κ levels were calculated.

RESULTS

Patients

A total of 212 eyes, 100 right and 112 left, of 141 patients were included. Mean patient age was 64 ± 14.2 years (SD; range 25–78 years). Mean visual acuity was 0.56 ± 0.42 log minimum angle of resolution, ranging from 0 to 1.40. Diabetes duration ranged from 3 to 39 years, mean 12 ± 11.4 years. Of all patients, 59% were using insulin and 41% were on oral medication. Mean HbA_{1c} was $6.7 \pm 1.8\%$ (range 5.4–11.6%). Systemic blood pressure values were systolic 146 ± 20 mmHg (range 110–185 mmHg) and diastolic 81 ± 9 mmHg (range 65–95 mmHg). In total, 82% of the patients were on at least one medication for high blood pressure.

Overall comparison

Distribution of severity levels of DR as graded on a nine-step ETDRS scale is

given in Table 1 for grader 1. The table shows that, overall, a high agreement in grading results was obtained for both independent graders. κ for grader 1 was 0.792 (SE = 0.039) and 0.774 (SE = 0.039) for grader 2, indicating a highly substantial agreement between the imaging methods. Regarding CSME, κ was 0.73 (SE = 0.061) for grader 1 and 0.77 (SE = 0.056) for grader 2, which means a highly substantial agreement between the imaging methods.

Intergrader agreement

For grading of DR level, similar levels of agreement were found for Optomap and 7-field photography. Agreement between readers was higher for Optomap than for 7-field photography in assessing CSME: exact agreement was 91 vs. 87.5%, and agreement ± one step was 100 vs. 98.6%. κ was 0.89 (SE = 0.03) for Optomap and 0.84 (SE = 0.04) for 7-field photography.

Comparison of DR levels based on thresholds

In Fig. 2, agreement levels for DR between Optomap and 7-field photography are shown. Given the almost perfect agreement between graders for DR rating, only grader 1 results are shown. Agreement decreases with higher DR levels, which appears to be caused by photographic readings assessing higher DR levels less severe than Optomap readings.

Agreement of imaging with clinical assessment

To assess agreement of imaging with clinical assessment, the ETDRS scale was converted to the analogous five-part clinical scale: no DR (level 10–14), mild non-PDR (NPDR) (level 15–20), moderate NPDR (level 35–47), severe NPDR (level 53), and PDR (≥ level 61). Almost perfect agreement of Optomap readings with clinical assessment was observed, well comparable with 7-field photographic imaging: exact agreement was 95.8 vs. 90.3%, and agreement ± one step was 100 vs. 96.5%. κ was 0.93 (SE = 0.03) for Optomap and 0.83 (SE = 0.04) for 7-field photography.

For CSME, gradings from Optomap scans showed substantial gradings from 7-field photography, moderate agreement to findings from slit-lamp BIO: exact agreement was 87.7 vs. 83.2%, and κ was 0.72 (SE = 0.06) for Optomap compared with 0.59 (SE = 0.07) for 7-field photography.

CONCLUSIONS—In the U.S., 16 million people suffer from diabetes, and 12,000–24,000 new cases of blindness secondary to DR are reported each year. Three million diabetes patients report visual impairment, and the number of individuals >40 years of age with DR is expected to increase from 4.1 to 7.2 million in 2020 (3,20,21). The projected increase in diabetes prevalence is likely to overwhelm current healthcare structures and capacities for currently recommended annual dilated retinal examinations as the standard of care. Therefore, alternatives, such as telemedicine, should be harnessed as cost-effective strategies to improve early detection of DR as a means of reducing the risk of permanent visual impairment (5,6,12).

Although developed almost 25 years ago, both EDTRS imaging and grading protocols for standardized evaluation of DR and CSME are still today's benchmark (7,8). Numerous clinical trials have validated the use of mydriatic ETDRS 7-field stereo photography for DR screening. However, imaging techniques have evolved; digital photography has outlived analog color slide film, as it becomes less and less available, in clinical practice. In addition, several limitations exist, as mydriatic ETDRS 7-field stereo photography is time consuming and highly dependent on both the photographer's experience and the patient's compliance (6,22,23). Therefore, although remaining standard for clinical trials, it is not well suited for screening purposes. In an environment that demands cost reduction, efficiency, and effective disease screening, nonmydriatic digital fundus screening offers many advantages (6,12,14,23). One important advantage inherent to nonmydriatic digital techniques is patient comfort (no need for dilating pupils causing the inability to drive a car) and facilitation of remote diagnostic image generation and interpretation. These factors are likely to improve patient compliance in screening programs (6,12,14,23). Retinal imaging using the novel nonmydriatic Optomap Panoramic 200 SLO allows nonmydriatic imaging not only of the posterior pole but even extending over the equator. It covers 180–200° with no need for pupil dilation and far exceeds the area covered by the ETDRS photographs (12,14). Therefore, this imaging technique may provide advantages for DR screening. On the other hand, this technique provides no real color images, only two monochromatic red and green SLO scans that can be viewed separately or superimposed, resulting in a semirealistic bicolor Optomap fundus image. The possibility to view the two simultaneously generated red and green SLO scans separately potentially provides additional image information, as the green, "redfree" scan may inherit more selective information about the superficial layers of the neurosensory retina, and the red laser scan may better reflect the deeper retinal layers, including retinal pigment epithelium and choroid (12,14). However, diagnostic image quality is an important concern for clinical research and telemedicine, and the lack of additional color information, compared with color fundus photography, may also provide a potential source for misinterpretation. In this study,

Table 1—*ETDRS DR severity level from Optomap vs. 7-field ETDRS photographs*

DR level (nine-step scale), Optomap grader 1	DR level (nine-step scale), 7-field photo grader 1									Total
	10	15/20	35	43	47	53	61	65	71/75	
10	**22**	0	0	0	0	0	0	0	0	22
15/20	1	**3**	0	0	0	0	0	0	0	4
35	0	1	**25**	6	0	0	0	0	0	32
43	0	0	3	**49**	0	0	0	0	0	52
47	0	0	0	3	**2**	0	0	0	0	5
53	0	0	0	0	1	**0**	0	0	0	1
61	0	0	0	1	1	1	**7**	0	0	10
65	0	0	0	2	1	1	1	**9**	0	14
71/75	0	0	0	0	0	0	0	0	**4**	4
Total	23	4	28	61	5	2	8	9	4	144

ETDRS DR severity level from Optomap versus 7-field ETDRS photograph nine-step ETDRS scale: 10, no retinopathy; 15/20, microaneurysms or retinal hemorrhages only; 35, mild NPDR; 43, moderate NPDR; 47, moderately severe NPDR; 53, severe NPDR; 61, mild PDR; 65, moderate PDR; 71/75, severe PDR. Boldface numbers indicate perfect agreement.
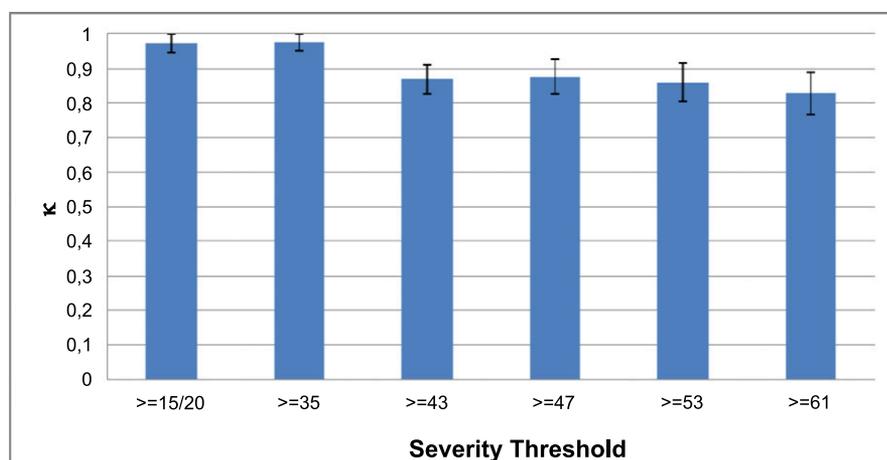
Number of eyes						
	>=15/20	>=35	>=43	>=47	>=53	>=61
Optomap	122	118	86	34	29	28
7-field photo	121	117	89	28	23	21

Figure 2—*Diabetic retinopathy severity threshold of Optomap vs. 7-field photography. (A high-quality color representation of this figure is available in the online issue.)*

κ values of 0.795 for grader 1 and 0.774 for grader 2 demonstrate a good correlation between nonmydriatic ultra-widefield SLO (Optomap) and ETDRS-type, stereoscopic, mydriatic, 30°, 7-field, stereo color photography. In addition, a good intergrader reproducibility and a good correlation with clinical assessment of DR were shown for both imaging techniques. Of note, Optomap imaging had a lower rate of nongradable images, compared with 7-field ETDRS.

Regarding the detection of CSME, a moderate/substantial correlation of both imaging techniques with clinical assessment was detected. This is especially worth mentioning, as Optomap is primarily a two-dimensional imaging technique and no stereoscopic information is obtained. However, this result regarding the detection of CSME with Optomap is in accordance with a previous investigation, where a comparable validity for both assessment of DR level and detection of CSME with Optomap in comparison with clinical stereoscopic slit-lamp fundus examination was found (14). One reason may be that the lack of the stereoscopic aspect is at least partially compensated by the possibility to view both red and green laser scans with their different penetration and image information, which may give a certain impression of tissue swelling and edema that is helpful for detection of macular edema.

Regarding the grading of DR, there is evidence that color photography is superior to clinical fundoscopy alone (14,24,25).

However, the smaller area imaged, especially with nonmydriatic imaging techniques, may result in a decrease in sensitivity. Aptel et al. (26), for example, demonstrated that nonmydriatic 3 × 45° color fundus images still resulted in 92% sensitivity and 97% specificity. In contrast, DR grading by using a single 45° image of the central retina led to a significant reduction of sensitivity to 77%. This may be explained by the fact that particularly the nasal retina is of importance for a valid assessment of the DR level. However, large coverage of the retina allows the assessment of peripheral pathologies that would otherwise be overlooked in any case when only a smaller angle is imaged. This may also compensate, together with the possibility to easily zoom and view red and green channels separately, for the lack of full color information, as provided by color photography. Therefore, widefield fundus imaging may additionally help to improve valid assessment. One disadvantage of the technology is that compared with other approaches, such as simpler camera-based ones (9–11), the widefield scanning laser technology is more costly. Given the increasing availability of those machines, however, at least for several countries such infrastructure already exists.

The American Academy of Ophthalmology has emphasized the importance of early screening and recommends annual dilated eye examinations in type 2 diabetic patients and retinal examinations 3–5 years after diagnosis of type 1

diabetes, followed by annual eye examinations (27). However, annual dilated retinal examinations are most cost-effective for patients with advanced DR or elevated HbA$_{1c}$ but may be less cost-effective in subjects with no, or mild, NPDR (28–30). In addition, a number of barriers, including poor access to eye care and shortage of retinal specialists in rural areas, exist, leading to a high number of patients who are not screened for DR.

The nonmydriatic ultra-widefield SLO Optomap allows imaging not only of the posterior pole of the retina but even beyond the equator. It covers up to 200° of the retina with no need for pupil dilation, which implicates theoretical advantages over 7-field ETDRS photography (Fig. 1). In addition, the results of this study clearly demonstrate that Optomap imaging provides at least similar results for assessment of DR levels and presence of CSME compared with ETDRS 7-field stereo color photographs and correlates well with clinical assessment of DR. The Optomap examination affords little experience by the photographer and has a fast learning curve; it also can be performed easily by trained medical care personnel (12,14). Therefore, Optomap provides promising properties for peripheral screening programs and telemedicare in diabetes patients.

References
1. Ehrlich R, Harris A, Ciulla TA, Kheradiya N, Winston DM, Wirostko B. Diabetic macular oedema: physical, physiological and molecular factors contribute to this pathological process. Acta Ophthalmol (Copenh) 2010;88:279–291
2. Williams R, Airey M, Baxter H, Forrester J, Kennedy-Martin T, Girach A. Epidemiology of diabetic retinopathy and macular oedema: a systematic review. Eye (Lond) 2004;18:963–983

3. Fong DS, Aiello L, Gardner TW, et al.; American Diabetes Association. Retinopathy in diabetes. Diabetes Care 2004;27 (Suppl. 1):S84–S87

4. Cummings DM, Morrissey S, Barondes MJ, Rogers L, Gustke S. Screening for diabetic retinopathy in rural areas: the potential of telemedicine. J Rural Health 2001; 17:25–31

5. Olayiwola JN, Sobieraj DM, Kulowski K, St Hilaire D, Huang JJ. Improving diabetic retinopathy screening through a statewide telemedicine program at a large federally qualified health center. J Health Care Poor Underserved 2011;22:804–816

6. Taylor CR, Merin LM, Salunga AM, et al. Improving diabetic retinopathy screening ratios using telemedicine-based digital retinal imaging technology: the Vine Hill study. Diabetes Care 2007;30:574–578

7. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation therapy for diabetic eye disease. JAMA 1985;254:3086

8. Li Q, Puro DG. Diabetes-induced dysfunction of the glutamate transporter in retinal Müller cells. Invest Ophthalmol Vis Sci 2002;43:3109–3116

9. Ting DS, Tay-Kearney ML, Kanagasingam Y. Light and portable novel device for diabetic retinopathy screening. Clin Experiment Ophthalmol 2012;40:e40–e46

10. Blanckenberg M, Worst C, Scheffer C. Development of a mobile phone based ophthalmoscope for telemedicine. In *Proceedings of the 33rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Boston, MA, 2011.* IEEE Engineering in Medicine and Biology Society, p. 5236–5239

11. Kumar S, Wang EH, Pokabla MJ, Noecker RJ. Teleophthalmology assessment of diabetic retinopathy fundus images: smartphone versus standard office computer workstation. Telemed J E Health 2012;18: 158–162

12. Kernt M, Pinter F, Hadi I, et al. Diabetic retinopathy: comparison of the diagnostic features of ultra-widefield scanning laser ophthalmoscopy Optomap with ETDRS 7-field fundus photography. Ophthalmologe 2011;108:117–123[in German]

13. Kernt M, Ulbig MW. Images in cardiovascular medicine. Wide-field scanning laser ophthalmoscope imaging and angiography of central retinal vein occlusion. Circulation 2010;121:1459–1460

14. Neubauer AS, Kernt M, Haritoglou C, Priglinger SG, Kampik A, Ulbig MW. Nonmydriatic screening for diabetic retinopathy by ultra-widefield scanning laser ophthalmoscopy (Optomap). Graefes Arch Clin Exp Ophthalmol 2008;246:229–235

15. Kirkpatrick JN, Manivannan A, Gupta AK, Hipwell J, Forrester JV, Sharp PF. Fundus imaging in patients with cataract: role for a variable wavelength scanning laser ophthalmoscope. Br J Ophthalmol 1995;79: 892–899

16. Wilkinson CP, Ferris FL 3rd, Klein RE, et al.; Global Diabetic Retinopathy Project Group. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 2003;110:1677–1682

17. Lin DY, Blumenkranz MS, Brothers R; Digital Diabetic Screening Group (DDSG). The role of digital fundus photography in diabetic retinopathy screening. Diabetes Technol Ther 1999;1:477–487

18. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. Arch Ophthalmol 1985; 103:1796–1806

19. Altman DG. Statistics in medical journals: developments in the 1980s. Stat Med 1991;10:1897–1913

20. The DCCT Research Group. Epidemiology of severe hypoglycemia in the diabetes control and complications trial. Am J Med 1991;90:450–459

21. Icks A, Trautner C, Haastert B, Berger M, Giani G. Blindness due to diabetes: population-based age- and sex-specific incidence rates. Diabet Med 1997;14:571–575

22. Danis RP, Hubbard LD. Imaging of diabetic retinopathy and diabetic macular edema. Curr Diab Rep 2011;11:236–243

23. Lopez-Bastida J, Cabrera-Lopez F, Serrano-Aguilar P. Sensitivity and specificity of digital retinal imaging for screening diabetic retinopathy. Diabet Med 2007;24: 403–407

24. Lin DY, Blumenkranz MS, Brothers RJ, Grosvenor DM. The sensitivity and specificity of single-field nonmydriatic monochromatic digital fundus photography with remote image interpretation for diabetic retinopathy screening: a comparison with ophthalmoscopy and standardized mydriatic color photography. Am J Ophthalmol 2002;134:204–213

25. Neubauer AS, Rothschuh A, Ulbig MW, Blum M. Digital fundus image grading with the non-mydriatic Visucam(PRO NM) versus the FF450(plus) camera in diabetic retinopathy. Acta Ophthalmol (Copenh) 2008;86:177–182

26. Aptel F, Denis P, Rouberol F, Thivolet C. Screening of diabetic retinopathy: effect of field number and mydriasis on sensitivity and specificity of digital fundus photography. Diabetes Metab 2008;34:290–293

27. American Academy of Ophthalmology Retina/Vitreous Panel Preferred Practice Patterns Committee. *Diabetic Retinopathy.* San Francisco, CA, American Academy of Ophthalmology, 2008

28. Porta M, Rizzitiello A, Tomalino M, et al. Comparison of the cost-effectiveness of three approaches to screening for and treating sight-threatening diabetic retinopathy. Diabetes Metab 1999;25:44–53

29. Wareham NJ. Cost-effectiveness of alternative methods for diabetic retinopathy screening. Diabetes Care 1993;16:844

30. Fendrick AM, Javitt JC, Chiang YP. Cost-effectiveness of the screening and treatment of diabetic retinopathy. What are the costs of underutilization? Int J Technol Assess Health Care 1992;8:694–707