A health economic analysis

RetinaLyze™

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The Danish Committee for Health Education

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1 Object

To implement an operational economic evaluation of the Retinalyze^{TM} software system used for the automated detection of the diabetic eye disease, retinopathy, by means of fundus photography. The analysis is for Retinalyze Danmark A/S.

2 Background

The number of diabetic patients is steadily growing these years. The Danish National Diabetes Register counted the number of diabetics in Denmark to be 226,463 people as per 31st of December 2006, with an annual increase rate of 7.1 percent from 1997 to 2006. Apart from a small increase in the population, the relative annual increase is stated to be 6.8 percent (1). It is assumed that a corresponding number of people has not been diagnosed with the disease yet.

The metabolic disorders occurring with the type-2 diabetes may cause late complications in the form of damages of the organism blood vessels and the nervous system. Diabetic complications are classified in five main groups: diabetic eye disease (retinopathy), diabetic kidney disease, diabetic neuritis, diabetic foot complications and diabetic cardiovascular disease/arteriosclerosis. The negative consequences of the late complications can be prevented and limited by an early detection/screening and treatment (2).

The Retinalyze^{TM} software system is a fairly new technology which by means of fundus photography automatically screens for retinopathy. The use of the Retinalyze^{TM} software system means that the time which an eye doctor spends on evaluating the fundus image is reduced while the use of other personnel is increased. In addition, the use of the Retinalyze^{TM} software system involves costs as well. Thus, a total operational economic analysis is necessary to make an economic evaluation of the Retinalyze^{TM} software system.

3 Retinopathy

The description of retinopathy is based on the Medical Technology Assessment (MTA) of screening, diagnostics, and treatment of the type 2 diabetes, 2003 (2). The MTA has been prepared by the Danish Health and Medicine Authority with the participation of the Danish Committee for Health Education.

Morbidity

Roughly, the eye can be compared to a camera – In front, it has an optical system (cornea, pupil opening, and lens), in the middle, it has a camera house (the vitreous body), and behind, it has a photographic film (the retina). All eye components are influenced by the diabetes disease. Most impacts are not an actual threat to the eyesight function and can be treated relatively simply, e.g. an operation of cataract related to diabetes. However, diabetes is a threat to the eyesight due to the damages which may occur on the retina in the form of a diabetic retina disease, diabetic retinopathy. Diabetic retinopathy is characterized through several lesions which are all caused by disorders in the retinal blood supply (bleedings, precipitations of albumen from the bloodstream, oedema, and several abnormalities in the blood vessels). The changes start in the retinal periphery and may develop into two eyesight-threatening forms; diabetic maculopathy (DKma) where the changes spread to the central parts of the retina and damage the central eyesight; and proliferative diabetic retinopathy (PDR) where the new blood vessels sprout up to replace the closed blood vessels in the eye periphery. However, the structure of blood vessels is abnormal, and thus, they cause bleedings in the vitreous body or detachment of the retina causing a severe impact on the eyesight.

Diabetic retinopathy is not detected by the patient in the early stages where the changes have not caused an impact on the eyesight. However, through systematic detection of non-symptomatic changes, a permanent impact on the eyesight can be prevented and treated effectively.

Frequency

No studies are available yet on the occurrence of retinopathy in an unselected diabetes population. According to the national clinical quality database for systematic screening for diabetic retinopathy, it appears that while early retina changes with type 1 diabetics are rarely present at the time of diagnosis, approx. 25 %, however, have retina changes after five years with diabetes. This percentage makes almost 80 % after 15 years with diabetes. Among type 2 diabetics, nearly 30 % have early retina changes already at the time of diagnosis. Thus, the disease has been present for a number of years. Annually, approx. 2 % of the type 1 diabetics and approx. 0.5 % of the type 2 diabetics have one of the eyesight-threatening forms of diabetic retinopathy: proliferative diabetic retinopathy and diabetic maculopathy (3).

Screening and treatment

Efficient screening for late complications in case of type 2 diabetes, including retinopathy requires that screening is available to everybody. At screening, the rate of specialization of the person carrying out the screening is crucial to the research quality. This could speak in favor of centralization and teambuilding e.g. by grading of diabetic retinopathy.

The object of detecting/screening for diabetic retinopathy is to prevent loss of eyesight. Basically, the examination will find out whether there are any changes requiring treatment (proliferative diabetic retinopathy or diabetic maculopathy) meaning that the patient must be referred to further diagnosing or treatment in a special hospital department. – If the examination finds that there are no changes requiring treatment, the results are used for the detection/screening to define the optimum time interval to the next check-up.

Optimum screening frequency

All diabetic patients are at risk of developing diabetic retinopathy. As a general guideline, the Danish Health and Medicines Authority recommends an annual consultation for diabetics, i.e. once a year, to ”decide on eye screening: fundus photo and visus or eye examination at the eye doctor's every second year (more frequently in case of more conspicuous retinal changes and in case of pregnancy)” (4). In addition, the Authority's procedure programs works on stratification where different efforts are recommended depending on the stadium of the disease.

Screening efficiency

The benefit of screening for diabetic retinopathy is so well established that, based on the present knowledge available, it is not considered ethically proper to omit screening where possible. Consequently, there are no systematic examinations with a high level of evidence of the comparison of screening versus no screening for diabetic retinopathy in case of the type 2 diabetes.

Cost efficiency of screening

In the medical technology evaluation of type 2 diabetes, a cost efficiency analysis has been carried out to assess the cost efficiency of screening patients with type 2 diabetes for diabetic retinopathy. The following conclusions have been reached:

♦ The values calculated in the model state that systematic screening for retinopathy will result in a net saving for society compared to the » hypothetical « without screening. Furthermore, the patients' life quality are improved as well. However, such calculations are based on several assumptions, but the sensitivity analyses have not changed the overall conclusions.

♦ From a health economic perspective, systematic screening for retinopathy should be carried out even though the strengths and weaknesses of alternative screening models should be analyzed more thoroughly than it has been possible in this study.

Screening technologies

Diabetic retinopathy meet the criteria of a meaningful disease screening: The disease is a serious medical problem; it is well-defined and classifiable; its natural progression is known; it can be diagnosed by means of sensitive, specific tests when it is still asymptomatic, and; a known and efficient treatment of the disease is available (5). The basic competing screening technologies are:

♦ Ophthalmoscopy, i.e. a direct observation of the retina through the pupil opening with the use of an ophthalmoscope (eye binoculars).

♦ Fundus photography where the changes are documented on a photographic or a digital medium.

Most places in Europe, it is common to measure the visual power as well. However, the independent value of this examination to detect eyesight-threatening changes has not been identified.

At fundus photography, the analysis can take place with manual visual image analysis or by automated digital image analysis. The operational economic difference between the two competing technologies is analyzed subsequently.

For further information of ophthalmoscopy and fundus photography respectively, please see the MTA for type 2 diabetes, 2003 (2).

The organization

An efficient screening for diabetic retinopathy in case of type 2 diabetes requires that the patients are offered and receive a screening offer. However, this is far from reality. A survey from Vejle County found that only 46% of type 2 diabetic patient had been examined by an eye doctor during the year of 1997, while 26% had not been examined in the period 1993-1997 (2). The reason for this disproportion has not been clarified in details. No later studies describing the proportion more thoroughly are available at the moment.

Screening for diabetics retinopathy can be carried out by people with different ophthalmologic levels of education:

♦ Eye doctors specialized in diabetic retinopathy

♦ Non-specialized eye doctors or nurses/technicians within the profession of eye care ♦ medical

practitioners.

There is a clear coherence between the screening quality and the screener's educational level. Thus, a survey found that the quality of screening for retinopathy with type 2 diabetics carried out by medical practitioners was significantly lower than the optimum standard (ophthalmoscopy / fundus photo) with a sensitivity of (62.6% / 79.2%). The specificity for the detection of early changes was (75.0% / 73.5%) and for the detection of eyesight-threatening changes was (93.8% / 84.8%). Another study found that the detection of early or eyesight-threatening changes can be carried out by medical practitioners with a sensitivity of 52% and a specificity of 84% compared to non-specialized eye doctors, while a third study found that the detection of early or eyesight-threatening changes can be carried out by medical practitioners with a sensitivity from 41% to 67% and a specificity from 86% to 94% compared to a technician educated within eye care (2).

With ophthalmoscopy, there is, even for the trained specialist, a risk of up to 50% to overlook the earliest changes which may lead to wrong recommendations of the interval until the next check-up. (2).

It may be expected that telescreening where the examination with fundus photography can be carried out decentralized and sent for gradation with a centrally located specialist through the internet, may be an alternative organizational solution for screening for diabetic retinopathy in the future. This organizational principle may be an alternative in case of eye doctor shortage or in areas with large geographical distances to those, and furthermore, it may provide an opportunity for central registration of the screening activities with reference to systematic quality assurance (2).

Sub-conclusion

♦ An efficient screening for late complications in case of type 2 diabetes requires that screening is available to everybody. ♦ All diabetic patients are at risk of developing diabetic retinopathy. As a general guideline, the Danish Health and Medicines Authority recommends an annual consultation for diabetic once a year with the decision of eye screening: Fundus photo and visus or eye examination at the eye doctor's every second year (more frequently in case of more conspicuous retinal changes and in case of pregnancy).

♦ The benefit of screening for diabetic retinopathy is so well established that, based on the knowledge available, it is not considered ethically proper to omit screening where possible.

♦ Diabetic retinopathy is not detected by the patient in the early stages where the changes have not caused any visual impacts. Through systematic detection of non-symptomatic changes, a permanent visual impact may be prevented and treated efficiently, however.

♦ Eyesight-threatening diabetic retinopathy can be detected by screening and subsequently treated with laser beams which reduces the occurrence of eyesight loss by minimum 50%.

♦ The rate of specialization with the person carrying out the screening is crucial to the screening quality.

♦ Telescreening for diabetic retinopathy can combine the need to increase the availability of examinations decentrally and to carry out the specialized grading centrally. This can be an alternative in case of eye doctor shortage or in areas with large geographical distances to those. Furthermore, telescreening provides the opportunity for a central registration of the screening activities with reference to systematic quality assurance. It may be expected that telescreening may be an alternative organizational solution for screening for diabetic retinopathy in the future.

4 Description and evaluation of Retinalyze

The background description, cf. section 2, describes diabetic retinopathy in relation to screening and treatment, organization and screening technology.

The Retinalyze™ screening system is a software system used for automated digital fundus image analysis when screening for diabetic retinopathy. The screening is carried out with the use of an algorithm which automatically identifies red lesions / bleedings when analyzing the digital fundus photos.

The object of the Retinalyze screening system is to:

♦ Identify diabetic lesions / eye bleedings.

♦ Validate the automatic identification of diabetic lesions / bleedings

Competing technologies

Competing technologies using fundus photography for the identification of bleedings and microaneurysms caused by diabetic retinopathy, are currently:

♦ Visual image analysis, towards

♦ Automated image analysis

Technological equality

Retinalyze vs. visual image analysis

Larsen M et al, 2003 (6) compare automated identifications of bleedings and microaneurysms with the use of fundus image analysis algorithm with a visual identification of retinopathy in a study of 400 fundus images (35 mm. color photo transparencies), among 200 eyes / 100 diabetic patients, randomly selected from the Welsh Community Diabetic Retinopathy Study. For the automated image analysis of (digitalized) fundus images, the Retinalyze software system was used.

The study found a specificity for diabetic patients correctly identified without retinopathy of 71.4%, see Table 1, and a sensitivity for diabetic patients correctly identified with retinopathy of 96.7% with the use of the Retinalyze automated screening system, with a total clinical efficiency of 79%.

Table 1 Classicifcation of diabetic patients with or without retinopathy by analyzing digitalized fundus images with automated vs. visual image analysis

	Automated classification based on digital analysis					
	No Diabetic Retinopathy		Diabetic Retinopathy		Total (n)	
Overall classification	Number	%	Number	%	Number	%
No Diabetic Retinopathy	50	71.4	20	28.6	70	100
Diabetic Retinopathy	1	3.3	29	96.7	30	100
Total number of patients	51		49		100	

The part of patients correctly classified with retinopathy identified through automated image analysis was 59.2% (positive predictive value), while the part of patients correctly classified without retinopathy was 98% (negative predictive value).

The clinical efficiency is raised to 85% with the adaptation of one custom screening parameter with an associated specificity of 85.7% and a sensitivity of 83.3%, which reveals an opportunity to adjust the algorithm used for specific purposes.

The match between the automated identification of bleeding with overall visual expert classification of 0.659 (Cohen's weighted kappa value) was comparable to the average congruity between the six ophthalmologists 0.648 (Cohen's weighted kappa value). The kappa value states the congruity rate between a classification carried out by experts ('gold standard') as the overall reference frame, compared to the Retinalyze automated analysis and the result achieved by the six ophthalmologists respectively.

The study concluded that the detection of diabetic retinopathy by automated identification of bleedings/lesions could be achieved with a system performance directly comparable to the one of experienced ophthalmologists. The results prove further examination of automated fundus image analysis as a screening tool for diabetic retinopathy.

The negative predictive value of 98% concludes that there is congruity between the automated image analysis and practice in the form of visual image analysis which provides a basis for substitution between the technologies. As the congruity is not 100 %, one should, when interpreting the result, be aware of legal aspects etc. which could consequently arise in the long term.

Efficiency

In another study (a retrospective cross-section analysis), Larsen N et al, 2003 (7) evaluates the efficiency of using an algorithm for automated fundus image analysis to separate diabetic patients with untreated diabetic retinopathy from diabetic patients without retinopathy. The Retinalyze software system was used for the automated analysis of (digitalized) fundus images. The analysis was carried out with a high sensitivity as well as high specificity. The examination involved 260 non-photocoagulated eyes of 137 patients involved in the routine photographic retinopathy screening. The

Mydriatic 60° fundus photography of 35 mm color transparencies with one output area was used. The routine classification was based on visual analysis of the transparencies carried out by experts. Reference classification was carried out with a special emphasis on achieving high sensitivity. Computer-assisted automated identification of bleedings/red lesions was carried out on digitalized transparencies.

The study found that, when screening a population consisting of diabetes patients with untreated retinopathy in each eye and without retinopathy respectively, with the use of automated fundus image analysis, 90.1 % of the diabetes patients with retinopathy (sensitivity) were correctly identified, while 81.3 % of the patients without retinopathy were identified correctly (specificity), cf. Table 2, in which the number refers to the number of patients, with the percentages stated in the brackets. The part of fake negative patients (i.e. patients with retinopathy which was not identified through the algorithm) was 9.9%, while the part of fake positive patients was 18.8%. All patients with the fake negative classification were identified with expert reference classification to have questionable retinopathy or minimal proliferative retinopathy. The total clinical efficiency was 86.8%.

Table 2 Automated identification of bleedings/microaneurysms

	Automated identification of blood extractions (screening settings recommended)					
Expert examination	0		> 0		Total	
	Number	%	Number	%	Number	%
No Diabetic Retinopathy	39	81.3	9	18.8	48	100
Diabetic Retinopathy	8*	9.9	73	90.1	81	100
Total	47		82		129	

* Questionable or minimal proliferative diabetic retinopathy

An isolated analysis of each eye found that automated fundus image analysis for the identification of eye bleedings can be adjusted in accordance with the simulation of different evaluation strategies.

With system adaptation with the use of high sensitivity, the system proved a sensitivity of 83.5 % with the automated screening and a specificity of 71.6%, with a clinical efficiency of 83.5 %. With the system adaptation with the use of high specificity, the system proved a sensitivity of 76.4 % with the automated screening and a specificity of 96.6%, with a clinical efficiency of 85.4%. The result of the system adaptation with the use of high specificity is close to the routine visual classification with a sensitivity of 76.4% and a specificity of 98.3%, with a clinical efficiency of 86.2%.

The system adaptation with the use of high sensitivity was also used at the visual re-classification where the same specialist examined the 260 fundus images on a PC with a mandatory assessment of the classified images, with the identified lesions set off with contrast color on the digitalized fundus images. By means of a few image-editing facilities, the specialist achieved a correct identification of eyes with retinopathy of 91.0% (sensitivity) and a correct identification of eyes without retinopathy of 95.7% (specificity), with a clinical efficiency of 93.1%. Thus, the result of system adaptation and the subsequent visual assessment proved an obvious improvement, with a performance better than both the routine visual classification and automatied identification only, with a fake negative part of 9.0 % and a fake positive part of 4.3 %.

The study concludes that automated fundus image analysis for the identification of untreated diabetic retinopathy from a screening population of patients with diabetes can be done with system adaptation, which empathizes either the high sensitivity by identification of diabetic retinopathy or the high specificity by the identification of the absence of retinopathy involving opposite extremities of evaluation strategies carried out by human analytics.

Procedure review and time study

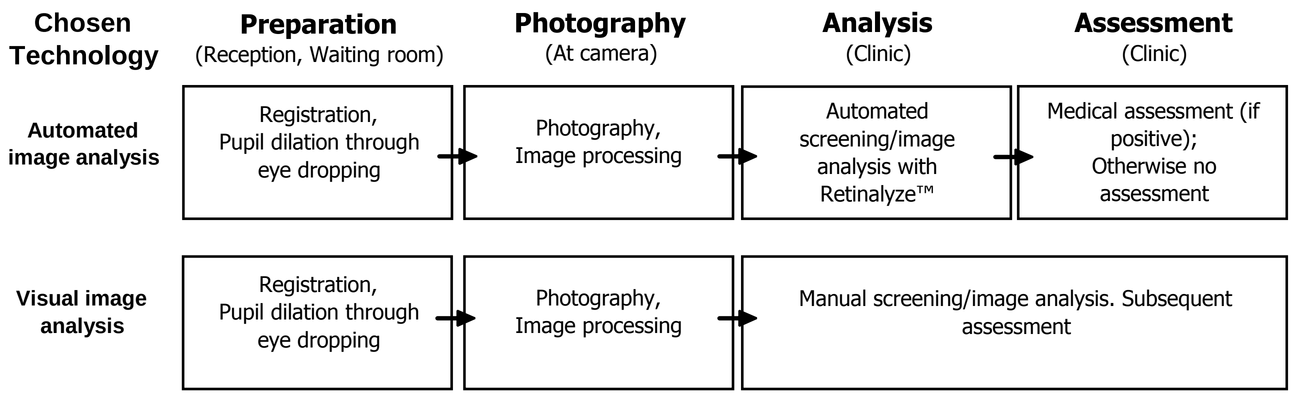
The basis for the procedure review and time study is the 'Retinalyze time report' by Kønig et al (8), which compares the procedure and the time spent on fundus photography and a subsequent analysis, carried out with a visual image analysis and automated image analysis respectively by means of Retinalyze.

No further time-series studies for the analysis have been carried out.

As a basis for the time report, the method/procedure below is stated, which is typically used for the assessment of diabetic retinopathy in the primary and secondary sector as well.

The procedure is outlined in Figure 1.

Figure 1 Procedure for the assessment of diabetic retinopathy (fundus photo analysis)



Thus, the analysis and assessment phase differs, depending on the technology used in the process.

In preparation for further analysis, it is considered advantageous to divide the procedure into two overall phases: Preparation and Photography (Phase 1) and Analysis and Assessment (Phase 2).

The time report states the time measured and used in each element in connection with the fundus photography and the subsequent analysis/assessment of both eyes. The time spent on the following elements has not been measured: Dialogues at the reception, seating of the patient in front of the camera, the time passed when walking into or out of the waiting room as well as conversations between patient and eye doctor, which is assessed to be identical for both technologies.

Phase 1: Preparation and Photography

The figure illustrates how the procedure for preparation and photography in the form of patient registration, fundus photography, subsequent data collection for electronic image and patient registration system is identical for both technologies.

With automatic analysis through Retinalyze, the system is connected to the Electronic Health Record (EHR), where the patient data are automatically transferred between the fundus camera system, the Retinalyze screening system, and EHR.

The resource consumption for the eye doctor's clinic for the installation and setup of the Retinalyze system is not included in the operational analysis.

Preparation and photography are carried out by a nurse or specially trained paramedical personnel. The total average time spent on preparation and fundus photography is 6.5 minutes. A detailed time report appears from Appendix B.

As the procedure is approximately identical for both technologies, this phase will not have any influence on the incremental analysis. However, this may still be interesting in an overall economic view.

Phase 2: Analysis and Assessment

After the preparation and the fundus photography, an image analysis and assessment are carried out. The carrying out of the phase depends of the chosen technology.

Visual image analysis: It is an overall process where an ophthalmologist analyses the fundus photograph on a PC and evaluates whether diabetic retinopathy is present. The most used patient registration system (EHR) among eye doctor clinics and hospitals is the PC-Praxis Ophthalmological system which can be connected to biometric equipment.

At e.g. Aarhus Community Hospital, specially trained nurses take the photos and evaluate which of them to be reviewed by an eye doctor subsequently. This circumstance is not considered relevant, but it could be an example of how to solve the division of tasks locally and how to solve the local ophthalmologist shortage in practice.

The total average time spent on fundus image analysis and the assessment is 4.50 minutes. A detailed time report appears from the Appendix B.

Automated image analysis : When using the Retinalyze automated image analysis, the analysis and assessment are separated into two processes, cf. Figure 1.

The fundus image is automatically analyzed by means of the Retinalyze software screening system. The automated analysis with Retinalyze is started manually. However, it can by started automatically in accordance with a fixed time schedule as well, e.g. for image analysis in the night, in the middle of the day etc. If the Retinalyze system identifies any bleedings / red lesions which might indicate diabetic retinopathy, the patient is marked for a subsequent eye doctor assessment.

Through the camera system, Retinalyze is connected to the EHR and PC-Praxis Ophthalmological system. Thus, patient data can be transferred between the systems. This practically means that when a patient is registered in the EHR, the patient’s fundus photographs are saved and uploaded by pressing only a few keys. This is an advantage in connection with telescreening.

The automated analysis is initiated in continuation of the preparation and the photo taking (phase 1) by a nurse or paramedical personnel. The average time spent on the automated image analysis is between 0.00 minutes and 1.50 minutes. A detailed time report appears from the Appendix B. With the preprogramed automated analysis in the night, the time spent is set to be 0.00 minutes, while the time spent on automated analysis during a normal workday is set to be 1.50 minutes.

An automated analysis does not require the presence of the personnel during the process. However, it is not estimated that the personnel could be allocated for another meaningful work permanently as the time spent for this is too short. It is mentioned that the time may be spent for dialogues with the patient, for cleaning-up, closing etc.

If the analysis follows an automatically fixed time schedule, patients suspected of having diabetic retinopathy are identified and subsequently assessed at an appropriate time. The time consumption is identical, regardless of the time of assessment.

If the screening result is positive, an assessment of retinopathy is carried out by an ophthalmologist on a PC after the image analysis. The total average time spent on the assessment is 2.50 minutes, cf. Appendix B.

If the screening result is negative, and the patient is screened not to have retinopathy, it is not necessary that the image is subsequently assessed by an ophthalmologist, and the patient does not need further examination until the next screening.

Summary

The difference between the resources consumed with the two technologies can be summarized as follows:

♦ The resource consumption for preparation and fundus photography does not depend on the chosen technology. ♦ There is a task-shifting between ophthalmologists and nurses/specially trained paramedical personnel, depending on whether the image analysis is carried out manually or automatically. ♦ Two minutes are released from the analysis of the fundus image carried out by an ophthalmologist, with the use of Retinalyze automated image analysis instead of a manual analysis.

♦ When using the Retinalyze automated image analysis instead of manual analysis, 2.5 more minutes are released from the image assessment of the fundus image carried out by an ophthalmologist, in case of a negative analysis result (the fundus image indicates no retinopathy).

♦ Maximum 1.5 more minutes are spent on the fundus image analysis carried out by a nurse or paramedical personnel, with the use of Retinalyze automated image analysis instead of a manual analysis.

♦ With a preprogramed automated image analysis outside working hours, no extra time is spent on the fundus image analysis carried out by a nurse or paramedical personnel, with the use of Retinalyze automated image analysis instead of manual analysis.

Task-shifting

The task-shifting in connection with the fundus image analysis and assessment have an impact on the average costs as stated above. In case of staff shortage as an inadequate resource and a production-limiting factor, task-shifting may have an impact on the whole production and the economy due to lack of supplies and any changes of the quality. Here, the total production refers to the number of screenings for retinopathy carried out.

In 2005, there are approx. 288 ophthalmologists among approx. 40 % consultants and 60 % general practitioners in Denmark. The prediction for 2010 is 296 eye doctors (9). Among those eye doctors, approx. 54% work at a practice and 46 % work at a hospital (10).

Thus, the supply of eye doctors is not significantly increased and is still under pressure due to the continuously unequal age composition among the present eye doctors, which is seeked to be compensated through an increased number of training posts (11). However, there is a doctor shortage within several specialties, which complicates the situation (9).

The aging population in Denmark and the subsequent increasing number of diabetics, as stated in section 1, increase the demand for eye doctor services. In addition, there will be an increased focus on homogeneous quality and a desire for regular screening of diabetics, which are potential demand-increasing factors as well.

Supply and demand tend to point towards an increased pressure on the ophthalmologists as an inadequate resource in the form of more treatments per doctor.

It is estimated that automated screening may remedy this problem to a certain extent.

5 Operational economic assessment

The object of the analysis is to assess the operating economy with the use of the Retinalyze software system compared to visual image analysis at the identification of retinopathy.

Analysis model

An operational economic assessment is carried out whose method is to carry out an incremental analysis of the costs with and without the use of Retinalyze for the identification of retinopathy. This analysis focuses on changes in the eye doctor's time consumption and the costs associated with the introduction and operation of the Retinalyze screening system.

The analysis is a cost-minimization analysis (CMA), a special case of a cost effectiveness analysis (CEA), which is used when the efficiency of the technologies are estimated to be equal. The CMA generally follows the CEA-methodology with technological equality as a basic condition.

In the light of Larsen M et al (6), it is concluded that automated identification / classification of diabetic retinopathy with the use of the Retinalyze technology is just as good or better compared to common visual image analysis with the use of experienced ophthalmologists.

The assumption of technological equality does no influence the respective effect of the technologies which are identical.

Operational costs

Operational costs including establishment prices and user fees for the use of the Retinalyze screening system appear from the Appendix C (Retinalyze operational costs) and have been provided by Retinalyze Denmark.

The differences in the time spent on screening appears from the review above (procedure review and time study).

The hourly rates for a nurse and specialist/ophthalmologist are based on MTA's rates for cervical cancer, 2005 (12), extrapolated with an annual salary increase rate of 4.0% on average for prices of 2008 (13).

The cost difference (variable costs), when using the Retinalyze automated image analysis compared to visual image analysis, per patient/2 eyes is as follows:

Preparation and fundus photography	= DKK 0.00
Image analyses, Nurse, approx. 1.5 minutes at approx. DKK 6.20	= DKK 9.30
Fee per analysis (Click fee) at DKK 30 per eye	= DKK 60.00
Fee per import (Click fee), photography	= DKK 0.00
Image analysis, Specialist, approx. 2.0 minutes at approx. DKK 11.25	= DKK 22.50
Image assessment, Specialist, approx. 2.5 minutes at approx. DKK 11.25	= DKK 28.10

Operational costs

Fixed costs for the Retinalyze software license to the fundus camera incl. introductory course at the clinic are DKK 26,000, while the annual subscription is DKK 7,950. Installation, setup, and software calibration for the fundus camera is DKK 5,250, while the integration for PC-Praxis is DKK 4,350. These costs are written off over 5-10 years.

If it is estimated that a typical eye doctor's practice carry out 4,000 eye screenings a year, divided among 20 eyes/10 patients a day 200 days a year, the start-up and subscription costs total DKK 3.77 per eye screening (DKK 7.54 per patient) if the expenses are written off over a 5-year period.

Cost difference with diabetic retinopathy

The task-shifting when using automated image analysis from ophthalmologist to nurse/paramedical personnel causes a net reduction of DKK 13.20 per patient/2 eyes which is ascribed to a lower salary scale for nurses/paramedical personnel.

Thus, the variable cost is DKK 46.80 per patient/2 eyes, corresponding to DKK 23.40 per eye screening.

Thus, the marginal cost totals DKK 54.32 per patient/2 eyes, corresponding to DKK 27.16 per eye screening.

Cost differences without diabetic retinopathy

As a rule, the cost differences when screening a patient without diabetic retinopathy are identical with the cost differences when screening a patient with diabetic retinopathy. As the fundus image of a patient without diabetic retinopathy is automatically analyzed with the Retinalyze technology (the fundus image shows no retinopathy), the image must not subsequently be assessed by an eye doctor, which means that the costs for the eye doctor's time spent on image assessment are released. Thus, 2.50 minutes of the eye doctor's time are released, cf. Table 11, corresponding to DKK 28.10 per patient/2 eyes.

As a result of the task-shifting, the reduction by using automated image analysis from ophthalmologist to nurse/paramedical personnel thus causes a net reduction of DKK 13.20 per patient/2 eyes, which is ascribed to a lower salary frame for nurses/paramedical personnel. In addition, 2.50 minutes of the doctor's time are released corresponding to DKK 28.10 per patient/2 eyes.

Thus, the variable cost is DKK 18.70 per patient/2 eyes, corresponding to DKK 9.35 per eye screening.

Thus, the marginal cost totals DKK 26.20 per patient/2 eyes, corresponding to DKK 13.10 per eye screening.

The total costs depend on whether the screening is carried out at the eye doctor's practice or at a hospital.

The general appearance of diabetic retinopathy among patients has not been documented conclusively and for example, it depends on whether the eye examinations are carried out at an eye doctor's clinic or at a hospital. Thus, patients having eye doctor's examinations at a hospital are typically more likely to have retinopathy than patients having eye examinations at an eye doctor's practice.

Thus, unpublished numbers from the Eye Doctor Department at Aarhus Hospital state that approx. 62% of the patients, corresponding to 2,074 of 3,313 patients, had a special examination at the risk of diabetics retinopathy. A corresponding unverifiable number for the eye doctor's practice is 15%.

In the light of the present number, the annual costs based on the fact that a typical eye doctor's practice carries out 4,000 eye screenings per year (2,000 patients) are between 60,800 (eye doctor's practice) and DKK 87,300 (hospital).

This presupposes, as calculated, that the savings have been achieved through task-shifting. The total costs must be compared to the activity progress expected in the number of eye screenings caused by the task-shifting and the related incomes in the form of health insurance services and DRG rates. In addition to this, there are non-quantified gains in the form of qualitative implications of the screenings, improved opportunities for time-series studies accompanied by image database development as well as improved opportunities for telescreening.

The marginal cost per patient is reduced with the inclusion of an additional user/client caused by the advantages of large-scale operations. However, a cost estimate will not be prepared as this depends on the specific circumstances for individual clinics.

Incremental analysis

The Danish Health and Medicines Authority recommends a decision on eye screenings in the form of fundus images and visus or eye examination at the eye doctor's every second year (more frequently in case of more distinct retina changes and pregnancy) (4). If all diagnosed diabetics in 2007 followed the recommendation of the Danish Health and Medicines Authority to have a screening every second year, 113,231 diabetics were screened in 2007. According to the MTA of the Danish Health and Medicines Authority on type 2 diabetes (2), the number of diabetics who had an annual screening was 46%, while 26 % had never been screened. The percentage might have fallen subsequently, or it might have risen. However, the relatively high number for fixed annual screenings indicates an even higher number of screenings per year than recommended, depending on the screening frequency for the remaining 28%. An assumption that 50% of all diabetics are screened every year is thus conservative.

According to conversations with managing ophthalmologists, the examination frequency for a specialist with a normal screening rate is 6 patients per hour. In the MTA of the Danish Health and Medicines Authority on cervical cancer (12), a time study finds that cyto-technicians spend almost half of their time on registered examinations, while the other half is spent on absence, knowledge maintenance, research / development, administration etc. (courses etc.), which is in accordance with previous time studies in Herlev and Aalborg. Furthermore, the time studies from Herlev and Aalborg find that this also regards doctors and secretaries. This information is important, as you, in order to meet a function, actually have to allocate (salary) money for the double time.

The Retinalyze time report uses the stopwatch method instead of the frequency method. The Retinalyze time report, cf. Appendix B, indicates, that approx. 4.5 minutes of the eye doctor's time is spent on each screening with manual image analysis and assessment, corresponding to 13.3 screenings per hour. As found in the time study in connection with the MTA for cervical cancer, only almost half of the working hours is patient-related. Thus, the treatment of approx. 6 patients per hour seems realistic.

Based on this, it is estimated that about 11.1 full-time jobs for eye doctors (18,872 hours) per year is spent on examinations in connection with diabetic retinopathy with the current number of diabetics.

With the use of the Retinalyze software system for automated image analysis, task-shifting, as stated above, will influence the number of eye doctor positions used for examinations in relation to diabetic retinopathy.

An estimated number for the distribution of eye doctor patients between the eye doctor's practice and the hospitals is 80% at the eye doctor's practice and 20% at the hospital.

This corresponds to a saving potential, obtained as a time release, of 76% of the current time spent by the eye doctors (time release of 38% at a hospital, 85% at the eye doctor's practice) caused by the task-shifting from eye doctors to nurses or specially trained paramedical personnel. With 11.1 full-time eye doctor positions per year spent on examinations in connection with diabetic retinopathy, the time release among eye doctors corresponds to 8.4 full-time eye doctor positions per year.

Totally, automated screening could release time corresponding to 8.4 full-time eye doctor positions per year divided between:

- Eye doctor's practice 7.5 full-time jobs
- Hospital 0.9 full-time jobs

Where it is assumed that a typical eye doctor's practice carries out 4,000 eye screenings per year, distributed among 20 eyes/10 patients a day, 200 days a year, this corresponds to 0.17 full-time jobs (the corresponding number at a hospital is 0.07 full-time jobs per 4,000 eye screenings).

In addition to this, there is a rationalization of the eye doctor's time spent if patients are screened not to have diabetic retinopathy (the fundus image shows no retinopathy) where the eye doctor would be able to attend to more patients per hour or use the released resources somewhere else.

With a doctor's salary of DKK 650,000 per year, this causes a total saving in the form of released time, corresponding to gross DKK 5,449,000 per year. The gross saving is achieved by automated screening of 113,232 diabetes patients / 226,463 eye screenings, which cost between DKK 13.10 and DKK 27.16

per eye screening, a total of DKK 3,743,000. Overall, the introduction of automated systematic screening for diabetic retinopathy thus causes a net saving of DKK 1,705,000 per year where the positive effects primarily create value in the form of time release.

Any additional incomes caused by the fact that an eye doctor would be able to attend to more patients per hour are not included. Furthermore, additional costs for paramedical personnel are not included either as the focus of the analyses is on eye doctors as an inadequate resource.

Sensitivity analysis

The basis of the sensitivity analysis is conservative based on the fact that automated screening would be able to release time corresponding to 8.4 full-time eye doctor positions per year, cf. the Incremental analysis.

Where the sensitivity analysis uses the term ’saving’, it refers to the ’saving obtained in the form of released time’.

The analysis results depend on several important factors, including the development in the number of diabetics, the number of screenings carried out, the opportunity of task-shifting in the health sector, the organizational development and use of telescreening as well as the chosen evaluation strategy.

The evidence for the number of screenings carried out is insufficient. The number of screenings carried out influences the estimate for full-time jobs used for screening for retinopathy. The number of full-time equivalents used influence the saving potential with the introduction of automated screening.

Table 3 Sensitivities, Number of screenings carried out

Number of screened patients	40%	50%	60%	66%	75%
Number of screenings	90,585	113,232	135,878	149,466	169,847
Full-time equivalent for screening	8.9	11.1	13.3	14.6	16.6
Saving	6.7	8.4	10.1	11.1	12.6

The estimate of 50% of the diabetic population who are annually screened is estimated to be conservative, and a downward change is estimated to be less likely than an upward change. At 60%, 13.3 full-time equivalent is spent on screening in connection with diabetic retinopathy, with an estimated saving potential of 11.3 full-time equivalent with the introduction of automated screening, cf. Table 3.

The evidence of the percentage saving potential with automated instead of visual screening, measured in the number full-time jobs used for screening annually, is insufficient. The saving potential (time release) is 76%. If this percentage changes to 70%, the saving potential is reduced, measured in full-time jobs, from 8.4 jobs to 7.8 jobs, cf. Table 4.

Table 4 Sensitivities, Percentage saving potential

Saving (%)	60%	70%	76%	80%	90%
Number of screenings	113,232	113,232	113,232	113,232	113,232
Full-time equivalent for screening	11.1	11.1	11.1	11.1	11.1
Saving	6.7	7.8	8.4	8.9	10.0

The estimate of the number of screenings per hour is central to the total estimates. More and larger time-series studies should be completed to ensure better documentation of the screening frequency.

Changing the working procedure influences the screening frequency, cf. Table 5.

Table 5 Sensitivities, Screening speed, eye doctors

Screening frequency (patient/hour)	4	5	6	7	8

Number of screenings	113,232	113,232	113,232	113,232	113,232
Full-time equivalent for screening	16.6	13.3	11.1	9.5	8.3
Saving	12.6	10.1	8.4	7.2	6.3

Regardless of the chosen sensitivity analysis, the conclusion of the analysis is not changed as the saving potential is still estimated to be important, especially in a situation with eye doctor shortage, relatively long waiting lists and an expected increase in the demand for screenings.

Discussion

A review of the present literature on automated fundus image analysis finds that the technology is just as good as or better than a conventional visual image analysis. The analysis proves a good potential for rationalization of the eye doctor's time spent with the introduction of automated image analysis due to reduced analysis time, as well as a task-shifting between ophthalmologists and nurses / specially trained paramedical personnel.

The potential seems to be large. However, whether it can be fulfilled or not e.g. depends on the willingness to adapt among the operators in the health sector and the viability of the system during an adaptation and development phase. Conversely, the willingness to adapt depends on the collection of more empirical data and documentation.

The analysis finds potential savings in the eye doctor's time spent. Conversely, a marginal cost appears with the implementation of the system. This marginal cost must be compared to the larger number of screenings which can be carried out and the related income in the form of health insurance services and DRG rates.

Automated image analysis possibly cost money; possibly, it may cause savings besides the savings in the eye doctor's time spent. With long waiting lists, which are hardly going to be reduced, as well as a rapidly increasing number of diabetics, the inadequate resource no longer seem economic but an inadequate supply of eye doctors and the total screening potential of society.

The opportunity for screening in the night as well as the opportunity for telescreening are estimated to contain great potentials as well.

In addition, the present literature proves a qualitative advantage of digitalized automated image analysis. Transfer and storage of the digitalized fundus images may cause increased quality in the assessment of retinopathy over time. Moreover, transfer and storage of digitalized fundus images support the development of telescreening as an organizational principle. Furthermore, large photo databases are estimated to contribute to system development and further improvements and quality assurance as well.

Conclusion

The background description found that at the end of 2006, there were 226,463 diabetics in Denmark. Over the past 10 years, this number has increased by 7.1 percent per year. All diabetic patients are at risk of developing diabetic retinopathy, and as a general guideline, the Danish Health and Medicines Authority recommends a thorough consultation once a year, with the decision on eye screening or eye examination every second year.

The benefit of this screening is so well established that it, with the current knowledge available, is not estimated ethically proper to omit screening where possible.

Retinopathy can be detected with an ophthalmoscope or with automated or visual image analysis. With the review of the present literature, it is concluded that the detection of diabetic retinopathy by means of automated image analysis can be achieved with a system performance directly comparable to the one for experienced ophthalmologists with visual image analysis. The results prove further examination of automated fundus image analysis as a screening tool.

Automated image analysis instead of visual image analysis causes a task-shifting, with a shift of tasks from ophthalmologists to nurses / specially trained paramedical personnel.

For the carrying out of an operational economic analysis it was estimated that:

- ♦ The marginal cost per screening is between DKK 13.10 and DKK 27.16 with the automated analysis instead of the visual. At e.g. annual screenings at a typical eye doctor's practice, the costs total between DKK 60,800 and DKK 87,300, varying with the number of patients screened positive. This presupposes internalization of savings achieved through task-shifting (time release for doctors).
- ♦ The total costs must be compared to an expected activity progress in the number of eye screenings caused by the task-shifting and the related incomes in the form of e.g. health insurance services. In addition to this, there are non-quantified gains in the form qualitative implications of the screenings, improved opportunities for time-series studies accompanied by image database development as well as improved opportunities for telescreening.
- ♦ With conservative model assumptions, about 11.1 full-time eye doctor positions are used on examinations per year in connection with diabetic retinopathy, with the present number of diabetics and with the use of ophthalmoscopy and/or visual image analysis.
- ♦ With the use of the Retinalyze software system for automated image analysis, the task-shifting will influence the number of eye doctor positions used for examinations in connection with diabetic retinopathy on the decline and causes a saving potential in the form of released time corresponding to 8.4 full-time eye doctor position per year, based on conservative conditions.
- ♦ Sensitivity analysis do not change the conclusion of the analysis significantly, as the saving potential obtained as time release is still estimated to be important in a situation with eye doctor shortage, relatively long waiting lists and an expected increase in the demand for screenings.

Appendixes

Appendix A: Terms – sensitivity and specificity.

Source: MTA Type 2 diabetes, 2003 (2)

Possible results of screening tests. The person found ill at the test can actually be ill or well, and the person found well at the test may be well or sick.

Table 6 Sensitivity/specificity

	Diagnosis		
Test	Ill	Well	
Ill	True positive: a	Fake positive: b	PPV: a/(a+b)
Well	Fake positive: c	True negative: d	NPV:d/(c-d)
	Sensitivity: a/(a+c)	Specificity: d/(b+d)	

Table 6 indicates the possible categorization of a person at a screening test.

The sensitivity is the probability of being tested positive, given you are ill, i.e. how big a part of ill people are captured at a given test.

The specificity is the probability of being tested negative, given you are well. The sensitivity and the specificity are objects used for the assessment of the validity of screening tests. Their objects is to find out how good each test is at distinguishing between ill and well people. Thus, they are important objects for the health authorities to make decisions on the implementation of a given test. The number of fake positives as well as fake negatives should be reduced. At a high sensitivity, there will be a few fake negative answers, and at a high specificity, there will be a few fake positive answers. The sensitivity increases at the expense of specificity. The achievement of a higher sensitivity will cause more well people being tested positive, and thus the specificity will decline. The optimum achievement is a test where the sensitivity as well as the specificity are as high as possible.

A true positive rate (positive predictive value (PPV)): is the likelihood that a person is ill, given a positive test. In other words, how sure is it that the person is ill when the test is positive? A true negative rate (negative predictive value (NPV)): is the likelihood that a person is well, given a negative test; i.e. how sure is it that the person is well when the test is negative?

The predictive values are very important objects for the practitioner and the patient as well. At a low positive predictive value, you must interpret the result very cautiously, i.e. you must tell the patient that even though the test is positive it is not sure that the patient is ill. On the other hand, a high negative predictive value could be used to assure the patient and the practitioner that the patient is well.

The predictive values depend on the incidence of the disease (the prevalence) in an individual population group. In population groups with a high incidence of diseases, the predictive values of a test will always be higher than in populations with a lower incidence of diseases.

In addition to the above assessment of screening tests, they should also be simple, close to the patient (it might be an advantage if they can be used in a general practice), cost effective, safe, and acceptable for the health authorities and the population in general.

Appendix B: Time reports

Source: Kønig et al, 2008 (8)

The use of the term time report in this context, it means that 'time report' refers to the personnel's time spent in connection with fundus photography/assessment/analysis.

Table 7 includes a time report for a nurse / paramedical personnel in connection with fundus photography. The time report is identical for visual and automated image analysis.

Table 7 Time report for fundus photography (nurse/paramedical personnel)

Location	Action	Average time in minutes
Reception (PC)	Registration of the patient, civil registration number, name, address etc. in the EHR system (by means of medical card)	0.25
Waiting room	Eye dropping with mydriacyl	2.00
At camera (PC)	Input of patient data, transfer of patient data to the camera system	0.25
At camera (photo equipment)	Fundus photography of both eyes, incl. image quality control	3.00
At camera (PC)	Transfer of images and final medical record notes.	1.00
Total		6.50

Table 8 includes a time report for an eye doctor for image analysis and assessment at visual image analysis.

Table 8 Time report for fundus image analysis and assessment

Location	Action	Average time in minutes
Clinic (PC)	Input of patient data in the EHR system	0.10
Clinic (PC)	Input of the patent data in the image system from EHR	0.10
Clinic (PC)	Input of 2 fundus photographs	0.25
Clinic (PC)	Fundus assessment of both eyes	4.00
Clinic (PC)	Closing of image program and closure	0.05
Total		4.50

Table 9 includes a time report for a nurse/paramedical personnel for image analysis at automated image analysis carried out in the night.

Tabel 9 Time report for automated fundus image analysis, night (nurse/paramedical personnel)

Location	Action	Average time in minutes
Automated reporting (on PC or SERVER)	Retinalyze automated batch analysis running, scheduled to run in the night with an automated report printing and electronically transferred to the EHR system. Requires no personnel action.	0.00
Total		0.00

Table 10 includes a time report for a nurse/paramedical personnel for image analysis at automated image analysis carried out during a normal working day.

Table 10 Time report for fundus image analysis and assessment

Location	Action	Average time in minutes
At camera (PC)	Manual initiation of automated fundus image analysis of both eyes.	0.25
At camera (PC)	The analysis takes approx. 0.5 – 1 minute for both eyes depending on the processor power of the computer and the size of the image, but the presence of the personnel is not required. Typically, this time is spent on dialogues with the patient, cleaning-up, closing etc.	1.00
At camera (PC)	Opening of the result window for both eyes, note for medical record	0.25
Total		1.50

Table 11 includes a time report for an eye doctor for the assessment of an automated image analysis, provided that the screening result is positive (if the screening result is negative (absence of retinopathy), the image analysis is omitted and the patient is closed).

Table 11 Time report for fundus image assessment accompanied by an automated image analysis

Location	Action	Average time in minutes
Clinic (PC)	Input of the patient's data in the EHR system	0.10
Clinic (PC)	Input of the patient's data in Retinalyze from EHR	0.10
Clinic (PC)	Input of 2 fundus photographs	0.25
Clinic (PC)	Fundus assessment of both eyes based on the Retinalyze markings	2.00
Clinic (PC)	Closure and ending	0.05
Total		2.50

Appendix C: Operational costs

Source: Kønig et al, 2008 (14)

Table 12 Operational costs, Retinalyze

	Ex. VAT	Incl. VAT
Retinalyze software license for 1 fundus camera, incl. introductory course in the clinic	26,000	32,500
Installation, setup and software calibration for 1 fundus camera	5,250	6,563
Installation of an additional Retinalyze client software license each	4,000	5,000
Annual subscription and hotline, 1 client	7,950	9,938
Annual subscription and hotline for each additional client	1,250	1,563
Click fee per analysis	30	38
Integration for PC-Praxis	4,350	5,438

Appendix D: Routine classification

Source: Larsen N et al (2003)

Table 13 Automated identification of bleedings/microaneurysms

	Standard settings					
Expert examination	No Diabetic Retinopathy		Diabetic Retinopathy		Total	
	Number	%	Number	%	Number	%
No Diabetic Retinopathy	114	98.3	2	1.7	116	100
Diabetic Retinopathy	34	23.6	110	76.4	144	100
Total	148		112		260	

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