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**Title**

# Evidence-based Danish guidelines for screening of diabetic retinopathy.

**Authors**

Jakob Grauslund[1,2,3]

Nis Andersen[1,4]

Jens Andresen[1,4]

Per Flesner[1,4]

Per Haamann[1,4]

Steffen Heegaard[1,5]

Michael Larsen[1,5]

Caroline Schmidt Laugesen[1,6]

Katja Schielke[1,7]

Jesper Skov[1,4]

Toke Bek[1,8]

**Affiliations**

1. Danish Ophthalmological Society, Copenhagen, Denmark.
2. Department of Ophthalmology, Odense University Hospital, Odense, Denmark.
3. Department of Clinical Research, University of Southern Denmark, Odense, Denmark.
4. Organization of Danish Ophthalmologists, Copenhagen, Denmark.
5. Department of Ophthalmology, Rigshospitalet-Glostrup, Copenhagen, Denmark.
6. Department of Ophthalmology, Zealand University Hospital Roskilde, Roskilde, Denmark.
7. Department of Ophthalmology, Aalborg University Hospital, Aalborg, Denmark.
8. Department of Ophthalmology, Aarhus University Hospital, Aarhus, Denmark.

**Corresponding author**

Professor Jakob Grauslund, MD, PhD, DMSci

Department of Ophthalmology

Odense University Hospital

Sdr. Boulevard 29

DK-5000 Odense C, Denmark

Phone: +45 65 41 27 82

Fax: +45 66 12 63 87

E-mail: jakob.grauslund@rsyd.dk

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**Abstract**

Diabetic retinopathy (DR) is among the leading causes of visual loss in the working-age population. It is generally accepted that screening of DR is cost-effective and can detect DR before it becomes sight-threatening to allow timely treatment. A group of retinal specialists was formed by the Danish Ophthalmological Society with the aim to formulate contemporary evidence-based guidelines for screening of DR in order to implement these in the Danish screening system. We hereby present evidence for DR-screening regarding 1) classification of DR, 2) examination techniques, 3) screening intervals, and 4) automated screening. It is our recommendation that the International Clinical Retinopathy Disease Severity Scale should be used to classify DR. As a minimum, mydriatic two-field disc- and macular-centred images are required. In the case of suspected clinically significant diabetic macular oedema, supplementary optical coherence tomography can increase the diagnostic accuracy. There is solid evidence to support a flexible, individualized screening regimen. In particular, it is possible to prolong screening intervals to 24-48 months for patients with no or mild non-proliferative diabetic retinopathy (NPDR), but it is also possible to use extended intervals of 12-24 months for patients with moderate NPDR given that these are well-regulated regarding glycaemic control (HbA1c ≤ 53mmol/mol) and blood pressure (≤130/80 mmHg). Automated screening of DR is encouraging but is not ready for implementation at present. In conclusion, Danish evidenced-based guidelines for screening of DR support high-quality imaging and allow flexible, individualized screening intervals with a potential for extension to patients with low risk of DR-progression.

**Introduction**

It has been estimated that 320,000 Danes have diabetes, and the number is expected to increase in the coming years.(Green et al. 2016) Diabetic retinopathy (DR) is the most common complication in diabetic patients (Klein et al. 2008; Grauslund et al. 2009) and a feared cause of blindness.(Grauslund et al. 2009; Klein et al. 2010)

The World Health Organization has recommended that screening should be performed for diseases given that a number of criteria are met.(Wilson & Jungner 1968) These include that: 1) the condition should be an important health problem, 2) there should be an accepted treatment for patients with recognized disease, 3) facilities for diagnosis and treatment should be available, 4) there should be a recognizable latent or early symptomatic stage, 5) there should be a suitable test or examination, 6) the test should be acceptable to the population, 7) the natural history of the condition, including development from latent to declared disease, should be adequately understood, 8) there should be an agreed policy on whom to treat as patients, and 9) the cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole. These criteria are all met in DR, and it has been demonstrated that eye screening in diabetes is cost-effective.(Stefansson et al. 2000) To illustrate this, the introduction of the nationwide DR-screening programme in England and Wales was followed by data demonstrating that DR for the first time in five decades was no longer the leading cause of blindness in the working-age population in UK (Liew et al. 2014)

The aim of eye screening in diabetes is to detect sight-threatening DR prior to irreversible visual loss. Sight-threatening levels of DR include proliferative diabetic retinopathy (PDR) and clinically significant diabetic macular oedema (CSMO), and patients with these complications should be referred for treatment which can at least halve the risk of visual loss.(DRS. 1976; ETDRS. 1985)

Even though screening for DR has been fully implemented in Denmark, there are still substantial regional differences given an unequal distribution of eye care providers and a wide range of interpretation of the pre-existing guidelines.(Andersen et al. 2016) Patients attend eye screening either at private practicing ophthalmologists or at hospitals. At both sites, financial reimbursement is provided by the public health care system and regardless of screening-origin, patients with suspected vision-threatening DR are referred for treatment at eye departments at public hospitals. As part of the screening programme it is mandatory that results are reported to a national clinical quality database (DiaBase).(Andersen et al. 2016; DDD. 2016)

Screening is predominantly performed in Denmark by fundus photography including measurement of corrected visual acuity. Retinal images are evaluated by an ophthalmologist or a trained grading specialist, and the examination is supplemented by indirect ophthalmoscopy in patients with insufficient retinal visualisation by photography.

In 2009 the Danish Ophthalmological Society implemented a clinical guideline to address DR,(DOS. 2009) but given the clinical and technological landmarks made within the last decade it was decided to introduce an evidence-based clinical guideline to be implemented in the Danish screening programme. To achieve this, a group of retinal specialists was formed by the Danish Ophthalmological Society. The aim of this paper is to present the contemporary Danish guidelines for screening of DR as of 2018 including the supporting evidence and the specific recommendations.

**Evidence for classification of DR**

Scale for classification of DR

It is important to have a standardized set of characterisations to define the severity of DR. Such a classification scheme was developed for the Early Treatment of Diabetic Retinopathy Study (ETDRS) based on the modified Airlie House classification of DR.(ETDRS. 1981) This scale has been commonly accepted as a gold standard model and is in particular used in research settings. However, its practical use is limited by the high complexity and the high number of steps on the grading scale. To address this, the American Academy of Ophthalmology launched an initiative to develop a new clinical severity scale for DR. A 5-step scale was proposed in order to stratify patients according to risk of DR-progression.(Wilkinson et al. 2003) In particular, it was important to identify patients with a high risk of PDR-progression in order to monitor these closely. The International Clinical Diabetic Retinopathy Disease Severity Scale addressed this by defining a level of severe non-proliferative diabetic retinopathy (NPDR, Level 3) which approximates ETDRS level 53. Eyes with this level can be identified based on the 4:2:1-rule according to number of retinal quadrants with either more than 20 intraretinal haemorrhages (four) or definite venous beading (two) or prominent intraretinal microvascular abnormalities (IRMA, one). As compared to patients with moderate NPDR (Level 2), patients with severe NPDR (Level 3) had a much higher 1- and 3- year risk of developing PDR (50% and 71%, respectively).

The International Clinical Diabetic Retinopathy Disease Severity Scale has been widely accepted and included in daily clinic and screening programmes even though it has not been fully validated but is based on workshop consensus among a group of leading retinal experts. Given its simplicity, it is clinically useful, and it is in particular in screening settings important to identify patients with a high short-term risk of progression to PDR.

Scale for classification of diabetic macular oedema (DMO)

In the ETDRS it was tested if macular laser photocoagulation could reduce the risk of moderate visual loss for patients with DMO. This was not possible in cases where DMO was defined as retinal thickening within

1 disc diameter from the macular centre.(ETDRS. 1985) However, when treatment was applied to macular oedema closer to the fovea (as given by the CSMO definitions stated in the next section), the risk of moderate visual loss decreased by 50% as compared to untreated eyes. Based on this, the definitions of CSMO by the ETDRS-scale have been widely accepted as a classification scheme to identify screening patients in need of treatment.

**Recommendations regarding classification of DR**

1. The International Clinical Diabetic Retinopathy Disease Severity Scale should be used to classify DR, (Wilkinson et al. 2003) and patients with Level 4 should be referred for additional examinations and/or treatment (Table 1).

   Levels of DR include:

   - Level 0: no DR.
   - Level 1: mild NPDR (microaneurysms and/or dot haemorrhages only).
   - Level 2: moderate NPDR (more than microaneurysms and/or dot haemorrhages but less than Level 3).
   - Level 3: severe NPDR (more than 20 intraretinal haemorrhages in each of 4 quadrants OR definite venous beading in at least 2 quadrants OR prominent IRMA in at least 1 quadrant AND no PDR).
   - Level 4: PDR (neovascularization (active or treated by panretinal photocoagulation) OR vitreous/preretinal haemorrhage).

2. The ETDRS-scale should be used to classify diabetic maculopathy,(ETDRS. 1985) and patients with CSMO should be referred for additional examinations and/or treatment (Table 1).

   Relevant definitions include:

   - DMO: diabetes-induced retinal thickening and/or hard exudates within 1 disc diameter from the macular centre. Can be sub-grouped according to presence or absence of CSMO.
     - DMO with CSMO: diabetes-induced retinal structural changes including 1) retinal thickening within 500µm from the macular centre, OR 2) hard exudates within 500µm from the macular centre with associated retinal thickening, OR 3) retinal thickening greater than 1 disc diameter with partial of full location within 1 disc diameter from macular centre. The classification does not specify if treatment for CSMO has previously been performed, but for a screening purpose it is important to consider if CSMO is in progression, stable or in regression (Table 1).

- DMO without CSMO: DMO that does not fulfil the criteria of CSMO and, hence, does not need referral for further examination and/or treatment.

3. Corrected visual acuity is not included in the classification given that this can be within the normal range despite sight threatening DR or be reduced secondary to concurrent eye disease.

**Evidence for examination methods**

Technical equipment

Even though it is obvious that modern camera technology offers better imaging solutions, there is no strong evidence to support any particular settings. Recommendations (as given in the upcoming section) would often be based upon tradition and available standards.

Retinal field of view

The ETDRS-scale was based on mydriatic 7-field 30 degree stereo images covering the posterior pole.(Early Treatment Diabetic Retinopathy Study Research 1991) Even though this examination has a higher sensitivity than indirect ophthalmoscopy,(Lin et al. 2002) the method is limited given that is it time-consuming, difficult to perform and a burden for patients. Therefore, several studies have examined if it is possible to achieve comparable results including fewer retinal fields or capturing non-mydriatic images.
In the EURODIAB IDDM Complications Study, Aldington et al validated the use of two 45 degree field mydriatic images.(Aldington et al. 1995) Forty eight images covering the entire DR-spectrum were evaluated by five retinal experts. Median agreement was 77%, and kappa was 0.85 and 0.83 for within-observer and between-observer agreement. The same field-of-views were compared by Boucher et al in 196 images, but in this study a non-mydriatic approach was tested.(Boucher et al. 2003) Sensitivities and specificities for referral ranged between 53.3-97.9% and 81.3-96.9%. However, among ten eyes with severe NPDR or PDR as evaluated by ETDRS, only one eye was correctly diagnosed in the non-mydriatic arm.
The introduction of ultra-wide field cameras has also introduced the possibility that these would be comparable, or even superior, to ETDRS standards. In a four-way comparison of non-mydriatic, mydriatic, and steered mydriatic ultra-wide field images, Rasmussen et al reported a very high agreement within one level of DR in 190 eyes evaluated on an 8-step ETDRS scale (99.0%, 98.9% and 100.0% as compared to ETDRS-standard images). Two eyes with ETDRS graded PDR were missed in ultra-wide field images (due to eye lashes), and conversely three eyes with ultra-wide field graded PDR were missed by ETDRS images. These results are consistent with other studies demonstrating that ultra-wide field images compare well to ETDRS-standards, but that they rarely lead to a better detection of peripheral treatment demanding lesions in eyes with PDR that would not have been detected otherwise.(Kernt et al. 2012; Silva et al. 2013)

Indications to include optical coherence tomography (OCT)

Even though the ETDRS definition of CSMO has successfully identified patients in risk of visual loss, it should be considered that the classification was based on stereo-evaluation at a time where OCT was not available. A better detection of CSMO in the screening phase could lead to a better allocation of health care resources given that only patients with treatment-demanding equiring macular oedema would be referred for treatment. In addition it is also possible to rule out CSMO at an early stage which may reduce concerns of the patients.(Mackenzie et al. 2011; Wong et al. 2017)

Wong et al demonstrated that among 352 patients with foveal haemorrhages, exudates or both, only 23.2%, 51.7% and 61.1% had OCT signs of oedema (retinal cysts, oedema, retinal thickening or changes in the internal limiting membrane contour).(Wong et al. 2017) This led to a false positive rate of referral for CSMO of 86.6% in a screening setup without OCT. These results were confirmed in the UK screening program which reported that spectral domain OCT could rule out macular oedema in 42.1% of cases that met the screening definitions.(Mackenzie et al. 2011) In a comparative study of 246 eyes, Wang et al concluded that there was a considerable inconsistency in the detection of DMO and CSMO when fundus photography and OCT were compared.(Wang et al. 2016) Differences went both ways, but in general the prevalence of DMO and CSMO was higher by fundus photography (61.4% and 48.5%) as compared to OCT (21.1% and 21.3%).

**Recommendations regarding examination methods**

Technical equipment

The following standards for fundus photography should be fulfilled:

1. Digital fundus camera with an image sensor including at least 3.0 mega pixels (NHS. 2014) and an optics with a central solution of 60 line pairs per mm. (ISO. 2009)
2. Image angle of at least 45 degrees.
3. Monitor with a vertical solution of at least 1080 pixels.(NHS. 2014)

Retinal field of view

1. Screening for DR should be based on fundus photography. Patients with blurry media or other factors limiting the retinal view should be evaluated by indirect ophthalmoscopy by a trained ophthalmologist.(Scanlon 2017)
2. Mydriatic fundus photography should be preferred.(Boucher et al. 2003; Shi et al. 2015) Alternatively, wide-field images of at least 70 degrees can be used. (Kernt et al. 2012; Rasmussen et al. 2015). Prior to pupil dilation it is important exclude risk of angle closure or allergic reaction.

3. At least two retinal images of 45 degrees are required (centred at the macula and the optic disc).(Aldington et al. 1995; Scanlon 2017)
4. Retinal images should cover at least 70-80 degrees horizontally and 45 degrees vertically.(Aldington et al. 1995)

Indications to include optical coherence tomography (OCT)

1. Supplementary macular OCT should be performed if possible in the case of suspected or overt CSMO, or clinically significant loss of vision (at least two Snellen lines) which cannot be explained by concurrent disease.(Virgili et al. 2007; Wang et al. 2016) In such cases it is possible to qualify the suspicion of CSMO, thereby optimizing referral for further examinations and/or treatment.

**Evidence for screening intervals**

Initiation and termination of screening

The risk of developing DR over time was addressed in the Wisconsin Study of Diabetic Retinopathy (WESDR), which was a population based study including 996 patients with type 1 and 1370 patients with type 2 diabetes. A higher prevalence of DR was found in patients with a longer duration of diabetes. In type 1 diabetes, the risk of DR and PDR increased from 17.0% and 0% (duration <5 years) to 97.5% and 25% (duration ≥15 years).(Klein et al. 1984) Corresponding numbers in type 2 diabetes were 28.5% and 2.0% (duration <5 years) to 77.8% and 15.5% (duration ≥15 years) for DR and PDR, respectively.(Klein et al. 1984) Even though WESDR reported an increasing risk of PDR over time, it was also noted that the risk was very low in children (0-15 years of age: 0%, 15-19 years of age: 1.9%). This is in contrast to type 2 diabetes, where PDR can be present at the time of diagnosis given a potentially preclinical, asymptomatic phase prior to diagnosis. Consequently, it is often recommended to defer screening in type 1 diabetes for the first five years of disease and to initiate this no earlier than at the age of nine.(Lueder et al. 2005) However, even though PDR is very unusual in the early years of type 1 diabetes, it should also be taken into account that an early introduction to the screening program may potentially increase the awareness of DR and the importance of screening attendance among patients.

Use of flexible and individualised screening intervals

It has been demonstrated that in comparison with fixed screening intervals, flexible and individualised screening intervals can be used to extend the screening intervals almost three times(Mehlsen et al. 2012) and reduce the number of screening episodes by 40%.(Aspelund et al. 2011; Lund et al. 2016) These benefits are in particular based upon an extended screening interval of more than 12 months in patients

with no or minimal DR.(Kristinsson et al. 1995; Hansson-Lundblad et al. 1997; Olafsdottir & Stefansson 2007; Misra et al. 2009; Agardh & Tababat-Khani 2011; Echouffo-Tcheugui et al. 2013; Taylor-Phillips et al. 2016)

In the Diabetes Control and Complication Trial (DCCT) and the following Epidemiology of Diabetes Interventions and Complications Study (EDIC) it was demonstrated that the screening interval that led to a 5%-risk of progression to PDR or CSMO would be 4 years (no DR), 3 years (mild NPDR), 6 months (moderate NPDR) and 3 months (severe NPDR), respectively.(DCCT. 2017) There was a close correlation between glycaemic regulation and the risk of 5-years progression from no DR to PDR which ranged from 1% to 4.3% for patients with HbA1c of 6% and 10%, respectively.

Patients in need of special care

*Pregnancy*

Risk factors for DR-worsening in pregnancy include long duration of diabetes, high blood sugar, fast glycaemic improvement, high blood pressure, elevated serum cholesterol, impaired kidney function, and high level of pre-existing DR. In addition there is an increased risk of post partum worsening of DR 6-12 months after birth has been given.(DCCT. 2000; Morrison et al. 2016)

In the DCCT it was demonstrated that as compared to non-pregnant women, pregnant women with type 1 diabetes had an increased risk of DR worsening of 1.63 to 2.48 according to level of glycaemic control prior to pregnancy (intensive and conventional control, respectively).(DCCT. 2000) In particular for patients with conventional glycaemic control, there was an increased risk of DR worsening in the second trimester (odds ratio [OR] 4.26) and at 0-6 months (OR 3.16) and 6-12 months (OR 2.87) after birth was given.

*Bariatric surgery*

Bariatric surgery gives a high chance of early weight loss and improved glycaemic control in patients with type 2 diabetes. Remission of diabetes is achieved for most patients. In particular for patients with no or early DR, the level of DR is often stable or improved after surgery.(Cheung et al. 2015; Brynskov et al. 2016; Kim et al. 2017) However, there have been reports of DR worsening after bariatric surgery, especially in patients with higher levels of DR, long duration of diabetes, high levels of HbA1c, blood pressure, serum cholesterol or impaired kidney function.(Kim et al. 2017)

*Dysregulated diabetes*

A higher risk of DR progression has consistently been demonstrated for patients with higher levels of DR, increased HbA1c.(Klein et al. 1984; Klein et al. 1984; Lueder et al. 2005; DCCT. 2017; AAO. 2017) This was in

particular demonstrated in landmark studies like DCCT(DCCT. 1993) and UK Prospective Diabetes Study (UKPDS).(UKPDS. 1998) In DCCT, patients with type 1 diabetes randomised to strict glycaemic control had a 76% lower risk to develop DR in 6.5 years, and in UKPDS strict glycaemic control reduced the 10-year risk of microvascular disease (including retinal photocoagulation) in type 2 diabetes by 25%.
Arterial hypertension has also been identified as a risk factor for DR. This was in particular found in type 2 diabetic patients with uncontrolled hypertension in the UKPDS, who had a 37% higher risk to receive retinal photocoagulation.(UKPDS. 1998) However, in recent years it has been demonstrated that additional blood pressure lowering in patients with type 2 diabetes and low degree of hypertension had no beneficial effect on DR-progression and moderate visual loss.(Chew et al. 2010)

*Vulnerable patients*

Non-attendance in DR-screening is a major concern and one of the most important risk factors for developing sight threatening DR.(Kashim et al. 2018) In a systematic review, Kashim et al identified socio-economic deprivation as the most important risk factor for non-attendance followed by younger age, being part of an ethnical minority and having a poor glycaemic control.(Kashim et al. 2018) It is vital to be aware of these factors in order to keep patients enrolled in screening programs.

**Recommendations regarding screening intervals**

Initiation and termination of screening

1. Patients with type 1 diabetes should be referred for screening after five years of diabetes duration, although no earlier than at the age of 12 years according to Danish diabetes guidelines.(Kristinsson et al. 1995; Lueder et al. 2005; DDD. 2016) Given that DR rarely is seen prior to the age of 18 years in countries with free access to health care services, the frequency of screening between 12 and 18 years should be individualized in consultation with the screening clinic.
2. Patients with type 2 diabetes should be referred for screening at the time of onset.(Klein et al. 1984; Klein et al. 1984; Lueder et al. 2005; Diabetes Prevention Program Research 2007; Donaghue et al. 2014; DDD. 2016; AAO. 2017)
3. Given that it is possible to develop sight threatening DR at all ages, patients should be kept in screening programme for life. This also applies to patients that are only treated with diets and exercise. (Klein et al. 1984; Klein et al. 1984; AAO. 2017)

Use of flexible and individualised screening intervals

1. Flexible and individualized screening intervals should be adopted according to Table 1.

2. In order to determine the optimal screening interval, it is important to determine the regulation of diabetes. Well-regulated diabetes is defined according glycaemic control (HbA1c ≤ 53 mmol/mol (7.0%)) and blood pressure (< 130/80 mmHg).(DCCT. 2017) In the case that the regulation of diabetes is not accounted for, screening intervals should primarily be set in alignment with intervals used for dysregulated diabetes (Table 1).

Patients in need of special care

*Pregnancy*

1. Prior to pregnancy an optimal glycaemic regulation is recommended.
2. Pregnant patients with diabetes should be screened 1) as soon as pregnancy has been established (first trimester), 2) between week 24 and 28 of pregnancy, and 3) 3-6 months post partum.
3. The addition of an extra screening examination between week 32 and 36 of pregnancy should be considered in the case of severe DR, fast progression of DR during pregnancy and for patients with systemic risk factors.
4. Eye screening between week 24 and 28 of pregnancy can be omitted for patients with no DR, good glycaemic regulation, and no systemic risk factors at the first episode of screening during pregnancy.
5. At one year post partum patients should be re-included in the same screening programme as non-pregnant patients.

*Bariatric surgery*

1. It is important to perform a screening examination within 12 months prior to bariatric surgery. Based on this, the risk of post-operative DR worsening can be estimated. In general, patients who have undergone bariatric surgery should have the same screening intervals as the general diabetes population.

*Dysregulated diabetes*

1. Information regarding glycaemic control and blood pressure should be available in order to determine the individualized risk of DR progression and to set the optimal interval for screening. In case of dysregulated diabetes, shorter screening intervals should in general be applied, based on an individual evaluation performed by the ophthalmologist (Table 1).

*Vulnerable patients*

1. Special care should be taken to include and keep patients with unstable adherence to monitoring and treatment in the screening programme. This may include shorter screening intervals and specific care of explaining the rationale behind screening and the importance of attendance (Kashim et al. 2018)

**Evidence regarding automated screening of DR**

Even though it has been demonstrated that DR screening is cost-effective, it is a concern that the number of patients with diabetes is expected to rise rapidly in the coming years.(Guariguata et al. 2014) Screening for DR is a laborious procedure, and the number of patients in need of referral for treatment is relatively low.(Yau et al. 2012; Andersen et al. 2016) With this in mind, upcoming screening strategies like automated screening should be considered.

At present, a number of systems have been built with sophisticated software algorithms based on advanced mathematical models to identify DR lesions. In general, these algorithms have a high sensitivity (87.0-92.5%), but a moderate specificity (49.6-68.8%).(Abramoff et al. 2016; Tufail et al. 2016; Norgaard & Grauslund 2018) In other words, systems are well suited to identify patients in need of additional human grading, but the number of false positives often limits the potential work load reduction.

In recent years, automated screening by deep learning algorithms has also been introduced. In deep learning an algorithm is trained by image recognition. A high number of images are labelled by the level of DR, and with no additional human input the algorithm is trained by self-adjustment of learning parameters. So far these systems have demonstrated impressive results.(Abramoff et al. 2016; Gulshan et al. 2016; Gargeya & Leng 2017) Gulshan et al demonstrated sensitivities and specificities up to 96.1% and 98.5% with area under curve of 0.99 for referable DR.(Gulshan et al. 2016) Even though these results are encouraging, caution should be taken given that results are at present not implementable in a real-life screening setting at present due to difference in screening populations and the fact that deep-learning algorithms are often performed in non-mydriatic one field images that are not sufficient for real-life DR screening.(Aldington et al. 1995; Bursell et al. 2001; Boucher et al. 2003) It is expected that this will be addressed in upcoming studies.

**Recommendations regarding automated screening of DR**

1. At present it is not recommended to include automated retinal image analysis in the screening program. Systems based on algorithms capable of detecting lesions have a sufficient sensitivity but only a moderate specificity. Deep learning systems have a sufficient performance regarding sensitivity and specificity, but additional validation is needed in real-life settings, and in addition

systems should be able to deal with images that visualize a sufficient retinal view for screening purposes.

**Conclusion**

Screening for DR is needed to prevent visual loss and blindness. Implementations of validated national screening programs provide the population with a high quality health care service in order to ensure timely detection and necessary treatment for sight-threatening DR. While the present recommendations have been specified for the Danish health care system, they are evidence based and, hence, may be fully or partially implementable for other health care systems.

The present evidence based Danish guidelines for DR screening include specific recommendations regarding 1) classification scales for DR and DMO, 2) examination methods (including technical specifications, requirements for retinal view and guidelines for inclusion of OCT in screening), 3) screening intervals (with specifications regarding initiation and termination of screening, optimal use of flexible and individualized screening intervals, and guidance for patients in need of special care), and 4) use of automated screening.

In conclusion, the Danish Ophthalmological Society recommends that screening of DR is performed in all patients with diabetes by private practicing ophthalmologists or at hospital based settings using at least two-field fundus photography with a sufficient retinal view. OCT can be included in patients with suspected CSMO in order to improve the diagnostic certainty and optimize referral of patients for hospital based treatment facilities. In order to optimize the use of health care resources, flexible and individualised screening intervals should be used as stratified by level of diabetes control and retinal morphology.

**Conflicts of interests**

None.

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**Table 1**

Recommended intervals until next screening episode in the Danish guidelines for screening of diabetic retinopathy (DR).

| Level of DR* | Sub-classification | Well-regulated diabetes** | Sub-optimal regulation of diabetes or lacking information hereof |
|---|---|---|---|
| 0 – No DR | | 24-48 months*** | 12-24 months |
| 1 – Mild NPDR | No DMO | 24 months | 12 months |
| | DMO without CSMO | 3-6 months (including OCT) | 3 months (including OCT) |
| 2 – Moderate NPDR | No DMO | 12-24 months | 6-12 months |
| | DMO without CSMO | 3-6 months (including OCT) | 3 months (including OCT) |
| 3 – Severe NPDR | No DMO | 3-6 months | 3 months |
| | DMO without CSMO | 3 months (including OCT) | 3 months (including OCT) |
| 4 – PDR | Newly detected or returning | Referral | Referral |
| | Stable (after treatment) | 6-12 months **** | 3-12 months |
| CSMO | Newly detected or returning | Referral | Referral |
| | Stable (after treatment) | 3 months (including OCT) **** | 3 months (including OCT) |

CSMO: Clinically significant diabetic macular oedema. DMO: Diabetic macular oedema (treated or untreated). NPDR: Non-proliferative diabetic retinopathy. OCT: Optical coherence tomography. PDR: Proliferative diabetic retinopathy.

*Level of DR given according to the International Clinical Diabetic Retinopathy Disease Severity Scale. (Wilkinson et al. 2003) **Well-regulated diabetes defined according to most important parameters: HbA1c ≤53 mmol/mol (7.0%) and blood pressure <130/80 mmHg. Level of serum lipids, type and duration of diabetes can be disregarding in this aspect given the low significance of these factors in the determination of the screening interval. (DCCT. 2017) ***An upper interval of 24 months is recommended at time of the

first screening episode. ****An individual estimate can be used to determine the upper limit of the screening interval after sufficient treatment of PDR or CSMO.