CLINICAL PRACTICE GUIDELINE

The Prevention and Treatment of Retinal Complications in Diabetes

Susanne Gabriele Schorr, Hans-Peter Hammes, Ulrich Alfons Müller, Heinz-Harald Abholz, Rüdiger Landgraf, and Bernd Bertram

SUMMARY

Background: Microvascular complications of diabetes mellitus can cause retinopathy and maculopathy, which can irreversibly damage vision and lead to blindness. The prevalence of retinopathy is 9–16% in patients with type 2 diabetes and 24–27% in patients with type 1 diabetes. 0.2–0.5% of diabetics are blind.

Methods: The National Disease Management Guideline on the prevention and treatment of retinal complications in diabetes was updated according to recommendations developed by seven scientific medical societies and organizations and by patient representatives and then approved in a formal consensus process. These recommendations are based on international guidelines and systematic reviews of the literature.

Results: Regular ophthalmological examinations enable the detection of retinopathy in early, better treatable stages. The control intervals should be based on the individual risk profile: 2 years for low-risk patients and 1 year for others, or even shorter depending on the severity of retinopathy. General risk factors for retinopathy include the duration of diabetes, the degree of hyperglycemia, hypertension, and diabetic nephropathy. The general, individually adapted treatment strategies are aimed at improving the risk profile. The most important specifically ophthalmological treatment recommendations are for panretinal laser coagulation in proliferative diabetic retinopathy and, in case of clinically significant diabetic macular edema with foveal involvement, for the intravitreal application of medications (mainly, vascular endothelial growth factor [VEGF] inhibitors), if an improvement of vision with this treatment is thought to be possible.

Conclusion: Regular, risk-adapted ophthalmological examinations, with standardized documentation of the findings for communication between ophthalmologists and the patients' treating primary care physicians/diabetologists, is essential for the prevention of diabetic retinal complications, and for their optimal treatment if they are already present.

▶ Cite this as:
Schorr SG, Hammes HP, Müller UA, Abholz HH, Landgraf R, Bertram B: Clinical practice guideline: The prevention and treatment of retinal complications in diabetes. Dtsch Arztebl Int 2016; 113: 816–23. DOI: 10.3238/arztebl.2016.0816

German Agency for Quality in Medicine (ÄZQ), Berlin: Dr. rer. nat. Schorr, Prof. Dr. med. Hammes, Prof. Dr. med. Müller, Prof. Dr. med. Abholz, Prof. Dr. med. Landgraf, Prof. Dr. Bertram

Diabetic retinopathy and maculopathy are microvascular complications of diabetes that can permanently damage vision, potentially leading to blindness. In Germany, the age- and sex-standardized prevalence of diabetes among persons covered by statutory health insurance is nearly 10% (e1).

In German population-based health care studies, the prevalence of diabetic retinopathy has been found to be

- 9–16% (1–6) in patients with type 2 diabetes and
- 24–27% in patients with type 1 diabetes (1, 7).

Between 0.2% and 0.5% of diabetics are blind (3, 8). Many more have impaired vision because of diabetic retinopathy, although retinopathy does not cause subjective worsening of vision in every case. Any subjectively noticeable impairment of vision may be very significant to the patient. No data are available on the prevalence of impaired or worsened vision, and the available data on retinopathy and blindness can only be considered rough estimates, since all of the underlying studies have methodological limitations.

A National Disease Management Guideline (NDMG) on the prevention and treatment of retinal complications in diabetes was developed in the framework of the national disease management guidelines program of the German Medical Association (*Bundesärztekammer,* BÄK), the National Association of Statutory Health Insurance Physicians (*Kassenärztlicher Bundesvereinigung,* KBV), and the Association of the Scientific Medical Societies in Germany (*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften,* AWMF), with the purposes of

- improving the care of patients with impending or already existing retinal damage due to diabetes,
- defining suitable evidence-based methods of prevention, diagnosis, and treatment, and
- optimizing the flow of information among all physicians involved.

A further goal of the NDMG is to heighten diabetics' awareness of their risk of retinal damage and to encourage them to have regular ophthalmological examinations. The second, comprehensively updated version of the NDMG will be in effect until the next update, or until the end of September 2020, whichever comes first.

Methods

NDMGs are created in accordance with the principles of the G-I-N (Guidelines International Network), the

TABLE 1

Summary of important recommendations

No.	Recommendation	GoR	Consensus (source)
Symptoms and risk factors			
2–1	The patient should have regular ophthalmological examinations, because: – early (initial) stages of diabetic retinopathy may not be noticeable by the patient, – structural changes with implications for treatment often arise before there is any functional impairment, and – treatment in an early stage, if indicated, can improve the functional outcome.	↑↑	expert consensus
2–2	The following are warning signs of retinal complications: – worsening visual acuity despite best refractive correction (glasses/lenses) – difficulty reading or inability to read – impaired perception of color – general worsening of vision (blurred vision) – distorted vision (metamorphopsia) – spots before the eyes due to vitreal hemorrhages; in the extreme case, blindness due to recurrent vitreal hemorrhages or traction retinal detachment	statement	expert consensus
2–3	Important general risk factors for the appearance or progression of diabetic retinopathy and/or maculopathy are: – the duration of diabetes – the degree of hyperglycemia – the presence of / the degree of arterial hypertension – nephropathy Further risk factors are: – pregnancy – in type 1 diabetes: male sex	statement	expert consensus (9–15)
Clinical examination and general treatment strategies			
3–2	On referral to the ophthalmologist, the patient should be told not to drive a motor vehicle for a few hours after the ophthalmological examination because the pupils must be dilated as part of the procedure.	↑↑	expert consensus
3–3	The ophthalmological examination for the detection of retinopathy and/or maculopathy and the determination of its severity should include the following: – measurement of visual acuity – examination of the anterior segment of the eye – binocular retinal examination with the pupils dilated to enable assessment of the peripheral portions of the retinae	↑↑	expert consensus
3–4	The intraocular pressure should be measured in patients with advanced retinopathy. In certain clinical situations, fluorescein angiography is indicated.	↑↑	expert consensus (16, 17)
Interval between ophthalmological examinations			
4–1	The regular ophthalmological examination of diabetics enables the early diagnosis of pathological changes so that the patient's treatment can be adjusted as needed and any indicated ophthalmological treatments can be provided.	statement	expert consensus
4–2	Ophthalmological screening should be performed – in patients with type 2 diabetes shortly after the diagnosis is made (first examination), – in patients with type 1 diabetes after the age of 10 or after they have had diabetes for 5 years.	↑↑	
4–6	Patients should be seen promptly by an ophthalmologist if they develop any of the following new symptoms: – worsening of vision – distorted vision, blurred vision – spots before the eyes	↑↑	expert consensus
Treatment by the primary care physician/diabetologist			
5–2	The patient should be told that the presence of retinopathy is not a contraindication for cardioprotective ASA treatment, as the latter does not elevate the risk of retinal hemorrhage.	↑	expert consensus (18–20)
5–7	If both focal and panretinal laser coagulation are indicated in a patient with combined proliferative diabetic retinopathy and diabetic macular edema without foveal involvement, the maculopathy should be treated first.	↑	expert consensus
Severe complications of proliferative diabetic retinopathy			
5–8	Vitrectomy should be offered to patients who have a non-resorbing vitreal hemorrhage or a present or impending central traction retinal detachment.	↑↑	expert consensus (21–23)

No.	Recommendation	GoR	Consensus (source)
Treatment of clinically significant diabetic macular edema			
…without foveal involvement			
5–9	Focal laser coagulation can be offered to patients with clinically significant diabetic macular edema that spares the fovea but threatens to impair visual acuity.	↔	(24–27)
… with foveal involvement			
5–11	Intravitreal steroid therapy can be offered to patients with an inadequate or absent response to intravitreal therapy with VEGF inhibitors.	↔	expert consensus (28)
Provision of magnifying visual aids			
5–14	Patients who lose the ability to read despite best refractive correction and whose blood glucose levels and ophthalmological findings are stable should be offered magnifying visual aids (either optical or electronic).	↑	expert consensus

Recommendations are numbered as in the guideline. ↑↑ strong recommendation, ↑ weak recommendation, ↔ open recommendation.
ASA, acetylsalicylic acid; GoR, grade of recommendation; PDR, proliferative diabetic retinopathy; VEGF, vascular endothelial growth factor

guideline assessment criteria of the BÄK and KBV (e2), the regulatory framework for guidelines of the AWMF (e3), and the German Guideline Assessment Instrument (*Deutsches Leitlinienbewertungsinstrument,* DELBI) (e4). The basic underlying method is described in a general method report (e5), and the specific method by which this guideline was created is described in the report on this particular NDMG (29).

The first version of this NDMG concerning the prevention and treatment of retinal complications in type 2 diabetes was issued in 2007 (e6). The creation of the second, updated version was organized by the German Agency for Quality in Medicine (*Ärztliches Zentrum für Qualität in der Medizin,* ÄZQ) and took place from November 2013 to September 2015. The guideline was created by a multidisciplinary group *(eBox)*.

Conflicts of interest

The potential conflicts of interest of all participants were determined in a structured procedure specified by the AWMF and published in the guideline report (29). These potential conflicts of interest were openly discussed, and it was not felt that any of the participants needed to be excluded.

Search strategy

In accordance with the basic general procedures of the NDMG program (e5), the guideline-developing group decided to make use of existing evidence-based guidelines from Germany and abroad as the evidence base for this guideline. To identify such guidelines, a search was carried out in the Medline database (via PubMed) and in multiprofessional and mono-disciplinary guideline databases of different guideline providers. Pertinent guidelines were assessed with domains 3 and 6 of the DELBI (e4). Guidelines with a standardized domain value greater than 0.33 were considered in the consensus process. The search strategies, an overview of the process of guideline screening, and the DELBI evaluation are all discussed in the guideline report (9).

Moreover, systematic searches were carried out for aggregated evidence and primary studies on the topics of optical coherence tomography (OCT), intervals between examinations, and special ophthalmological treatments. A three-step procedure was used to search for studies on intervals between examinations *(eFigure 3)*. In the first step, relevant information from the identified guidelines was summarized; in the second step, a search was carried out in Medline (via PubMed) and in the Cochrane Library for systematic reviews; in the third step, the same search strategy was used to find primary studies published after the end of the search period of the most recent, relevant systematic review. All hits were inspected in a two-step procedure, and the identified studies were summarized and assessed in evidence tables. These steps were all carried out by the ÄZQ. Search strategies, an overview of the screening of retrieved literature, and the evidence tables have all been published in the guideline report (29). Further selective literature searches were performed on the epidemiology of retinal complications and the general risk factors for them.

Evidence levels and recommendation grades

The evidence underlying the recommendations in the guideline was graded according to the scheme of the Scottish Intercollegiate Guidelines Network (e7). The grading of the recommendations themselves was loosely based on the GRADE procedure (Grading of Recommendations, Assessment, Development and Evaluation) (e8, e9). Two arrows indicate a strong recommendation, a single arrow indicates a weak recommendation, and a double arrow with arrowheads pointing in both directions indicates an open recommendation. Recommendation grades were assigned in consideration of the strength of the underlying

TABLE 2

The interval between ophthalmological examinations

	General risk	Ophthalmological risk	Interval
Low general risk	low	no	2 years
Other risk constellations	high	no	1 year
Unknown general risk	unknown	no	1 year
Diabetic retinal changes		yes	1 year or less
Diagnosis of type 2 diabetes after the age of 10, or 5 years after the onset of type 1 diabetes			short-term
Visual worsening, distorted vision, blurry vision, spots before the eyes			short-term

evidence, ethical obligations, the clinical relevance of the effect strengths indicated by the studies, the applicability of the study findings to the target group of patients, patient preferences, and the implementability of the recommendations in everyday clinical practice given the existing care structures in Germany.

Formal consensus procedure

In a formal procedure to reach a consensus on the recommendations, consensus conferences took place in which nominal group processes were carried out (e10–e12) under the moderation of the AWMF and the ÄZQ. Of the 32 recommendations, 31 were issued with a strong consensus. The remaining recommendation was issued with 75% agreement and a particular objection from the scientific medical society that voted against it (29). The most important recommendations are reported and explained in the text of this article in the Results section, below. Further recommendations are listed in *Table 1*.

External review

In July 2015, a draft of the guideline was made available on a publicly accessible website (www.versorgungsleitlinien.de) so that comments could be made on it. The start of this external evaluation process was announced in a statement to the press. The assembled comments were considered anonymously. These comments and the resulting decisions and changes are documented in the guideline report (29).

Results

Ophthalmological examinations and general treatment strategies

The goal of screening for diabetic retinal changes and treating them is essentially to limit or prevent subjectively noticeable visual loss. Regular examinations should make it possible to detect retinal complications of diabetes in an early, often asymptomatic stage. Nonetheless, screening for diabetic retinal changes, like all types of screening for the early detection of disease, carries with it a risk of overtreatment, i.e., the treatment of patients whose abnormal ophthalmological findings would never have led to any relevant visual impairment. This fact should be disclosed to patients both in medical consultations and in diabetes training.

The ophthalmological examination is intended to detect diabetic retinopathy and determine its severity. It involves measurement of visual acuity, split-lamp microscopy, and ophthalmoscopy with dilated pupils (30).

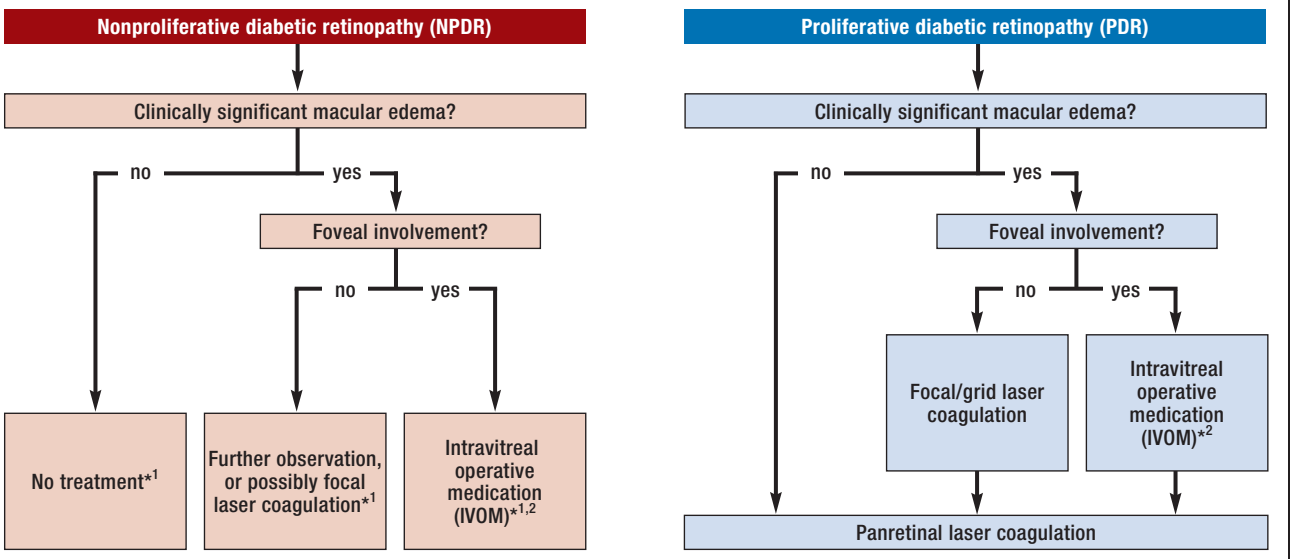
Patients with advanced retinopathy may need further tests such as intraocular pressure measurement or fluorescein angiography. Optical coherence tomography (OCT) can be used to diagnose central, clinically relevant macular edema with 78% sensitivity (95% confidence interval [CI]: [72%; 83%]) and 86% specificity (95% CI: [76%; 93%]) (16). The guideline therefore contains an open recommendation for OCT for the differential-diagnostic assessment of maculopathy potentially requiring treatment. However, OCT should always be used to establish the indication for intravitreal drug administration and to monitor the response to such treatment, as OCT was used for this purpose in all of the pertinent drug-approval studies.

The communication and transmission of findings among primary care physicians/diabetologists and ophthalmologists need to be improved. To this end the authors of the guideline recommend the use of the structured documentation forms developed specifically in the framework of this NDMG *(eFigures 1, 2)*.

The interval between examinations

The patient may have diabetic retinal complications even before receiving the diagnosis of diabetes. Therefore, the international guidelines that were identified and evaluated as methodologically sound all contain a recommendation for an ophthalmological examination as soon as possible after type 2 diabetes is diagnosed (e13–e19). Patients with overt retinopathy should have further examinations at intervals of one year or less (e13–e19). As for the interval between examinations in diabetics without retinopathy, some guidelines recommend examinations once a year (e17, e20) or every two years

FIGURE



Treatment options for diabetic retinopathy and maculopathy

*1 in advanced nonproliferative retinopathy, panretinal laser coagulation may be useful

*2 possibly, focal laser coagulation in addition or as an alternative

(e18, e19), while others recommend adjusting the interval to the individual risk (e13–e16).

A systematic literature search revealed no randomized, controlled, prospective trials on the benefits and harms of different intervals between ophthalmological examinations. The best available evidence is derived from two systematic reviews of observational and modeling studies (31, 32) and two subsequently published observational studies (33, 34).

These studies are of limited informational value for the development of recommendations on intervals between examinations because they were characterized by a wide diversity of intervals, examination techniques, and indications for treatment and referral—and because they also differed in these important respects from the system of ophthalmological care in Germany. These studies also have a risk of bias because of dropouts in the screening groups.

Because of these considerations, the authors of the guidelines recommend that the primary care physician/diabetologist should base the determination of the patient's so-called general risk on the following risk factors, as well as on the patient's overall state of health:

- Type of diabetes
- Duration of diabetes
- Nephropathy
- HbA_{1c} value
- Hypertension.

The patient's general risk status is then documented on a form specially developed for this guideline *(eFigure 1)* to facilitate communication among primary care physicians/diabetologists and ophthalmologists.

In addition to the general risk, each patient has an individual ophthalmological risk that is assessed on the basis of the previous fundoscopic findings, above all any pre-existing retinopathy or maculopathy and their degree of severity. Both of these types of risk are components of the general risk that determines whether the patient should be re-examined by an ophthalmologist once a year (or more often) or once every two years (*Table 2*).

Treatment

Medical treatment by the primary care physician or diabetologist

The primary care physician or the diabetologist is responsible for the treatment of risk factors for retinal complications, including diabetes, arterial hypertension, and renal disease. It was concluded in a recent review that intense antihyperglycemic therapy in patients with type 2 diabetes leads to an approximately 3% absolute reduction of the risk of retinopathy. Intensified antihyperglycemic therapy (e21) was associated with a higher risk of hypoglycemia. Patients with high HbA_{1c} values stand to benefit more from such therapy; for patients with low HbA_{1c} values, whose risk of diabetic complications is significantly lower, the benefits

and risks of treatment intensification must be jointly discussed by the patient and the physician. The effect of intensified treatment of either diabetes or hypertension on retinal complications is but one of many factors (some of them still inadequately defined) to be considered in weighing its benefits against its risks. More information on this topic can be found in the evidence-based guidelines on the individualized treatment of diabetes and its complications (www.diabetes.versorgungsleitlinien.de, www.awmf.org/leitlinien/detail/ll/057–013.html).

Special ophthalmological treatment

The ophthalmologist is responsible for appropriate diagnostic evaluation and treatment corresponding to the patient's stage of disease, and for monitoring the course of diabetic retinopathy and/or maculopathy. The treatment options for diabetic retinal complications include laser therapy and intravitreal operative medication (IVOM). The most important considerations for the choice of treatment are the distinction between proliferative and nonproliferative retinopathy and the presence or absence of clinically significant macular edema, with or without foveal involvement *(Figure)*.

For the comparison of laser treatment versus no treatment or delayed treatment, the literature search revealed a review article (35) that was based, in particular, on the ETDR study (24). No improvement was found in the primary endpoint, moderate worsening of vision (relative risk [RR] 0.99 [0.89; 1.11]), but there was a marked, statistically significant reduction of the risk of severe worsening of vision (RR 0.46 [0.24; 0.86]), progression of diabetic retinopathy (RR 0.49 [0.37; 0.64]), and vitreal hemorrhage (RR: 0.56 [0.37; 0.85]) (35). A differential analysis of proliferative and nonproliferative diabetic retinopathy (PDR and NPDR) was not possible because of the mixed populations in the studies that were included in the analysis. The authors of the review estimate that, in one year, ten of 1000 untreated patients with moderate or severe NPDR will suffer a severe worsening of vision, and that laser coagulation reduces this number to five (95% CI [2; 9], number needed to treat [NNT] 200). For patients with PDR, they estimate that 50 of 1000 untreated patients will suffer severe worsening of vision in one year, and that laser coagulation reduces this number to 23 (95% CI [12; 43], NNT 37) (35). In view of its risk–benefit profile, laser therapy is unrestrictedly recommended only for patients with PDR. Panretinal laser coagulation can, however, be considered for certain patients with severe NPDR who are at high risk.

Foveal involvement is the key factor determining the proper mode of treatment for clinically significant macular edema *(Figure)*. Focal laser therapy is an option if there is no foveal damage, particularly if the patient still has good vision (27). Two review articles were identified in which IVOM with vascular endothelial growth factor (VEGF) inhibitors was compared to laser therapy or placebo for the treatment of clinically significant macular edema with foveal involvement. These studies showed the superiority of VEGF inhibitor treatment to placebo with respect to the number of patients who sustained either a moderate improvement or a moderate worsening of vision (28, 36). The NNT for moderate improvement of vision with VEGF inhibitor treatment, compared to laser treatment alone, was five (RR 3.6 [2.7; 4.8]), while that for the avoidance of moderate worsening of vision was ten (RR 0.11 [0.05; 0.24]) (36). Depending on the specific findings and individual risk–benefit considerations, IVOM may be necessary at once, or a period of further observation may be indicated. The authors of the guideline therefore issued a weak recommendation for the administration of VEGF inhibitors if the morphology of the macular findings suggests that such treatment will improve vision. Nonetheless, the German College of General Practitioners and Family Physicians (*Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin,* DEGAM) disagreed and preferred to restrict this recommendation to patients with current, subjectively symptomatic loss of vision. IVOM should be terminated when no benefit for vision is to be expected (37, 38). If IVOM is not indicated or cannot be performed, laser therapy can be offered instead, despite its low benefit (39, 40).

The coordination of care

The treating primary care physicians/diabetologists are responsible for coordinating the treatment of their diabetic patients *(eFigure 4)*. Ophthalmologists are involved in the treatment of diabetics by providing regular ophthalmological examinations to detect potential retinal damage. Furthermore, they perform ophthalmological examinations as soon as any visual complication arises; whenever necessary (as determined by the ophthalmologists) for closer monitoring; or for ophthalmological treatments or follow-ups after treatment.

The primary care physician/diabetologist also bears the primary responsibility for ensuring that regular ophthalmological examinations are actually performed, particularly in their patients who do not (yet) have diabetic retinopathy.

Conflict of interest statement

Prof. Hammes has served as a paid consultant for Bayer and Boehringer Ingelheim and has received lecture honoraria and reimbursement of travel expenses from Bayer and Novartis. He has received financial support for research (third-party funding) from Boehringer Ingelheim and Sanofi.

Prof. Müller has received financial support for research (third-party funding) from Novo Nordisk, Haemopharm, Abbott, and Pfizer.

Prof. Landgraf has received consultant's fees or lecture honoraria from Lilly Deutschland, MSD, Novo Nordisk Pharma, and Roche Diagnostics.

The other authors state that they have no conflicts of interest.

Manuscript received on 25 July 2016, revised version accepted on 5 September 2016.

Translated from the original German by Ethan Taub, M.D.

KEY MESSAGES

- All diabetics should undergo ophthalmological screening, because diabetic retinal changes can cause significant loss of vision.
- In patients who do not have diabebetic retinopathy, the interval between ophthalmological examinations should be set according to the individual risk profile (2 years for low-risk patients, otherwise 1 year).
- The ophthalmological examination includes measurement of visual acuity, split-lamp microscopy, ophthalmoscopy with dilated pupils, and further tests in certain situations.
- Diabetic retinal changes should be monitored and treated by an ophthalmologist as appropriate for their stage and according to the proper indications.
- Standardized documentation forms should be used for communication between the primary care physician/diabetologist and the ophthalmologist.

REFERENCES

1. Nordrheinische Gemeinsame Einrichtung Disease-Management-Programme, Hagen B, Altenhofen L, et al.: Qualitätssicherungsbericht 2013. Disease-Management-Programme in Nordrhein. Brustkrebs, Diabetes mellitus Typ 1/Typ 2, Koronare Herzkrankheit, Asthma/COPD. Düsseldorf: Nordrheinische Gemeinsame Einrichtung DMP 2014.
2. Hesse L, Grusser M, Hoffstadt K, Jorgens V, Hartmann P, Kroll P: Population-based study of diabetic retinopathy in Wolfsburg. Ophthalmologe 2001; 98: 1065–8.
3. Blum M, Kloos C, Müller N, et al.: Prevalence of diabetic retinopathy. Check-up program of a public health insurance company in Germany 2002–2004. Ophthalmologe 2007; 104: 499–500, 502–4.
4. Icks A, Rathmann W, Haastert B, et al.: Quality of care and extent of complications in a population-based sample of patients with type 2 diabetes mellitus. The KORA Survey 2000. Dtsch Med Wochenschr 2006; 131: 73–8.
5. Huppertz E, Pieper L, Klotsche J, et al.: Diabetes mellitus in German primary care: quality of glycaemic control and subpopulations not well controlled—results of the DETECT study. Exp Clin Endocrinol Diabetes 2009; 117: 6–14.
6. Böhler S, Pittrow D, Pieper L, et al.: Diabetes mellitus in der primärärztlichen Versorgung: Häufigkeit von mikro- und makrovaskulären Komplikationen – Ergebnisse der DETECT Studie. 41. Jahrestagung der Deutschen Diabetes-Gesellschaft. Diabet Stoffw 2006; 1(S1): 1-A315.
7. Hammes HP, Kerner W, Hofer S, Kordonouri O, Raile K, Holl RW: Diabetic retinopathy in type 1 diabetes-a contemporary analysis of 8,784 patients. Diabetologia 2011; 54: 1977–84.
8. Nordrheinische Gemeinsame Einrichtung Disease-Management-Programme: Qualitätssicherungsbericht 2007. Disease Management Programme in Nordrhein. Brustkrebs, Diabetes mellitus Typ 1 / Typ 2, Koronare Herzkrankheit, Asthma / COPD. Düsseldorf: Nordrheinische Gemeinsame Einrichtung DMP 2008.
9. Yau JW, Rogers SL, Kawasaki R, et al.: Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care 2012; 35: 556–64.
10. Bundesärztekammer (BÄK), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF), Kassenärztliche Bundesvereinigung (KBV): Nationale VersorgungsLeitlinie Therapie des Typ-2-Diabetes – Langfassung, 1. Edition. Version 3. http://doi.org/10.6101/AZQ/000203 (last accessed on 5 June 2014).
11. Bundesärztekammer (BÄK), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF), Kassenärztliche Bundesvereinigung (KBV): Nationale VersorgungsLeitlinie Nierenerkrankungen bei Diabetes im Erwachsenenalter – Langfassung, 1. Auflage, Version 5. http://doi.org/10.6101/AZQ/000126 (last accessed on 22 June 2015).
12. Girach A, Vignati L: Diabetic microvascular complications—can the presence of one predict the development of another? J Diabetes Complications 2006; 20: 228–37.
13. DCCT Research Group: Effect of pregnancy on microvascular complications in the diabetes control and complications trial. The Diabetes Control and Complications Trial Research Group. Diabetes Care 2000; 23: 1084–91.
14. Kaaja R, Loukovaara S: Progression of retinopathy in type 1 diabetic women during pregnancy. Curr Diabetes Rev 2007; 3: 85–93.
15. Rasmussen KL, Laugesen CS, Ringholm L, Vestgaard M, Damm P, Mathiesen ER: Progression of diabetic retinopathy during pregnancy in women with type 2 diabetes. Diabetologia 2010; 53: 1076–83.
16. Virgili G, Menchini F, Casazza G, et al.: Optical coherence tomography (OCT) for detection of macular oedema in patients with diabetic retinopathy. Cochrane Database Syst Rev 2015; 1: CD008081.
17. Early Treatment Diabetic Retinopathy Study Research Group (ETDRS): Focal photocoagulation treatment of diabetic macular edema. Relationship of treatment effect to fluorescein angiographic and other retinal characteristics at baseline: ETDRS report no. 19. Early Treatment Diabetic Retinopathy Study Research Group. Arch Ophthalmol 1995; 113: 1144–55.
18. Bergerhoff K, Clar C, Richter B: Aspirin in diabetic retinopathy. A systematic review. Endocrinol Metab Clin North Am 2002; 31: 779–93.
19. American Diabetes Association (ADA): Standards of medical care in diabetes 2014. Diabetes Care 2014; 37: S14–S80.
20. Canadian Diabetes Association (CDA), Advani A, Altomare F, Stockl F: Retinopathy – clinical practice guidelines 2013. Can J Diabetes 2013; 37: S137–41.
21. Diabetic Retinopathy Vitrectomy Study Research Group: Early vitrectomy for severe vitreous hemorrhage in diabetic retinopathy. Four-year results of a randomized trial: Diabetic Retinopathy Vitrectomy Study Report 5. Arch Ophthalmol 1990; 108: 958–64.
22. Helbig H, Kellner U, Bornfeld N, Foerster MH: Vitrektomie bei diabetischer Retinopathie: Ergebnisse, Risikofaktoren, Komplikationen. Klin Monatsbl Augenheilkd 1998; 212: 339–42.
23. Ostri C: Intraocular surgery in a large diabetes patient population: risk factors and surgical results. Acta Ophthalmol 2014; 92 Thesis1:1–13.
24. Early Treatment Diabetic Retinopathy Study Research Group (ETDRS): Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology 1991; 98: 766–85.
25. Early Treatment Diabetic Retinopathy Study Research Group (ETDRS): Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. Early Treatment Diabetic Retinopathy study report number 2. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology 1987; 94: 761–74.
26. Early Treatment Diabetic Retinopathy Study Research Group (ETDRS): Techniques for scatter and local photocoagulation treatment of diabetic retinopathy: Early Treatment Diabetic Retinopathy study report no. 3. The Early Treatment Diabetic Retinopathy Study Research Group. Int Ophthalmol Clin 1987; 27: 254–64.

27. Mohamed QA, Ross A, Chu CJ: Diabetic retinopathy (treatment). BMJ Clin Evid 2011; 2011. BMJ Clin Evid 2011; 2011: 0702.
28. Ford JA, Lois N, Royle P, Clar C, Shyangdan D, Waugh N: Current treatments in diabetic macular oedema: systematic review and meta-analysis. BMJ Open 2013; 3: e002269.
29. Bundesärztekammer (BÄK), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF), Kassenärztliche Bundesvereinigung (KBV): Nationale VersorgungsLeitlinie Prävention und Therapie von Netzhautkomplikationen bei Diabetes – Leitlinien-Report, 2. Edition. Version 2. http://doi.org/10.6101/AZQ/000263 (last accessed on 18 November 2015).
30. Aiello LP, Gardner TW, King GL, et al.: Diabetic retinopathy. Diabetes Care 1998; 21: 143–56.
31. Echouffo-Tcheugui JB, Ali MK, Roglic G, Hayward RA, Narayan KM: Screening intervals for diabetic retinopathy and incidence of visual loss: a systematic review. Diabet Med 2013; 30: 1272–92.
32. Taylor-Phillips S, Mistry H, Leslie R, et al.: Extending the diabetic retinopathy screening interval beyond 1 year: systematic review. Br J Ophthalmol 201; 100: 105–14.
33. Leese GP, Stratton IM, Land M, et al.: Progression of diabetes retinal status within community screening programs and potential implications for screening intervals. Diabetes Care 2015; 38: 488–94.
34. Porta M, Maurino M, Severini S, et al.: Clinical characteristics influence screening intervals for diabetic retinopathy. Diabetologia 2013; 56: 2147–52.
35. Evans JR, Michelessi M, Virgili G: Laser photocoagulation for proliferative diabetic retinopathy. Cochrane Database Syst Rev 2014; 11: CD011234.
36. Virgili G, Parravano M, Menchini F, Evans JR: Anti-vascular endothelial growth factor for diabetic macular oedema. Cochrane Database Syst Rev 2014; (10): CD007419.
37. Mitchell P, Bandello F, Schmidt-Erfurth U, et al.: The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology 2011; 118: 615–25.
38. Korobelnik JF, Do DV, Schmidt-Erfurth U, et al.: Intravitreal aflibercept for diabetic macular edema. Ophthalmology 2014; 121: 2247–54.
39. Diabetic Retinopathy Clinical Research Network, Elman MJ, Bressler NM, et al.: Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2011; 118: 609–14.
40. Diabetic Retinopathy Clinical Research Network: A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. Ophthalmology 2008; 115: Ophthalmology 2008; 115: 1447–59.

Corresponding author
Dr. rer. nat. Susanne Gabriele Schorr
Ärztliches Zentrum für Qualität in der Medizin (ÄZQ)
Tiergarten Tower
Strasse des 17. Juni 106–108
10623 Berlin, Germany
schorr@azq.de

Supplementary material
For eReferences please refer to:
www.aerzteblatt-international.de/ref4816

eBox, eFigures:
www.aerzteblatt-international.de/16m0816

Supplementary material to:

The Prevention and Treatment of Retinal Complications in Diabetes

Susanne Gabriele Schorr, Hans-Peter Hammes, Ulrich Alfons Müller,
Heinz-Harald Abholz, Rüdiger Landgraf, and Bernd Bertram

Dtsch Arztebl Int 2016; 113: 816–23. DOI: 10.3238/arztebl.2016.0816

eREFERENCES

e1. Tamayo T, Brinks R, Hoyer A, Kuß O, Rathmann W: The prevalence and incidence of diabetes in Germany—an analysis of statutory health insurance data on 65 million individuals from the years 2009 and 2010. Dtsch Arztebl Int 2016; 113: 177–82.

e2. Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV): Beurteilungskriterien für Leitlinien in der medizinischen Versorgung – Beschlüsse der Vorstände der Bundesärztekammer und Kassenärztlicher Bundesvereinigung, Juni 1997. Dtsch Arztebl 1997; 94: A-2154–5.

e3. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF): Das AWMF-Regelwerk Leitlinien. München: Zuckschwerdt 2012.

e4. Ärztliches Zentrum für Qualität in der Medizin (ÄZQ), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF): Deutsches Instrument zur methodischen Leitlinien-Bewertung (DELBI). Fassung 2005/2006 + Domäne 8. www.leitlinien.de/mdb/edocs/pdf/literatur/delbi-fassung-2005–2006-domaene-8–2008.pdf (last accessed on 20 July 2016).

e5. Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF): Nationales Programm für VersorgungsLeitlinien. Methoden-Report 4. Auflage. www.leitlinien.de/mdb/downloads/nvl/methodik/mr-aufl-4-version-1.pdf (last accessed on 20 July 2016).

e6. Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF): Nationale VersorgungsLeitlinie Typ-2-Diabetes. Prävention und Therapie von Netzhautkomplikationen – Langfassung, 1. Auflage. Version 2.6. www.leitlinien.de/mdb/downloads/nvl/diabetes-mellitus/archiv/netzhautkomplikationen/dm-netzhautkomplikationen-vers2.6-lang.pdf (last accessed on 20 July 2016).

e7. Harbour R, Miller J: A new system for grading recommendations in evidence based guidelines. BMJ 2001; 323: 334–6.

e8. Atkins D, Best D, Briss PA, et al.: Grading quality of evidence and strength of recommendations. BMJ 2004; 328: 1490–7.

e9. Sackner-Bernstein JD, Kowalski M, Fox M, Aaronson K: Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. JAMA 2005; 293: 1900–5.

e10. Dunham RB: Nominal group technique: A users' guide. Madison: Wisconsin School of Business 1998.

e11. Stinner B, Bauhofer A, Sitter H, Celik I, Lorenz W: Nominaler Gruppenprozess als Konsensusinstrument zur Einschränkung der Therapieheterogenität in einer komplexen „outcome"-Studie. Intensivmed Notfallmed 2000; 37: 30.

e12. Murphy MK, Black NA, Lamping DL, et al.: Consensus development methods, and their use in clinical guideline development. Health Technol Assess 1998; 2: i-88.

e13. American Diabetes Association (ADA): Standards of medical care in diabetes 2014. Diabetes Care 2014; 37: S14–80.

e14. Canadian Diabetes Association (CDA), Advani A, Altomare F, Stockl F: Retinopathy—clinical practice guidelines 2013. Can J Diabetes 2013; 37: S137–41.

e15. Canadian Ophthalmological Society, Hooper P, Cruess A, et al.: Canadian Ophthalmological Society evidence-based clinical practice guidelines for the management of diabetic retinopathy. Can J Ophthalmol 2012; 47: S1–54.

e16. Bundesärztekammer (BÄK), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF), Kassenärztliche Bundesvereinigung (KBV): Nationale VersorgungsLeitlinie Nierenerkrankungen bei Diabetes im Erwachsenenalter – Kurzfassung, 1. Auflage, Version 5. http://doi.org/10.6101/AZQ/000127 (last accessed on 20 July 2016).

e17. National Institute for Clinical Excellence (NICE): Type 2 diabetes. National clinical guideline for management in primary and secondary care (update). London: Royal College Of Physicians 2008.

e18. Scottish Intercollegiate Guidelines Network (SIGN): Management of diabetes. A national clinical guideline. Edinburgh: SIGN 2010.

e19. Veterans Health Administration and Department of Defense (VADoD): VADoD clinical practice guideline for the management of diabetes mellitus. Version 4.0. healthquality.va.gov/guidelines/CD/diabetes/DM2010_FUL-v4e.pdf (last accessed on 20 July 2016).

e20. Ryden L, Grant PJ, Anker SD, et al.: ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J 2013; 34: 3035–87.

e21. Hemmingsen B, Lund SS, Gluud C, et al.: Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. Cochrane Database Syst Rev 2013; 11: CD008143.

eBOX

Editors and authors of the National Disease Management Guideline on the prevention and treatment of retinal complications in diabetes

Editors

- German Medical Association (*Bundesärztekammer,* BÄK), Conference of German State Medical Associations *(Arbeitsgemeinschaft der Deutschen Ärztekammern)*
- National Association of Statutory Health Insurance Physicians (*Kassenärztliche Bundesvereinigung,* KBV)
- Association of Scientific Medical Societies in Germany (*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften,* AWMF)

and

- Drug Commission of the German Medical Association (*Arzneimittelkommission der deutschen Ärzteschaft,* AkdÄ)
- German College of General Practitioners and Family Physicians (*Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin,* DEGAM)
- German Diabetes Society (*Deutsche Diabetes Gesellschaft,* DDG)
- German Society for Internal Medicine (*Deutsche Gesellschaft für Innere Medizin,* DGIM)
- German Ophthalmological Society (*Deutsche Ophthalmologische Gesellschaft,* DOG)
- Association of Diabetes Counseling and Training Professions in Germany (*Verband der Diabetesberatungs- und Schulungsberufe in Deutschland,* VDBD)
- National Association of Self-Help Groups (*Bundesarbeitsgemeinschaft Selbsthilfe e. V.,* BAG Selbsthilfe)

Authors of the second edition

- Prof. Dr. med. Ulrich A. Müller (AkdÄ)
- Dr. med. Til Uebel, Prof. Dr. med. Heinz Harald Abholz (DEGAM)
- Prof. Dr. med. Rüdiger Landgraf, Prof. Dr. med. Hans-Peter Hammes (DDG)
- Prof. Dr. med. Hans-Peter Hammes (DGIM)
- Prof. Dr. med. Bernd Bertram, Prof. Dr. med. Hansjürgen Agostini, PD Dr. med. Klaus-Dieter Lemmen (DOG)
- Dr. rer. medic. Nicola Haller (VDBD)
- Hannelore Loskill (BAG Selbsthilfe) – patient representative

Methodological supervision and coordination

- Dr. Susanne Schorr, Corinna Schaefer, Dr. med. Carmen Khan, Peggy Prien, Prof. Dr. rer. nat. Dr. med. Günter Ollenschläger (ÄZQ)
- Prof. Dr. med. Ina Kopp, Dr. med. Monika Nothacker (AWMF)

ÄZQ, German Agency for Quality in Medicine *(Ärztliches Zentrum für Qualität in der Medizin)*

Health insurance carrier or other payor		
Name of insuree (last name, first name)		Date of birth
Insurance carrier no.	Insuree no.	Insurance class
Processing center no.	Physician no.	Date

Information from the primary care physician/diabetologist to the ophthalmologist

The overall risk of a retinal complication in a patient with diabetes is composed of
- the general risk, as assessed by the primary care physician/diabetologist
- the ophthalmological risk, as assessed by the ophthalmologist.

This information sheet is to be used by the primary care physician/diabetologist to document the assessment of the general risk. The overall risk can only be estimated once the ophthalmologist has also assessed the ophthalmological risk.

Type of diabetes:	☐ Type 1 diabetes ☐ Type 2 diabetes
Duration of diabetes (time since diagnosis):	.....years (threshold*: >10 years)
HbA_{1c}:	.....% (threshold*: >7.5%)
Representative blood pressure measurement:	.....mmHg (threshold*: >140/85 mmHg)
Existing vascular complication, esp. renal:	☐ Yes ☐ No
Integrated assessment* of the general risk based on the above risk factors and the patient's general state of heath:	☐ Low risk ☐ Elevated risk

*Threshold values for elevated risk. A single risk factor that barely exceeds the threshold value does not lead to any substantial elevation of the risk; thus, there must always be an integrated assessment of all risk factors taken together.

Further general medical/diabetological diagnoses and remarks:

The ophthalmologist needs to dilate the pupils to perform a retinal examination. The patient should be informed that he/she will not be able to drive a vehicle for two to four hours afterward.

Date; signature and stamp of primary care physician/diabetologist

eFigure 1: Documentation form for communication from the primary care physician/diabetologist to the ophthalmologist

Health insurance carrier or other payor		
Name of insuree (last name, first name)		Date of birth
Insurance carrier no.	Insuree no.	Insurance class
Processing center no.	Physician no.	Date

Information from the ophthalmologist

The fundi should be examined after dilatation of the pupils.

	Right eye	Left eye
Anterior segments: rubeosis iridis	☐	☐
Stage of retinopathy		
No diabetic retinopathy	☐	☐
Mild or moderate diabetic retinopathy	☐	☐
Severe nonproliferative diabetic retinopathy	☐	☐
Proliferative diabetic retinopathy	☐	☐
Clinically significant diabetic macular edema	☐	☐
Findings compared to most recent prior examination		
Unchanged	☐	☐
Improved	☐	☐
Worse	☐	☐
Prior findings unknown	☐	☐
Procedure		
OCT	☐	☐
Fluorescein angiography	☐	☐
Panretinal laser coagulation	☐	☐
Focal laser coagulation at the posterior pole of the eye	☐	☐
Intravitreal drug application	☐	☐
Vitrectomy	☐	☐
Best corrected visual acuity (distance):	_____	_____

Further ophthalmological diagnoses/remarks:

Next follow-up examination for diabetic retinopathy:

☐ **in 2 years**

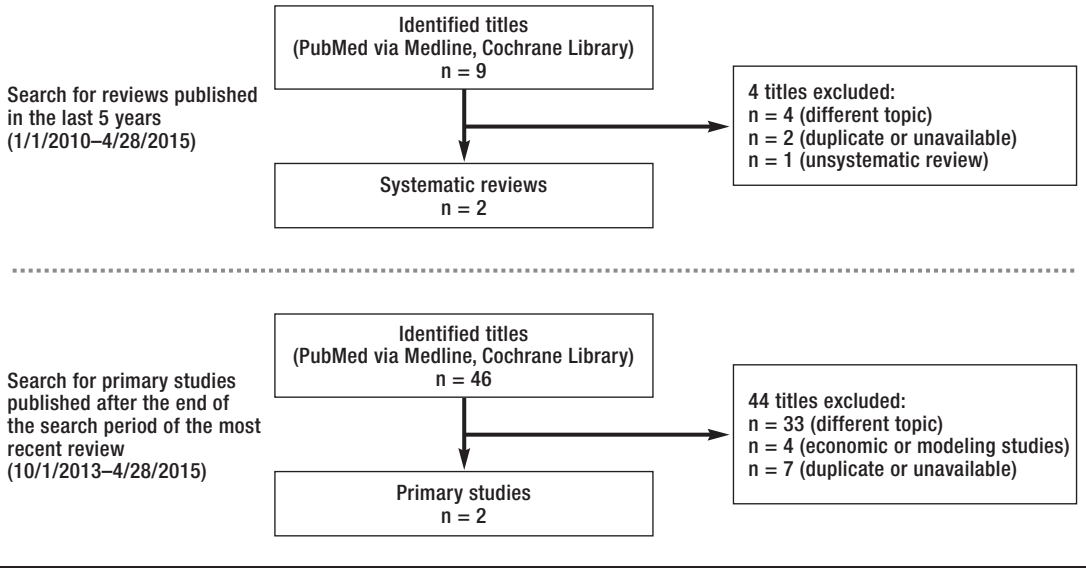
☐ **in 1 year**

☐ **in ..... months**

Date; signature and stamp of ophthalmologist

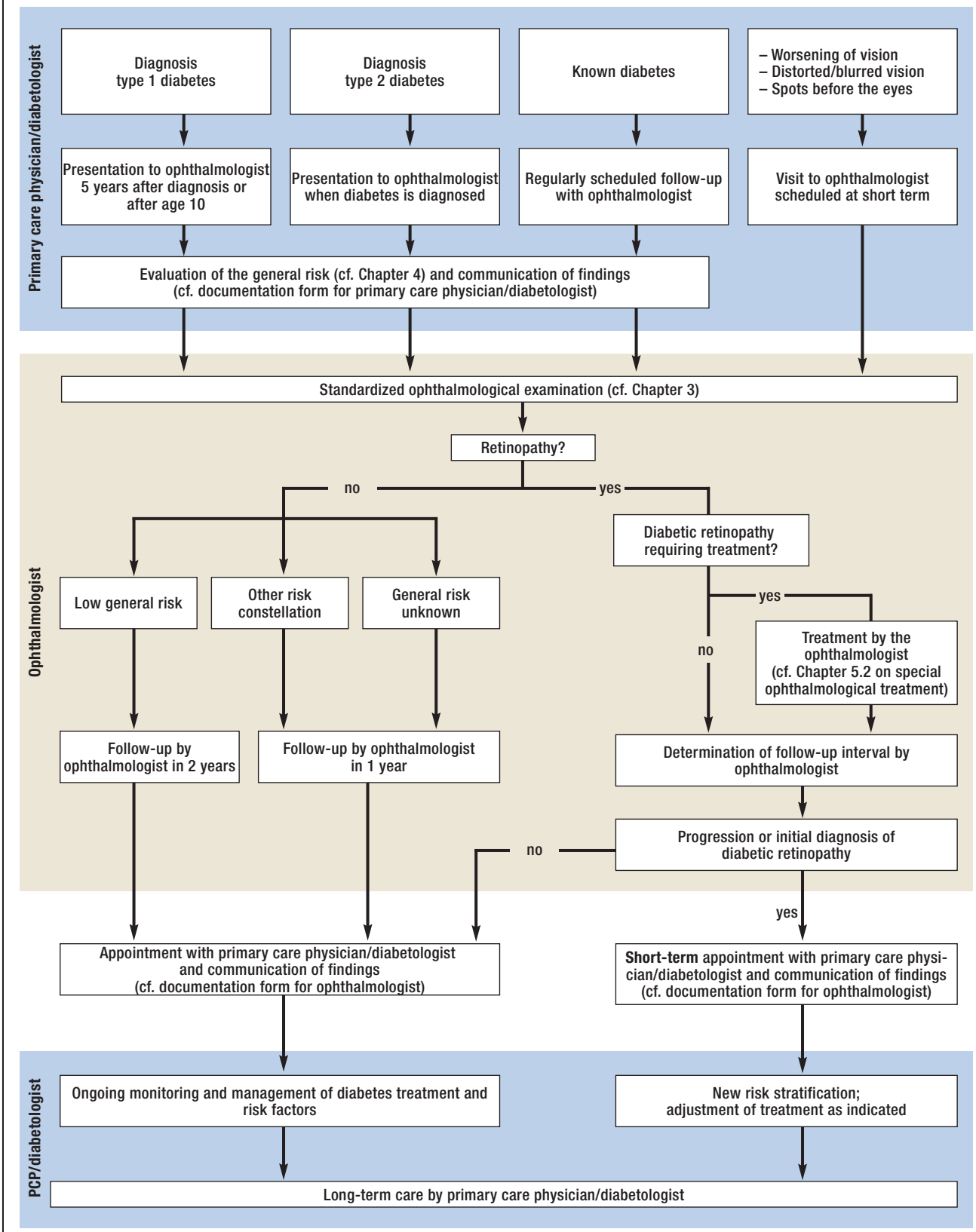
eFigure 2: Documentation form for communications from the ophthalmologist

eFIGURE 3



Search strategy for studies on the interval between ophthalmological examinations

eFIGURE 4



Care coordination flowchart. The chapter references are to the corresponding chapters in the long version of the National Disease Management Guideline.
PCP, primary care physician