Diabetic Retinopathy

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Diabetic retinopathy is a well-characterized, sight-threatening, chronic ocular disorder that eventually develops, to some degree, in nearly all patients with diabetes. Diabetic retinopathy is characterized by gradually progressive alterations in the retinal microvasculature, leading to areas of retinal nonperfusion, increased vasopermeability, and the pathologic intraocular proliferation of retinal vessels. The complications associated with increased vasopermeability and uncontrolled neovascularization can result in severe and permanent visual loss. With experienced ophthalmic evaluation, diabetic retinopathy can be detected in its early stages. Therapies exist that can be remarkably effective when administered at the appropriate time in the disease process. In addition, improvement of systemic glycemic control is associated with a delay in onset and a slowing of the progression of diabetic retinopathy. Nevertheless, diabetic retinopathy remains the leading cause of legal blindness among Americans of working age. Fortunately, there are extensive data available on most aspects of this disease from numerous epidemiological studies and clinical trials that provide a solid basis for developing the evaluation and management guidelines presented below. With appropriate medical and ophthalmologic care, >90% of visual loss resulting from diabetic retinopathy can be prevented (1).

GENERAL PURPOSE AND GOALS — The primary reason for the evaluation and management of diabetic retinopathy is to prevent, reverse, or delay the visual loss associated with this disease process. Appropriate management involves seven primary goals:

1. Identify individuals at risk of developing diabetic retinopathy
2. Assure appropriate systemic glycemic control
3. Provide appropriate lifelong evaluation of retinopathy progression
4. Provide therapy to individuals at risk of visual loss
5. Minimize the associated visual and functional side effects of this therapy
6. Provide rehabilitation for those with visual loss from the disease
7. Educate and involve the patients in the management of their disease

EPIDEMIOLOGY — Sixteen million Americans have diabetes, but only one-half are aware that they have the disease (2,3). Diabetic retinopathy is the leading cause of new cases of legal blindness among Americans between the ages of 20 and 74 years (4). There are two distinct forms of diabetes: type 1 (also known as juvenile-onset or insulin-dependent diabetes mellitus [IDDM]) and type 2 (also known as adult-onset or non-insulin-dependent diabetes mellitus [NIDDM]). As an operational definition, diagnosis of type 1 diabetes generally occurs before age 30 years, while identification of type 2 diabetes primarily occurs at or after age 30 years. There is a higher risk of more frequent and severe ocular complications in type 1 diabetes (5). Approximately 25% of type 1 patients have retinopathy after 5 years, increasing to 60 and 80% after 10 and 15 years, respectively. However, since there are more type 2 diabetes cases than type 1 diabetes cases, type 2 diabetes accounts for a higher proportion of patients with visual loss. The most threatening form of retinopathy, called proliferative diabetic retinopathy (PDR) (see APPENDIX: GLOSSARY), is present in ~25% of type 1 patients with diabetes of 15 years' duration (6).

IMPACT — There are an estimated 700,000 people with PDR: 130,000 with high-risk PDR, 500,000 with macular edema, and 325,000 with clinically significant macular edema (CSME) in the U.S. (7,8,12–14). An estimated 63,000 cases of PDR, 29,000 high-risk PDR, 80,000 macular edema, 56,000 CSME, and 5,000 new cases of legal blindness occur each year as a result of diabetic retinopathy (7,8). Blindness has been estimated to be 25 times more common in people with diabetes than in those without the disease (9,10). Estimates of the medical and economic impact of retinopathy-associated morbidity have been performed using computer simulations. The effect of applying accepted methods for evaluating and treating diabetic retinopathy have been studied for both type 1 and type 2 diabetes (11–15). The models incorporated the recommended evaluation guidelines of the Public Health Committee of the American Academy of Ophthalmology, cost estimates based on published Medicare reimbursement data, and treatment recommendations and efficacy derived from the Diabetic Retinopathy Study (DRS) (16–18) and the Early Treatment Diabetic Retinopathy Study (ETDRS) (19–21).

The models predict that, in the absence of good glycemic control, over their lifetime, 72% of patients with type 1 diabetes will eventually develop PDR, requiring panretinal photocoagulation, and that 42%

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Abbreviations: CSME, clinically significant macular edema; DCCT, Diabetes Control and Complications Trial; DRS, Diabetic Retinopathy Study; DRVS, Diabetic Retinopathy Vitrectomy Study; ETDRS, Early Treatment Diabetic Retinopathy Study; IRMA, intraretinal microvascular abnormality; NPDR, nonproliferative diabetic retinopathy; NVD, neovascularization at the optic disk; NVE, neovascularization elsewhere in the retina (i.e., not at the optic disk); PDR, proliferative diabetic retinopathy.

Table 1—*Stages of diabetic retinopathy*

Stage	Principal clinical findings
Early stages	Retinal vascular microaneurysms and blot hemorrhages
Mild NPDR	Increased retinal vascular permeability
	Cotton wool spots
Middle stages	Venous caliber changes or beading
Moderate NPDR	IRMA
Severe NPDR	Retinal capillary loss
Very severe NPDR	Retinal ischemia
	Extensive intraretinal hemorrhages and microaneurysms
Advanced stages	NVD
PDR	NVE
	Neovascularization of the iris
	Neovascular glaucoma
	Preretinal and vitreous hemorrhage
	Fibrovascular proliferation
	Retinal traction, retinal tears, retinal detachment

will develop macular edema (8). If type 1 patients receive treatment as recommended in the clinical trials, as of 1990, there is a predicted cost of $966 per person-year of vision saved from PDR and $1,120 per person-year of central acuity saved from macular edema. These expenditures are less than the cost of a year of Social Security disability payments and lost tax revenues to the federal government for those disabled by vision loss. Current estimates are that only 60% of patients in need of retinopathy treatment are receiving such care (22). Therefore, appropriate treatment for type 1 patients results in a savings of $101.0 million and 47,374 person-years of sight annually at the current 60% treatment implementation level (12). Similarly, treatment of patients with type 2 diabetes generates an annual savings of $247.9 million and 53,986 person-years of sight at current treatment levels (13). If all patients with both type 1 and type 2 diabetes were to receive currently suggested care, savings of $624.0 million and 173,540 person-years of sight would be realized. The indirect costs, in terms of lost productivity and human suffering, are even greater.

The Diabetes Control and Complications Trial (DCCT) showed that both the rate of development of any retinopathy, as well as the rate of retinopathy progression once it was present, was significantly reduced after 3 years of intensive insulin therapy (23–25). Applying DCCT intensive insulin therapy to all people in the U.S. with IDDM would result in a gain of 920,000 person-years of sight (26), although the costs of intensive therapy are three times that of conventional therapy (83).

NATURAL HISTORY — Some degree of retinopathy occurs in nearly all patients with diabetes of ≥20 years' duration (6). The natural history of retinopathy has been evaluated in four national multicenter clinical trials: the DRS (16–18), the ETDRS (19–20), the Diabetic Retinopathy Vitrectomy Study (DRVS) (27,28), and the DCCT (23–25). Principal clinical findings of the various stages of diabetic retinopathy are listed in Table 1.

Background diabetic retinopathy and preproliferative diabetic retinopathy are outdated terms referring to general levels or stages of nonproliferative diabetic retinopathy (NPDR). Since this terminology is not closely associated with disease progression, it should no longer be used and has been replaced by the various levels of NPDR, which correlate closely with disease progression.

Preclinical changes in diabetic retinopathy include alterations in retinal blood flow (29) and loss of retinal pericytes (30). The earliest clinical stages of diabetic retinopathy are characterized by microvascular abnormalities, including microaneurysms, intraretinal hemorrhages, and cotton wool spots, which represent stasis of axoplasmic flow due to ischemia of the nerve fiber layer (10,31). Increased vascular permeability can occur at this or any later stage, resulting in fluid accumulation in the retina (19). As the disease progresses, gradual loss of the retinal microvasculature occurs, resulting in retinal ischemia. Venous caliber abnormalities, intraretinal microvascular abnormalities (IRMAs), and more severe vascular leakage are common reflections of increasing retinal nonperfusion (31).

The most advanced stages of diabetic retinopathy are characterized by the onset of ischemia-induced new vessel proliferation at the optic disk (NVD) or elsewhere in the retina (NVE). The new vessels are fragile and prone to bleed, resulting in vitreous hemorrhage. With time, the neovascularization tends to undergo fibrosis and contraction, resulting in retinal traction, retinal tears, vitreous hemorrhage, and/or retinal detachment. New vessels can also arise on the iris or in the trabecular meshwork of the anterior chamber, resulting in neovascular glaucoma.

Retinopathy before the development of retinal neovascularization is termed NPDR (21). Once proliferation of new retinal vessels occurs, it is referred to as PDR (16,21).

CAUSES OF VISUAL LOSS — The predominant cause of visual loss in diabetic retinopathy is CSME or PDR, which results in tractional retinal detachment or nonclearing vitreous hemorrhage. PDR associated with defined retinal lesions that increase the likelihood of severe visual loss is termed high-risk PDR and prompt treatment is indicated (17,18). Treatment modalities are thus primarily directed toward preventing these complications. Several clinical trials have addressed the progression rates, visual outcomes, and treatment efficacy for these conditions. Detailed results from these studies are presented under SPECIFIC CLINICAL TRIALS OUTCOMES. Common threats to vision in diabetic retinopathy and the usual initial treatment supported by clinical trial data are detailed in Table 2.

PROVIDERS OF EYE CARE FOR PATIENTS WITH DIABETES — The onset of diabetic retinopathy can be delayed and the progression of diabetic retinopathy greatly slowed with glucose concentrations maintained in the near-normal range. However, strict glycemic control may be difficult, and some individuals may still develop sight-threatening diabetic retinopa-

thy. Most of the blindness associated with advanced stages of retinopathy can be averted with appropriate and timely diagnosis and therapy. Unfortunately, many diabetic patients do not receive adequate eye care at an appropriate stage in their disease (22,32). In one study, 55% of patients with high-risk PDR and CSME had never had laser photocoagulation (22). In fact, 11% of type 1 and 7% of type 2 patients with high-risk PDR necessitating prompt treatment had not been examined by an ophthalmologist within the past 2 years (32).

Dilated ophthalmic examination is superior to nondilated evaluation because only 50% of eyes are correctly classified for presence and severity of retinopathy through undilated pupils (33,34). Appropriate ophthalmic evaluation entails a directed detailed history and comprehensive ocular examination, including pupillary dilation, slitlamp biomicroscopy, examination of the retinal periphery with indirect ophthalmoscopy or mirrored contact lens, and sometimes gonioscopy as detailed below (35–38). Indeed, 27% of retinal abnormalities are found outside the central macular region (34). Because of the complexities of the diagnosis and treatment of PDR and CSME, ophthalmologists with specialized knowledge and experience in the management of diabetic retinopathy are required to determine and provide appropriate surgical intervention (39).

Thus, it is recommended that all patients with diabetes should have dilated ocular examinations by an experienced eye care provider (ophthalmologist or optometrist) and should be under the direct or consulting care of an ophthalmologist experienced in the management of diabetic retinopathy at least by the time severe diabetic retinopathy or diabetic macular edema is present.

PROVIDERS OF MEDICAL CARE FOR PATIENTS WITH DIABETES

— Diabetes is a multisytem disease requiring the regular care of a general physician, internist, or endocrinologist. A team approach involving multiple health care specialists, such as clinical endocrinologists, nutritionists, diabetes nurse educators, exercise physiologists, nephrologists, and others, may be necessary for optimal care of the patient with diabetes. Careful management of the metabolic and pathologic aspects of diabetes also positively impacts on the patient's visual prognosis, since such systemic processes as renal function (40), blood pressure (41), serum lipid concentrations (42), and glycemic control (24,25,84) affect the onset, progression, and prognosis of diabetic retinopathy. In addition, the team approach may help overcome barriers that often interfere with the delivery of appropriate ophthalmic care, including lack of patient-perceived eye problems, lack of health insurance coverage, competing priorities for patient resources, and patient fear of discovering eye problems (43,44).

Table 2— *Threats to vision from diabetic retinopathy and common initial treatment*

Complication threatening vision	Common initial treatment
CSME	Focal or grid laser photocoagulation surgery
High-risk PDR	PRP
Vitreous hemorrhage	Careful observation or vitrectomy
Traction and/or rhegmatogenous retinal detachment	Vitrectomy
Traction distorting macula	Vitrectomy
Neovascular glaucoma	PRP and/or cryotherapy and intraocular pressure management

PRP, scatter (panretinal) photocoagulation surgery.

COMPREHENSIVE EYE EVALUATION

— A comprehensive eye examination is recommended for any patient with or without diabetes being seen either for the first time or after an extended duration (37,38) and is of particular importance for patients with diabetes (38). Such an evaluation has four major components: history, examination, diagnosis, and treatment. As with any comprehensive eye examination, a thorough history should be obtained from the patient with diabetes. For patients with diabetes, particular emphasis should be placed on determining the type of diabetes, age at diabetes onset, duration of diabetes, degree of glycemic control, concurrent complications (neuropathy, nephropathy, retinopathy, cardiovascular disease, etc.), associated systemic findings (hypertension, elevated lipids or cholesterol, pregnancy status, onset of puberty, obesity, etc.), compliance with their general medical follow-up, and the extent of patient involvement in and understanding of their disease process.

The fundamentals of a comprehensive eye examination for the nondiabetic patient have been detailed by the American Academy of Ophthalmology and the American Optometric Association (37,38). The examination of the patient with diabetes should be similar, with additional emphasis on portions of the examination that relate to problems particularly relevant to patients with diabetes, as shown in Table 3. Thus, the examination should include the items listed in the table, but is not limited to them.

Additional procedures and further evaluation should be tailored to the abnormalities and findings identified during the examination. Diagnosis and treatment, as well as the indications for ancillary testing, such as fundus photography and fluorescein angiogram, are detailed below.

INITIAL EYE EVALUATION AND MINIMAL FOLLOW-UP

— Although ~80% of type 1 patients have retinopathy after 15 years of disease, only ~25% have any retinopathy after 5 years (6). Puberty and pregnancy can accelerate retinopathy progression. The onset of vision-threatening retinopathy is rare in children before puberty regardless of the duration of diabetes (6,48–51). However, if diabetes is diagnosed between the ages of 10 and 30 years, significant retinopathy may arise within 6 years of the disease (7). However, there are as yet no published data demonstrating that there is a statistically significant increased risk of retinopathy at 5 vs. 3 years after diabetes diagnosis in this age-group. The prevalence of PDR is <2% at 5 years and 25% by 15 years (6). Thus, the current recommendation is for initial ophthalmologic examination within 3–5 years after diagnosis of diabetes once patients are 10 years of age or older (52).

For type 2 diabetes, however, the onset date of diabetes is frequently not precisely known, and thus more severe disease can be observed soon after diagnosis. Up to 3% of patients first diagnosed after age 30 years (type 2) can have CSME or high-risk PDR at the time of initial diagnosis of diabetes

Table 3—*Elements of an eye examination with particular relevance to patients with diabetes*

Examination	Examples of particular relevance to patient with diabetes
Best corrected visual acuity	Quantitates level of high-contrast, high-frequency visual function. Decline can indicate onset of visually significant macular edema, vitreous hemorrhage, cataract, macular traction detachment, etc.
Ocular alignment and motility	Evaluates function of oculo-motor cranial nerves. Abnormalities can indicate ocular nerve palsies associated with diabetic nerve damage to cranial nerves III, IV, and VI.
Pupil reactivity and function	Evaluates pupil-motor pathway and structural integrity of the iris. Abnormalities can indicate neuropathy, iris neovascularization, or afferent pupillary defect.
Visual fields	Evaluates possible defects in peripheral vision. Confrontational fields provide a qualitative assessment, and perimetry provides a quantitative assessment. Abnormalities can indicate vitreous/preretinal hemorrhage, retinal detachment, vascular occlusion, etc.
Intraocular pressure	Measurement of intraocular pressure. Applanation tonometry is preferred. Abnormalities can indicate possible neovascular or open angle glaucoma.
Slitlamp examination	
Cornea	Assessment of ocular surface. Abnormalities can indicate epithelial abnormalities, defects, or infection.
Iris	Assess iris and when indicated gonioscopy for possible angle closure or angle neovascularization. Abnormalities can indicate neovascular glaucoma.
Lens	Assess lens nucleus, cortex, and posterior capsule. Abnormalities can indicate cataract.
Vitreous	Assess clarity and character of vitreous gel. Abnormalities can indicate vitreous hemorrhage (red cells), retinal tear or detachment (pigment cells), or possible vitreoretinal traction (posterior vitreous detachment).
Dilated fundus examination Slitlamp biomicroscopy and binocular indirect ophthalmoscopy	Assess presence, location, and extent of retinal-vitreal disease. Abnormalities include retinal thickening, hard exudates, retinal hemorrhages and microaneurysms, IRMA, venous beading, NVD or NVE, vitreous or preretinal hemorrhage, retinal traction, nonperfusion, retinal tears or holes, and tractional or rhegmatogenous retinal detachment.

(45). Thus, initial ophthalmic examination is recommended beginning at the time of diagnosis of type 2 diabetes (46,47).

Diabetic retinopathy can also become particularly aggressive during pregnancy in patients with diabetes (53–55). Ideally, patients with diabetes who are planning pregnancy should have a comprehensive eye examination within 1 year before conception. Patients who become pregnant should have a comprehensive eye examination in the 1st trimester of pregnancy. Close follow-up throughout pregnancy is indicated, with subsequent examinations determined by the findings present at the 1st trimester examination (46,52). This guideline does not apply to women who develop gestational diabetes because such individuals are not at increased risk of developing diabetic retinopathy.

Thus, the recommendations for initial evaluation of diabetic retinopathy vary according to the patient's age at diagnosis and medical and pregnancy status, as outlined in Table 4. Minimum requirements for follow-up examinations are also derived from these prevalence data, assuming no abnormal findings. Abnormal findings necessitate more frequent follow-up as detailed under MANAGEMENT OF DIABETIC RETINOPATHY. Symptoms and findings that suggest a higher risk of complication and should trigger more rigorous follow-up

Table 4—*Ophthalmologic examination schedule*

Patient group	Recommended first examination	Minimum routine follow-up*
29 years or younger†	Within 3–5 years after diagnosis of diabetes once patient is age 10 years or older	Yearly
30 years and older†	At time of diagnosis of diabetes	Yearly
Pregnancy in pre-existing diabetes	Prior to conception and during 1st trimester	Physician discretion pending results of 1st-trimester exam

*Abnormal findings necessitate more frequent follow-up. †As indicated in WESDR, these are operational definitions of type 1 and type 2 diabetes based on age (age <30 years at diagnosis, type 1, age ≥30 years at diagnosis, type 2) and not pathogenetic classification (6).

include floaters, distortion of vision, difficulty with night vision or reading vision, poor systemic control, advanced nephropathy, and concurrent hypertension.

Timely evaluation and treatment are critical for prevention of visual loss. Although follow-up may not be indicated for several years according to average disease progression data, extending the time until follow-up must be weighed against possible loss to follow-up in the intervening period. Cost-benefit analyses have demonstrated that initiating ophthalmologic examinations on diagnosis of diabetes for patients with type 1 diabetes, instead of after a 5-year deferral, would be cost-effective for the federal government if only 1 patient in 56 who would otherwise have been lost to follow-up instead receives appropriate care (12).

Data from a population-based cohort study show that patients with type 2 diabetes who receive ETDRS standard seven-field stereoscopic-color fundus photographs that reveal no retinopathy when evaluated by a skilled reader do not generally require another retinopathy examination for 4 years because of low risk of disease progression (56,57). However, patients with gross proteinuria or poor glycemic control (>2 SD from the mean of the nondiabetic population) should have annual examinations even if the initial review of ETDRS standard seven-field stereoscopic-color fundus photographs reveal no retinopathy. These data, indicating a low 4-year risk of developing clinically important retinopathy in patients with type 2 diabetes, are derived from a study that evaluated white northern European extraction patients with diabetes living in an 11-county area in southern Wisconsin. These results may not be applicable to black, Hispanic, Asian-American, or other populations in which it is unknown whether their retinopathy progresses in the same manner. In addition, precise photographic technique and evaluation must be accomplished to recommend the extended examination schedule. The potential for patient loss to follow-up induced by a 4-year hiatus from initial ophthalmic evaluation introduces further uncertainty. The recommendations for initial and subsequent ophthalmologic evaluation of patients with diabetes are indicated in Table 4.

Table 5—*Progression to PDR by NPDR level*

Retinopathy level	Chance of high-risk PDR in 1 year	Chance of high-risk PDR in 5 years
Mild NPDR	1	16
Moderate NPDR	3–8	27–39
Severe NPDR	15	56
Very severe NPDR	45	71
PDR with less than high-risk characteristics	22–46	64–75

Data are %. From the ETDRS Group (21).

NPDR LEVELS AND DISEASE PROGRESSION

— NPDR is categorized into four levels of severity based on clinical findings compared with stereo fundus photographic standards (31). The extent of hemorrhages and microaneurysms, presence of venous beading, and extent of IRMAs are the principal indicators of NPDR level (21,31). These levels are termed mild, moderate, severe, and very severe NPDR. Progression of NPDR to the visually threatening level of high-risk PDR is closely correlated with NPDR level, as shown in Table 5, and thus these data are used as guidelines for setting appropriate follow-up intervals (see MANAGEMENT OF DIABETIC RETINOPATHY). NPDR is best evaluated by dilated examination using slitlamp biomicroscopy and/or stereo fundus photography. "Background retinopathy" and "preproliferative retinopathy" are outdated terms without the associated clinical prognosis inherent to NPDR grading and thus should no longer be used.

PDR LEVELS AND DISEASE PROGRESSION

— The extent and location of neovascularization determine the level of PDR (17,18). NVD, larger areas of vessels, and presence of concurrent vitreous hemorrhage are the critical findings. PDR is often divided into high-risk PDR and less than high-risk PDR based on the relative association with sight-threatening sequelae. Without photocoagulation, patients with high-risk PDR have a 28% risk of severe visual loss within 2 years. This compares with a 7% risk of severe visual loss after 2 years for patients with PDR but without high-risk characteristics (17). Severe visual loss is defined as best corrected acuity of 5/200 or worse on two consecutive visits 4 months apart. Prompt scatter (panretinal) laser photocoagulation is indicated for all patients with high-risk PDR, often indicated for patients with less than high-risk PDR, and, on occasion, advisable for patients with severe or very severe NPDR, especially in the setting of type 2 diabetes (see MANAGEMENT OF DIABETIC RETINOPATHY) (17–19,21,58). PDR is best evaluated by dilated examination using slitlamp biomicroscopy combined with indirect ophthalmoscopy and/or stereo fundus photography.

MACULAR EDEMA LEVELS AND DISEASE PROGRESSION

— Macular edema may be present even when mild NPDR is present. Macular edema is defined as retinal thickening within 3,000 μm of the center of vision (fovea). Macular edema that threatens the center of vision is termed clinically significant macular edema (21). Specifically, edema that is at or within 500 μm of the fovea, that is associated with hard exudates at or within 500 μm of the fovea, or that is ≥1,500 μm in diameter and any part of which is at or within 1,500 μm of the fovea qualifies as CSME. Untreated CSME is associated with an ~25% chance of moderate visual loss after 3 years (defined as at least doubling the visual angle, e.g., 20/40 to 20/80) (21). Focal laser photocoagulation is generally indicated for patients with CSME. Macular edema is best evaluated by dilated examination using slitlamp biomicroscopy and/or stereo fundus photography. Although fluorescein angiography is useful for guiding therapy once CSME has been diagnosed, it is not generally indicated for the diagnosis of CSME itself.

TREATMENT OBJECTIVES

— The primary goal of current therapies for diabetic retinopathy is to reduce the risk of visual loss that would otherwise occur in the absence of treatment. In general, prompt treatment is advised for patients with high-risk PDR and for patients with CSME (17–20). Patients with PDR are now primarily treated with scatter (panretinal) photocoagulation surgery, although cryotherapy or vitrectomy with endophotocoagulation may be effective when photocoagulation is not feasible. Some

Table 6—*Study questions addressed by key diabetic retinopathy clinical trials*

Trial	*n*	Primary questions addressed
DRS	1,758	Is laser panretinal photocoagulation effective at preventing severe visual loss* from diabetic retinopathy?
ETDRS	3,711	At what stage of diabetic retinopathy should panretinal laser photocoagulation be performed? Will aspirin slow the progression of diabetic retinopathy? Will focal laser photocoagulation reduce the development of moderate visual loss† from CSME?
DRVS	370	Does early vitrectomy improve visual prognosis for patients with very severe PDR and severe vitreous hemorrhage? Does early vitrectomy improve visual prognosis for patients with very severe PDR and visual acuity 10/200 or better?
DCCT	1,441	Is intensive glycemic control effective in delaying the onset of any diabetic retinopathy in type 1 diabetes? Will intensive glycemic control slow the progression of NPDR in type 1 diabetes?

*Severe visual loss is defined as best corrected acuity of 5/200 or worse on two consecutive visits 4 months apart. †Moderate visual loss is defined as at least doubling of the visual angle (e.g., 20/40 to 20/80).

patients with less than high-risk PDR or with severe or very severe NPDR may also benefit from scatter (panretinal) photocoagulation, depending on such factors as type of diabetes, medical status, access to care, compliance with follow-up, status and progression of the fellow eye, and family history (19–21,58). CSME is treated with focal laser photocoagulation (19–21). An intraocular surgical procedure called vitrectomy can improve or stabilize visual acuity in carefully selected cases of severe PDR and vitreous hemorrhage or tractional retinal detachment of the macula (27,28).

The DCCT has demonstrated that intensive insulin therapy in type 1 patients significantly delays the onset of any diabetic retinopathy and slows the progression of NPDR once it is present (23–25). In addition, population-based data indicate that lower glycated hemoglobin levels are associated with a lower incidence and progression of diabetic retinopathy in type 2 patients. Similar findings in a much smaller study (~25 patients per subgroup) have been demonstrated in Japanese patients with type 2 diabetes (59). In that clinical trial, multiple insulin-injection treatment reduced the onset of retinopathy from 32 to 8% over 6 years and reduced a two-step progression of retinopathy from 44 to 19% over the same time period compared with people receiving conventional insulin treatment. The Japanese study participants, however, were nonhypertensive, nondyslipidemic, and lean. Thus, extrapolating these data to American and European populations must be done with caution. Careful maintenance of glycemic control in an attempt to achieve as near normal a level of HbA_{1c} as possible has, nevertheless, become a therapeutic cornerstone for patients with early stages of diabetic retinopathy. As noted earlier, maintenance of appropriate blood pressure (41) and serum lipid concentrations (42) have a positive impact on the patient's visual prognosis and should be carefully monitored in partnership with the patient's general medical physician.

DETERMINATION OF TREATMENT EFFICACY

— The efficacy of panretinal photocoagulation, focal photocoagulation, vitrectomy, and intensive glycemic control has been primarily defined by four national multicenter randomized clinical trials. The principal issues addressed and number of patients studied in each trial are detailed in Table 6.

GENERAL TREATMENT EFFICACY

— Treatment efficacy for the more common generalized indications are presented in Table 7. The key issue is that

Table 7— *Selected treatment efficacy results*

Indication	Treatment	Efficacy
CSME	Focal laser photocoagulation	50% reduction in moderate visual loss* after 3 years
High-risk PDR (all levels)	Scatter photocoagulation	60% reduction in severe visual loss† after 3 years
Development of high-risk PDR	Scatter photocoagulation	87% reduction in severe visual loss† after 3 years 97% reduction in bilateral severe visual loss† after 3 years 90% reduction in legal blindness after 5 years
Severe PDR and severe vitreous hemorrhage‡§	Vitrectomy	60% increased chance of 20/40 or better after 2 years
Severe PDR and vision 10/200 or better*	Vitrectomy	34% increased chance of 20/40 or better after 2 years
No diabetic retinopathy‡	Intensive glycemic control	76% reduction in onset of retinopathy
NPDR‡	Intensive glycemic control	63% reduction in retinopathy progression 47% reduction in development of severe NPDR and PDR 26% reduction in development of macular edema 51% reduction in need for laser treatment

*Moderate visual loss is defined as at least doubling of the visual angle (e.g., 20/40 to 20/80). †Severe visual loss is defined as best corrected acuity of 5/200 or worse on two consecutive visits 4 months apart. ‡For patients with type 1 diabetes only. §No benefit was observed in the adult-onset group.

Table 8—*DRS: onset of severe visual loss with and without panretinal photocoagulation*

Retinopathy level	Follow-up (years)	Untreated (%)	Treated (%)
NPDR	2	3	3
	4	13	4
PDR	2	7	3
	4	21	7
High-risk PDR	2	28	6
	4	42	12

treatment provided according to study guidelines can be remarkably effective. However, response to therapy is altered depending on method of treatment, patient subgroup, and numerous other confounding factors. Full discussion of these particulars is beyond the scope of this work. For more detailed analysis of the data, the reader is referred to SPECIFIC CLINICAL TRIALS OUTCOMES and the published study results themselves.

SPECIFIC CLINICAL TRIALS OUTCOMES — The DRS (Table 8) was designed to investigate the value of xenon arc and argon laser panretinal photocoagulation surgery in preventing severe visual loss among patients with NPDR and PDR (16–21,23,27,28). Severe visual loss was defined as best corrected acuity of 5/200 or worse at two or more consecutive visits 4 months apart. The study proved the benefit of scatter (panretinal) photocoagulation for reducing severe visual loss from diabetic retinopathy, but was not designed to address at what level of retinopathy laser therapy should be initiated.

The ETDRS investigated the benefit of laser panretinal photocoagulation in reducing severe visual loss among patients with various levels of NPDR or mild PDR to determine when laser therapy should be initiated (19–21). These results are detailed under NPDR LEVELS AND DISEASE PROGRESSION. The ETDRS also evaluated the effect of focal laser photocoagulation in reducing moderate visual loss from diabetic macular edema in patients with NPDR as shown in Table 9. Moderate visual loss was defined as at least a doubling of the visual angle (e.g., 20/40 to 20/80).

The DRVS investigated the role of early vitrectomy in managing patients with very severe PDR (27,28). A benefit of early vitrectomy was seen in type 1 patients as shown in Table 10; however, no such advantage was found among type 2 patients. The results of this study should be considered with caution because it was performed before the use of laser endophotocoagulation at the time of surgery, as is routinely performed today, and because vitrectomy procedures have evolved rapidly in recent years. Thus, current outcomes may be more favorable than reported in the DRVS.

The DCCT evaluated whether intensive insulin treatment in patients with type 1 diabetes, as compared with more standard attempts at blood glucose control, would reduce the risk of the secondary complications of diabetes. Specifically, would tight control reduce the risk of developing retinopathy in patients without retinopathy at baseline, and would tight control reduce the progression of retinopathy in patients with mild-to-moderate retinopathy at baseline? In addition, the study investigated the effects of intensive insulin therapy on other secondary complications of diabetes, including nephropathy, neuropathy, and cardiovascular disease (23–25). Intensive therapy entailed administration of insulin three or more times per day by injection or external pump, with dosage adjusted according to results of glucose self-monitoring performed at least four times per day. Intensive-therapy patients visited their study center once per month and were contacted even more frequently by telephone to review and adjust their regimens.

Intensive insulin therapy was clearly effective in improving glucose control and reducing the risk of developing retinopathy and in slowing the progression of NPDR once present. It also reduced the likelihood of developing macular edema, PDR, or severe NPDR and the need for laser treatment. Detailed results are shown in Table 11. Similar beneficial effects of intensive insulin treatment were also observed for nephropathy and neuropathy.

The DCCT showed a statistically significant benefit of intensive insulin therapy after 3 years. Intensive insulin treatment slowed the development of any retinopathy but did not completely prevent it over the 9-year study period. Results were better in patients with shorter duration of diabetes (60,61). Treatment benefit was greatest in the primary prevention group, but patients with existing retinopathy, including those with more advanced retinopathy (level 43/<43 or worse) showed some benefit. There was no threshold level of glycemic control that either conferred protection or was uniformly associated with retinopathy progression (62). At the 6- and 12-month visits, a small adverse effect of intensive treatment on retinopathy level was observed (early worsening), as had been described in earlier studies. However, at subsequent visits the beneficial effects increased with time, and beyond 3.5 years of follow-up, the risk of progression was five or more times lower with intensive treatment than with conventional treatment (85).

MANAGEMENT OF DIABETIC RETINOPATHY — In general, laser photocoagulation surgery is advised for patients with high-risk PDR and for patients with CSME, since both groups have better visual prognosis when treated (16–21). PDR is treated with scatter (panretinal) laser photocoagulation surgery, and CSME is treated with focal laser photocoagulation surgery (19–21). Some patients with less than high-risk PDR or with severe or very severe NPDR may also benefit from scatter (pan-

Table 9—*ETDRS: onset of moderate visual loss with and without focal laser photocoagulation*

Retinopathy level	Follow-up (years)	Untreated (%)	Treated (%)
CSME			
Visual center not involved	1	7.5	1.0
	2	15.8	6.1
	3	22.1	13.2
Visual center involved	1	13.3	7.5
	2	23.6	9.4
	3	33.0	13.8

Table 10—*DRVS: visual acuity results with and without early vitrectomy*

Patient group	Final visual acuity	Follow-up (years)	Early vitrectomy (%)	Deferred vitrectomy (%)
Very severe PDR and severe vitreous hemorrhage	20/40 or better	2	24.5	15.2
	NLP	2	25.0	29.0
Very severe PDR and initial acuity 10/200 or better	20/40 or better	2	41.5	30.9
	20/40 or better	3	47.4	24.7
	20/40 or better	4	44.1	28.3
	NLP	4	~23	~19

NLP, no light perception.

retinal) photocoagulation depending on such factors as diabetes type, medical status, access to care, compliance with follow-up, status and progression of the fellow eye, and family history. Neovascularization of the iris and angle is also an indication for scatter (panretinal) photocoagulation (35,36).

Typical management recommendations are shown in Table 12 (46,47,63). It should be noted that the appropriate management for a particular patient depends not only on level of retinopathy and extent of macular edema, but also on a wide array of additional factors as discussed below. Thus, the most appropriate management choice for any specific patient may vary from that shown in the table.

No or minimal NPDR typically requires annual follow-up because 5–10% of patients with no retinopathy will develop retinopathy within 1 year, and existing retinopathy will be exacerbated by a similar percentage (56,65). In the absence of other indications, laser treatment and fluorescein angiography are not indicated. Color fundus photography primarily helps only where there is a need to document baseline characteristics.

Non-CSME requires repeat examination within 4–6 months because of the risk of developing CSME. For patients with type 1 diabetes and early NPDR, the 4-year incidence of macular edema is 15%, while it is 20% for those with type 2 diabetes who are insulin dependent. With moderate NPDR, the risk increases to 23% for both groups (63,64). In the absence of other indications, laser treatment and fluorescein angiography are not indicated. Color fundus photography is often helpful to document extent of macular edema and for evaluation of interim change at subsequent follow-up.

CSME generally requires focal laser photocoagulation surgery to reduce the risk of moderate visual loss. Once a decision is made to treat CSME, fluorescein angiography is generally indicated before focal photocoagulation surgery to identify treatable lesions and guide laser placement. Color fundus photography is helpful to document extent of macular edema and for evaluation of interim change and treatment response at subsequent follow-up. Follow-up to evaluate treatment effect is scheduled after 3–4 months. Although all patients with CSME may benefit from treatment, some patients with 20/20 or better visual acuity may have less immediate risk of visual loss and thus, in certain instances, may be observed closely for progression or regression before initiating photocoagulation surgery. The decision to defer treatment in these cases should be made only after careful consideration of the risks and benefits as discussed between the patient and the ophthalmologist. If deferral of treatment is elected, careful follow-up at least every 3 months is essential (63,66) and color fundus photography should be considered.

Mild-to-moderate NPDR without macular edema generally requires follow-up examination within 6–12 months because as many as 16% of patients with mild retinopathy and type 1 diabetes can progress to proliferative disease within 4 years (64,65). In the absence of other indications, laser therapy and fluorescein angiography are not indicated. Color fundus photography is often helpful to document extent of retinopathy and for evaluation of interim change at subsequent follow-up.

Severe and very severe NPDR without macular edema is associated with a high risk of progression to proliferative disease. Between 10 and 50% of patients with this level of NPDR will develop PDR within 1 year (18,21,56,81). Thus, reexamination every 3–4 months is indicated. Panretinal laser photocoagulation is associated with a reduced risk of visual loss when one considers all patients with this level of retinopathy, although the benefit is not as dramatic as for those with high-risk PDR, while the side effects (decreased peripheral and night vision) and complications are similar. However, in patients with type 2 diabetes, scat-

Table 11—*DCCT: effects of intensive insulin therapy on diabetic retinopathy in patients with type 1 diabetes*

Complication	Conventional therapy (rate/100 patient-years)	Intensive therapy (rate/100 patient-years)	Risk reduction (%)
Primary prevention			
Onset of retinopathy	4.7	1.2	76
Secondary intervention			
Development of macular edema	3.0	2.0	26
Development of severe NPDR or PDR	2.4	1.1	47
Need for laser treatment	2.3	0.9	51

Table 12—*Typical management recommendations*

Diabetic retinopathy level	CSME	Panretinal laser photocoagulation	Focal laser photocoagulation	Fluorescein angiography	Color fundus photography	Minimum follow-up
None–minimal NPDR	No	No	No	No	No	1 year
	Yes	No	Possible*	Possible*	Yes	3–4 months
Mild–moderate NPDR	No	No	No	No	Possible	6–12 months
	Yes	No	Probable*	Probable*	Yes	3–4 months
Severe–very severe NPDR	No	Possible†	No	No	Yes	3–4 months
	Yes	Possible†‡	Yes‡	Yes	Yes	3–4 months
Less than high-risk PDR	No	Probable†	No	No	Yes	2–4 months§
	Yes	Probable†‡	Yes‡	Yes	Yes	2–4 months§
High-risk PDR	No	Yes	No	No	Yes	3–4 months
	Yes	Yes‖	Yes‖	Yes	Yes	3–4 months

Appropriate management for a particular patient depends not only on level of retinopathy and extent of macular edema but also on a wide array of additional factors. Thus, the most appropriate management choice for any specific patient may vary from that shown in the table. *Deferral of CSME treatment is an option with excellent visual acuity, ability for close follow-up, and patient understanding of risks. †Scatter (panretinal) photocoagulation surgery may be performed as patients approach high-risk PDR. Type 2 patients will especially benefit if treated at this stage. See text for further details. ‡Treatment of CSME should be performed before panretinal photocoagulation. §If panretinal photocoagulation is performed, follow up at 3–4 months; otherwise follow up at 2–3 months. ‖Treatment of CSME should be performed as part of first treatment session along with initial panretinal photocoagulation.

ter photocoagulation surgery at this stage is associated with a 50% reduction in the rate of severe visual loss or vitrectomy and a 50% reduction in the risk of progression to high-risk PDR (58). In contrast, the rate of vision loss was not improved by early laser surgery in patients with type 1 diabetes. Thus, the treatment decision for patients with severe and very severe NPDR is often based on an array of factors other than retinopathy level, including type of diabetes, medical status, access to care, compliance with follow-up, status and progression of the fellow eye, systemic diabetes control, and family history. Fluorescein angiography is generally not indicated, although it may be useful in selected cases to help determine the presence or absence of areas of nonperfusion and/or occult areas of retinal neovascularization. Color fundus photography is often helpful to document extent of retinopathy and for evaluation of interim change at subsequent follow-up.

Severe and very severe NPDR with macular edema involves the same management issues as described for severe and very severe NPDR without macular edema and for CSME discussed above. There is added emphasis on treating the macular edema in these patients, since a substantial number will eventually require scatter (panretinal) photocoagulation surgery for PDR and since focal treatment before scatter photocoagulation surgery is preferable (21). If CSME is to be treated, fluorescein angiography is indicated before focal photocoagulation to identify treatable lesions. Color fundus photography is helpful to document extent of macular edema and retinopathy and for evaluation of interim change or treatment effect at subsequent follow-up.

Less than high-risk PDR does benefit from panretinal laser photocoagulation (17), although the risk-benefit ratio for all patients with PDR but *without* DRS high-risk characteristics is less favorable than for high-risk PDR. However, patients with type 2 diabetes have a substantially lower risk of severe visual loss or vitrectomy when treated with scatter photocoagulation surgery at this time (58), as discussed above under severe and very severe NPDR without macular edema. Therefore, the indication for treatment may be influenced by factors such as diabetes type, medical status, access to care, compliance with follow-up, or status and progression of the fellow eye. If patients are not treated, follow-up within 2–3 months is essential because of the high rate of developing high-risk characteristics that require treatment. If panretinal photocoagulation is performed, follow-up is recommended at 3–4 months. In the absence of other indications, fluorescein angiography is not indicated. Color fundus photography is often helpful to document extent of retinopathy and for evaluation of interim change at subsequent follow-up.

Less than high-risk PDR with CSME is usually treated with focal laser photocoagulation first, although the benefit has not been specifically proven (19). The indications for scatter (panretinal) photocoagulation surgery, fluorescein angiography, and fundus photography are similar to those for patients with non–high-risk PDR or CSME, as discussed above.

High-risk PDR requires prompt scatter (panretinal) laser photocoagulation surgery (16–18,21). If CSME is also present, focal laser photocoagulation is usually performed along with initiation of panretinal photocoagulation at the first treatment session, since scatter photocoagulation can exacerbate macular edema (21). Except with concurrent CSME, fluorescein angiography is usually not indicated. Color fundus photography is often helpful to document extent of retinopathy and response to treatment.

High-risk PDR not amenable to photocoagulation can arise because of advanced disease, poor retinal visualization (i.e., severe vitreous hemorrhage or cataract), active neovascularization despite complete laser treatment, traction-macular detachment, or combined traction-rhegmatogenous retinal detachment. Therapeutic options include vitrectomy or, possibly, cryotherapy. Vitreous surgery has the potential for serious complications, including profound visual loss and permanent pain and blindness, and should be undertaken only after careful consideration of the potential risks and benefits (27,28).

EXERCISE — In general, exercise and physical activity have not been shown to accelerate diabetic retinopathy, and there is some indication that physical exercise has a positive effect on reducing the risk of diabetic complications (67–72). Strenuous activity in patients with active PDR may pre-

Table 13—*Relative value of stereoscopic color fundus photography in diabetic retinopathy*

Beneficial value	Setting	Benefits
Definite	Before treatment	Documentation of therapeutic need and treatment response
	Severe disease	Documentation, subsequent evaluation of progression
	Progressing disease	Documentation and evaluation of progression
Probable	At initial ophthalmic exam	Baseline for subsequent evaluation of progression
	After treatment	Documentation of appropriate treatment and/or response
Unlikely	Minimal retinopathy	Few, since any subsequent findings would indicate progression
	Stable retinopathy	Few, since no change from prior photographs

cipitate vitreous hemorrhage or traction retinal detachment (73,74), although one study showed that 84% of vitreous hemorrhages were associated with activity no more strenuous than walking (75). With a lack of definitive studies on this topic, it has been suggested that patients with advanced stages of diabetic retinopathy limit strenuous activities that involve extensive Valsalva maneuvers, pounding, or jarring of the head (76).

ASPIRIN THERAPY — The effect of 650 mg of aspirin per day was studied in 3,711 patients with all levels of NPDR and patients with less than high-risk PDR during the ETDRS (77). Aspirin did not alter the course of diabetic retinopathy, did not affect the development of high-risk PDR, did not reduce the risk of visual loss, and did not increase the risk of vitreous hemorrhage. These findings indicate that there are no ocular contraindications to aspirin therapy in patients with diabetic retinopathy when required for cardiovascular disease or other medical indications.

ANCILLARY TESTS — Several ancillary tests can greatly enhance care of the patient with diabetic retinopathy. However, they should only be employed when useful information will result. Excessive use of ancillary tests does not improve the quality of care and can place the patient at additional risk of complication or side effect.

Stereoscopic-color fundus photography (Table 13) is more sensitive at detecting retinopathy than is clinical examination, often detecting disease that would otherwise be overlooked (7). Clinical examination, however, is often superior for detecting retinal thickening and may be better at identifying fine-caliber NVE or NVD. Color fundus photography provides documentation of the disease status. Seven–standard field stereoscopic 30° photographs provide the most complete coverage and have been used in most multicenter trials (16–20). Fundus photography is valuable before treatment to permit evaluation of disease progression or regression. After treatment, photography is valuable in documenting therapeutic response. When retinopathy findings change, fundus photography is useful for documentation and subsequent evaluation. Fundus photography is probably not valuable in cases of minimal diabetic retinopathy or in cases in which diabetic retinopathy is unchanged since the previous retinal photographs.

Fluorescein angiography is not required to diagnose CSME or PDR, both of which are clinical diagnoses. Fluorescein angiography is not part of the examination of an otherwise normal patient with diabetes, and the procedure is usually contraindicated in patients with known allergy to fluorescein dye. Fluorescein angiography is a valuable test for guiding treatment of CSME, identifying macular capillary nonperfusion, and evaluating unexplained visual loss. The benefits of fluorescein angiography under various situations is presented in Table 14.

The risks associated with fluorescein angiography must be appreciated and discussed with the patient. Although serious complications are rare, they do occur (78–80). These complications include death (1 in 222,000 patients) and severe medical sequelae (1 in 2,000 patients). Although detrimental effects of fluorescein dye on the fetus have not been documented, fluorescein does cross the placenta into the fetal circulation. Rarely is a fluorescein angiogram absolutely necessary for treatment of macular edema in these circumstances, and because it would be difficult to prove that fluorescein was not responsible for a subsequent birth defect, should it occur, fluorescein angiography during pregnancy is generally not indicated.

Table 14—*Fluorescein angiography in diabetic retinopathy*

Indication	Benefits
Guiding treatment of CSME	Identification of "treatable lesions" and method of photocoagulation
Determining extent of macular nonperfusion	Extent and location may alter visual and treatment prognosis.
Evaluating unexplained visual loss	Additional information
Searching for subtle neovascularization	Rarely helpful since careful clinical exam is highly sensitive and high-risk neovascularization should usually be clinically identifiable
Diagnosis of NPDR Diagnosis of PDR Before panretinal photocoagulation Before intraocular surgery	In the absence of other indications, fluorescein angiography is not routinely indicated in these settings since the low likelihood of significant additional information does not usually justify the additional risk, discomfort and cost to the patient.

Ultrasonography is a valuable test for evaluating diabetic retinopathy when adequate view of the retina is not possible because of such problems as cataracts or dense vitreous hemorrhage. The test is particularly useful at determining presence of retinal traction or detachment that requires prompt surgical intervention. Repetitive studies are appropriate as long as the view is inadequate and active disease is likely.

PHOTOGRAPHY AND RETINAL SCREENING — As noted above, dilated ETDRS standard seven-field stereoscopic 30° fundus photography is more sensitive for detecting retinopathy than is clinical examination, although clinical examination is often superior for detecting retinal thickening associated with macular edema and may be better at identifying fine-caliber NVE or NVD (7). Photographs by this protocol represent the current gold standard and have been used in most multicenter trials (16–20,31,81). Proper evaluation of fundus photographs requires a photographer skilled in obtaining the rigorously defined and technically challenging ETDRS photographic fields of appropriate quality and a reader skilled in the interpretation of the photographs (17–19,31,81).

Recent technologies permit the acquisition of high-quality photographs through undilated pupils and the acquisition of images in digital format. Although these technologies may eventually permit nondilated photographic retinopathy screening via telemedicine, no rigorous and extensive studies to date validate the equivalence of these photographs with traditional standard seven-field stereoscopic 30° fundus photography for determining the level of diabetic retinopathy. Thus, at this time, these technologies are not considered a replacement for dilated ophthalmic examination by an eye care provider with experience in the management of diabetic retinopathy or dilated standard seven-field stereoscopic 30° fundus photography for the screening, diagnosis, grading, or treatment of diabetic retinopathy.

CONCLUSIONS — Diabetic retinopathy is a major cause of visual loss today. Fortunately, extensive reliable data exist concerning most aspects of the disease process, allowing for the development of well-substantiated evaluation, management, and treatment guidelines. Diabetes, however, is a multisystem disease in which each system can have significant influence on another. Thus, the appropriate care for patients with diabetic retinopathy must include the coordinated efforts of eye care providers along with a primary care provider, internist, or endocrinologist. Because of the sometimes subtle nature of clinical findings, the complexities of the disease itself, and the intricate therapeutic options associated with moderate-to-advanced stages of diabetic retinopathy, routine management by an ophthalmologist experienced in the care of diabetic retinopathy is essential in advanced stages of retinopathy, such as severe and very severe NPDR, PDR, and diabetic macular edema. However, the most critical factors in reducing morbidity associated with diabetic retinopathy are the identification of patients with diabetes, prompt enrollment into regular lifelong systemic and ocular evaluation, and timely referral. Both ophthalmologic and optometric eye care providers as well as general medical care providers have critical roles in this regard.

Some patients with diabetic retinopathy will lose vision despite timely and appropriate treatment (17,19). These individuals require proper professional support, counseling, rehabilitation, and social services (82). However, with early identification, prompt incorporation into the health care system, patient education, regular lifelong evaluation, appropriate referral, and timely treatment, the vast majority of severe visual loss from diabetes can be prevented. Full support by the entire medical profession will help eliminate needless blindness from diabetic retinopathy.

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APPENDIX: GLOSSARY

Background Diabetic Retinopathy (BDR): An outdated term referring to some stages of nonproliferative diabetic retinopathy. Since this terminology is not closely associated with disease progression, it should no longer be used and has been replaced by the various levels of nonproliferative diabetic retinopathy.

Clinically Significant Macular Edema (CSME): Thickening of the retina in the macular region that is of an extent and in a location that threatens central visual function.

Cotton Wool Spot: A gray or white area lesion at the nerve fiber layer of the retina resulting from stasis of axoplasmic flow as a result of infarction.

Diabetes Control and Complications Trial (DCCT): A multicenter randomized clinical trial designed to address whether intensive insulin therapy could prevent or slow the progression of systemic complications of diabetes.

Diabetic Retinopathy (DR): Retinal pathology related to the underlying systemic disease of diabetes.

Diabetic Retinopathy Study (DRS): The first multicenter randomized clinical trial to demonstrate the value of laser scatter (panretinal) photocoagulation in reducing the risk of visual loss among patients with all levels of diabetic retinopathy.

Diabetic Retinopathy Vitrectomy Study (DRVS): A multicenter clinical trial demonstrating the value of early vitrectomy for patients with very advanced diabetic retinopathy.

Early Treatment Diabetic Retinopathy Study (ETDRS): A multicenter randomized clinical trial that addressed at what stage of retinopathy scatter (panretinal) photocoagulation was indicated, whether focal photocoagulation was effective for preventing moderate visual loss from clinically significant macular edema, and whether aspirin therapy altered the risks for outcome or treatment of diabetic retinopathy.

Focal Laser Photocoagulation: A type of laser treatment used for patients with clinically significant macular edema whose main goal is to reduce vascular leakage either by focal treatment of leaking retinal microaneurysms or by application of therapy in a grid-like pattern.

Hard Exudate: Lipid accumulation within the retina as a result of increased vasopermeability.

High-Risk Proliferative Diabetic Retinopathy (HRC PDR): Proliferative diabetic retinopathy of a defined extent, location,

and/or clinical findings that is particularly associated with severe visual loss.

Microaneurysm: An early vascular abnormality consisting of an outpouching of the retinal microvasculature.

Neovascular Glaucoma (NVG): Elevation of intraocular pressure caused by the development of neovascularization in the anterior segment of the eye.

Neovascularization at the Disc (NVD): Retinal neovascularization occurring within ≤1,500 μm away from the optic disc.

Neovascularization Elsewhere (NVE): Retinal neovascularization that is located >1,500 μm away from the optic disc.

Neovascularization of the Iris (NVI): Neovascularization occurring on the iris (rubeosis iris), usually as a result of extensive retinal ischemia.

No Light Perception (NLP): The inability to perceive light.

Nonproliferative Diabetic Retinopathy (NPDR): The status of diabetic retinopathy that precedes the development of proliferative diabetic retinopathy. NPDR is subdivided into four levels: mild, moderate, severe, and very severe.

Preproliferative Diabetic Retinopathy: An outdated term referring to more advanced levels of nonproliferative diabetic retinopathy. Since this terminology is not closely associated with disease progression, it should no longer be used and has been replaced by the various levels of nonproliferative diabetic retinopathy.

Proliferative Diabetic Retinopathy (PDR): An advanced level of diabetic retinopathy in which proliferation of new vessels occurs on or within the retina.

Rubeosis Iridis: See Neovascularization of the Iris (NVI).

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