

DIABETIC RETINOPATHY:

FROM ONE MEDICAL STUDENT TO ANOTHER

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INTRODUCTION

Diabetic retinopathy (DR) is a vascular disease of the retina which affects patients with diabetes mellitus. It is the number one cause of blindness in people between the ages of 20-64 in the United States. It is, therefore, a worthwhile topic for all medical students to review. Diabetes mellitus is extremely common, so it is not surprising that DR affects 3.4 percent of the population (4.1 million individuals). Of the millions of people with DR, nearly one-fourth have vision-threatening disease (AAO 2008).

The likelihood of developing diabetic retinopathy is related to the duration of the disease. Type 2 diabetes has an insidious onset and can go unnoticed for years. As a result, patients may already have DR at the time of diagnosis. Type 1 diabetics, on the other hand, are diagnosed early in the course of their disease, and they typically do not develop retinopathy until years after the diagnosis is made. The risk of developing retinopathy increases after puberty. Twenty years after the diagnosis of diabetes, 80% of type 2 diabetics and nearly all type 1 diabetics show some signs of retinopathy (Klein 1984a, Klein 1984b).

While these numbers are eye-opening, diabetics can decrease their risk of retinopathy and slow the progression of the disease after it has begun with tight glucose control (DCCTRG 1993). Glucose control also has the added benefit of decreasing risk for other end-organ complications of diabetes, so it is important that diabetic patients are educated on the topic. Time since diagnosis and extent of hyperglycemia are the most significant risk factors for the DR, but other risk factors for development and progression include hypertension, dyslipidemia, smoking, nephropathy, and pregnancy (AAO 2008).

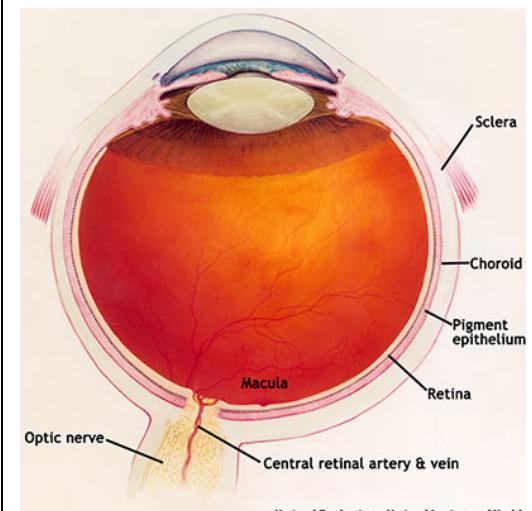
ANATOMY

The retina is a multi-layered sheet composed of neurons, photoreceptors, and support cells. It is one of the most metabolically active organs in the body, and as a result, it is extremely sensitive to ischemia and nutrient imbalances (Frank 2004). A perfused retina is a happy retina.

Normal Fundus



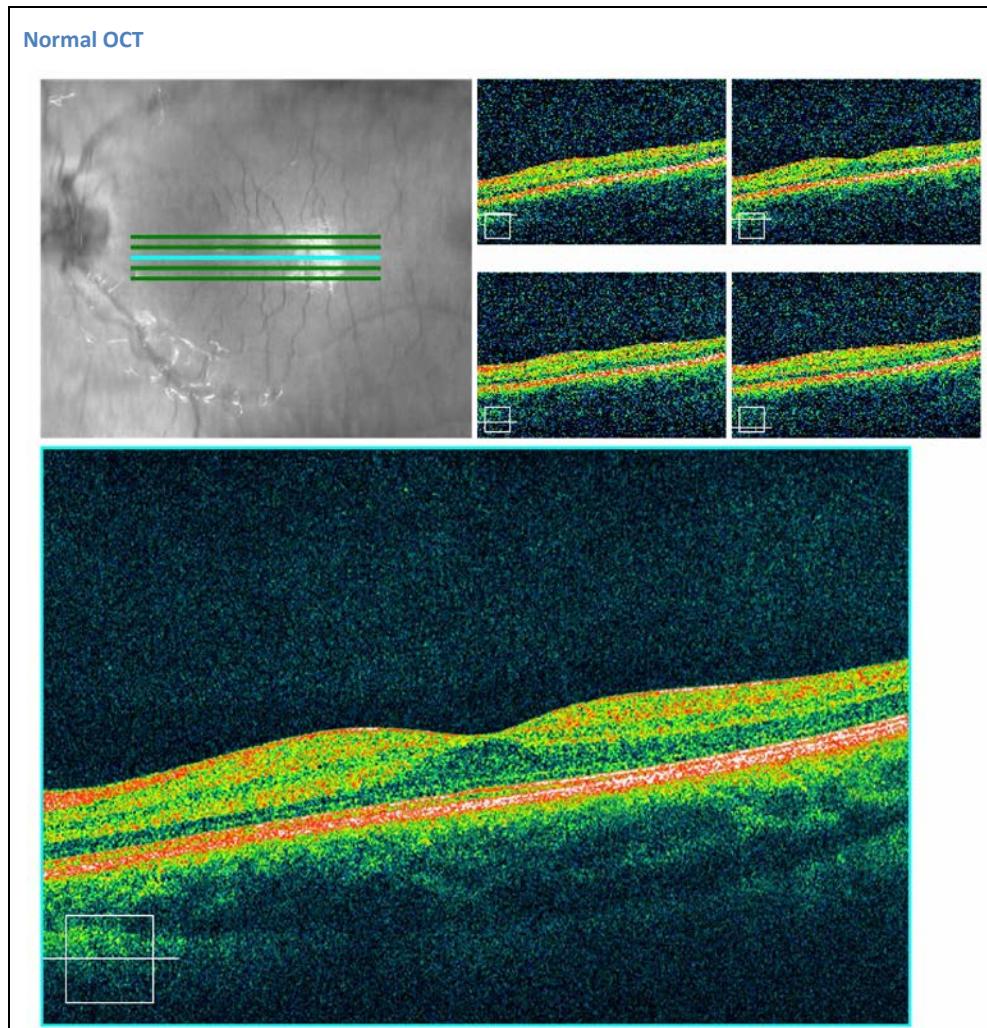
Diagram of Normal Eye



The outer one-third of the retina receives its blood supply from the choriocapillaris, a vascular network that lies between the retina and sclera. The inner two-thirds of the retina is supplied by branches of the central retinal artery, which comes from the ophthalmic artery (the first branch off of the internal carotid artery).

The central retinal artery exits out of the optic nerve, and its branches arch temporally both above and below the macula (the sensitive region of the retina responsible for central vision).

Although the exact pathophysiology of diabetic microvascular disease is unknown, hyperglycemia is thought to cause endothelial damage, selective loss of pericytes, and basement membrane thickening, all of which contribute to leaky, incompetent blood vessels



CLASSIFICATION

Diabetic retinopathy falls into two main classes: nonproliferative and proliferative. The word "proliferative" refers to whether or not there is neovascularization (abnormal blood vessel growth) in the retina. Early disease without neovascularization is called nonproliferative diabetic retinopathy (NPDR). As the disease progresses, it may evolve into proliferative diabetic retinopathy (PDR), which is defined by the presence of neovascularization and has a greater potential for serious visual consequences.

NPDR – Hyperglycemia results in damage to retinal capillaries. This weakens the capillary walls and results in small outpouchings of the vessel lumens, known as microaneurysms. Microaneurysms eventually rupture to form hemorrhages deep within the retina, confined by the internal limiting membrane (ILM). Because of their dot-like appearance, they are called “dot-and-blot” hemorrhages. The weakened vessels also become leaky, causing fluid to seep into the retina. Fluid deposition under the macula, or macular edema, interferes with the macula’s normal function and is a common cause of vision loss in those with DR. Resolution of fluid lakes can leave behind sediment, similar to a receding river after a flood. This sediment is composed of lipid byproducts and appears as waxy, yellow deposits called hard exudates. As NPDR progresses, the affected vessels eventually become obstructed. This obstruction may cause infarction of the nerve fiber layer, resulting in fluffy, white patches called cotton wool spots (CWS).

NPDR IS FURTHER SUBDIVIDED BASED ON RETINAL FINDINGS:

Early NPDR – At least one microaneurysm present on retinal exam.

Moderate NPDR – Characterized by multiple microaneurysms, dot-and-blot hemorrhages, venous beading, and/or cotton wool spots.

Severe NPDR – In the most severe stage of NPDR, you will find cotton wool spots, venous beading, and severe intraretinal microvascular abnormalities (IRMA). It is diagnosed using the “4-2-1 rule.” A diagnosis is made if the patient has any of the following: diffuse intraretinal hemorrhages and microaneurysms in 4 quadrants, venous beading in ≥2 quadrants, or IRMA in ≥1 quadrant. Within one year, 52-75% of patients falling into this category will progress to PDR (Aiello 2003).

PDR – As mentioned earlier, the retina has a high metabolic requirement, so with continued ischemia, retinal cells respond by releasing angiogenic signals such as vascular endothelial growth factor (VEGF). Angiogenic factors, like VEGF, stimulate growth of new retinal blood vessels to bypass the damaged vessels. This is referred to as neovascularization. In PDR, the fibrovascular proliferation extends beyond the ILM. This may sound like a good idea, but the new vessels are leaky, fragile, and often misdirected. They may even grow off the retina and into the vitreous. As the vitreous shrinks with age, it pulls on these fragile vessels and can cause them to tear, resulting in a vitreous hemorrhage and sudden vision loss. These vessels may also scar down, forming strong anchors between the retina and vitreous causing traction on the retina. If enough force is created, a tractional retinal

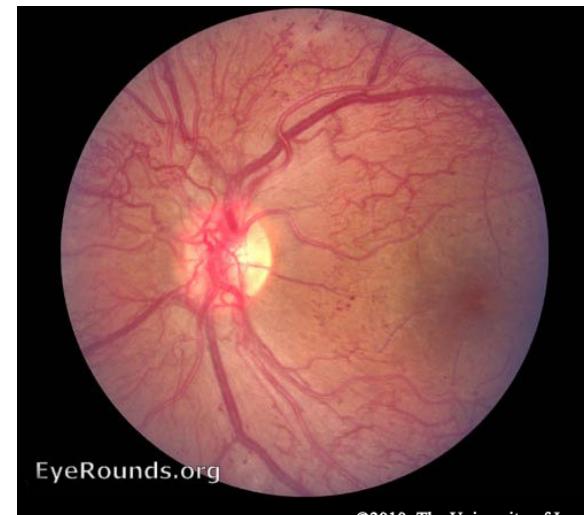
Nonproliferative Diabetic Retinopathy (NPDR)



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Proliferative Diabetic Retinopathy



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detachment may occur. This is another mechanism by which DR can cause sudden vision loss. If the retina is not re-attached soon, especially if the macula is involved, vision may be permanently compromised.

While the effects of neovascularization in PDR can be devastating, the most common cause of vision loss in diabetics is macular edema. Macular edema can occur in NPDR, but it is more common in more severe cases of DR due to the leakiness of the new blood vessels (Wani 2003).

Diabetics can also have problems located more anteriorly in the eye. The angiogenic molecules that are produced by the retina may float anteriorly, causing neovascularization of the iris. These vessels can grow into the angle of the anterior chamber where the trabecular meshwork, the drain of the eye, resides. This can obstruct outflow of aqueous fluid, raising intraocular pressure and causing acute glaucoma.

SYMPTOMS

Patients usually do not experience symptoms until late in the course of the disease when treatment may be ineffective. Late symptoms of DR vary depending on the cause. Bleeding into the vitreous can cause sudden loss of vision. Macular edema and ischemia are two other mechanisms of decreased vision.

SCREENING

Screening for DR is incredibly important since most patients do not experience any symptoms until advanced stages of disease. If recognized early, the vision-threatening side-effects of DR can often be prevented with appropriate management. Recommendations for screening are different for type 1 and type 2 diabetics. Because many patients with type 2 diabetes have retinopathy at the time their diabetes is diagnosed, it is recommended that their annual dilated eye exams begin shortly after the diagnosis of diabetes is made. Type 1 diabetics should begin annual eye exams 3-5 years after their diabetes diagnosis (AAO 2008).

DR can progress rapidly during pregnancy. Pregnant women with diabetes should have a dilated eye exam prior to conception, early in the first trimester, and then every 3 months until delivery. Unlike pre-existing diabetes, gestational diabetes does not place patients at increased risk of DR and these patients do not require frequent eye examinations (AAO 2008).

EXAMINATION

A proper diabetic eye exam should always begin by gathering a thorough history from the patient. Ask about any visual symptoms and systemic issues which may impact their risk for DR such as pregnancy, blood pressure, cholesterol levels, and renal status. Additionally, make sure to check their last hemoglobin A1c to gain an idea how their blood glucose control has been over the past 3 months. (AAO 2008)

Examination should begin with visual acuity, intraocular pressure measurements, and a slit-lamp exam, including careful inspection of the iris for neovascularization. If neovascularization of the iris is suspected or the patient has elevated intraocular pressures, gonioscopy should be performed to assess the iridocorneal angle. Gonioscopy utilizes a special mirrored lens which allows you to view the angle and trabecular meshwork. This cannot be accomplished using the slit lamp alone. Next, the patient should have his or her pupils dilated for a thorough fundus exam.

TREATMENT OPTIONS

NPDR is typically managed by optimizing the patient's general health. The best treatment for DR is prevention of its development and progression with tight glucose control (DCCTRG 1993). Patients should maintain a HbA1c $\leq 7\%$. Blood pressure management has also been shown to decrease disease progression (UKPDSG 1998) and patients should be counseled to stop smoking. Ophthalmologists should intervene if the patient has clinically significant macular edema (CSME) with NPDR. The causative microaneurysms are localized, often using fluorescein angiography, and then directly treated with laser therapy. If the leakage is more diffuse, a grid of light laser burns can slow the edema. Finally, several off-label medical options are available, such as intravitreous injections of triamcinolone and antibodies against VEGF such as Lucentis® or Avastin®.

Once a patient has developed PDR, there are several treatment modalities available. Treating macular edema in PDR is similar to treating NPDR. PDR, however, also has additional therapy options aimed at taming the growth of new, problematic vessels. The mainstay of treatment is panretinal photocoagulation (PRP), in which portions of retina are destroyed using thousands of laser burns while sparing the macula. It is hypothesized that this may reduce the amount of ischemic retina, and thus, reduce the production of angiogenic molecules. The treatment may sound extreme, but actually causes surprisingly little vision loss (Frank 1975). It has been found to be extremely effective, reducing the risk of severe vision loss by 50% (ETDRS 1987, Mohamed 2007) and resulting in regression of neovascularization in 30-55% of patients (DRS 1981, "Photocoagulation treatment" 1978).

Patients with non-resolving vitreous hemorrhages or severe traction causing retinal detachment may benefit from a vitrectomy. In this procedure, the vitreous gel and hemorrhage are removed from the eye and replaced with a saline solution.

SURGERY INDICATIONS

PRP is advised for patients with vitreous hemorrhage and areas of neovascularization or in patients with large amounts of neovascularization of the optic nerve. It can also be considered in patients with severe NPDR to prevent progression to PDR.

Macular edema should be treated once it becomes clinically significant. CSME is diagnosed if the patient has at least one of the following criteria (Friedman 2009):

- Retinal thickening within 500 μm of the fovea
- Hard exudates within 500 μm of the fovea with adjacent thickening
- Retinal thickening $\geq 1500 \mu\text{m}$ in diameter within 1500 μm of the fovea

The optic disc measures 1500 μm in diameter on average and can be used to estimate distances along the retina.

Vitrectomy should be performed when a vitreous hemorrhage fails to resolve after 6 months or after 1 month in type 1 diabetics (Meredith 1998). The procedure is also indicated for certain tractional retinal detachments.

Panretinal photocoagulation (PRP)



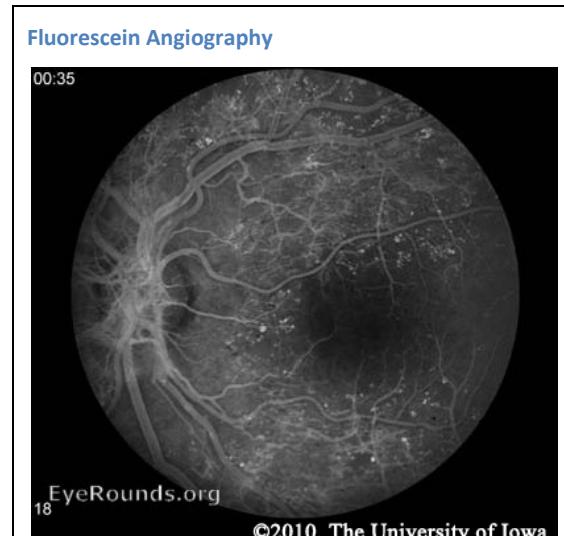
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PREOPERATIVE TESTING

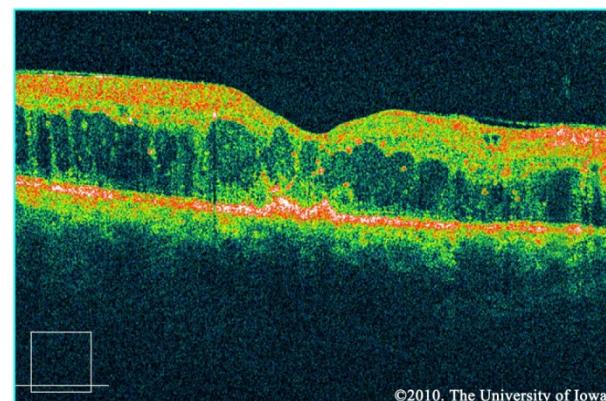
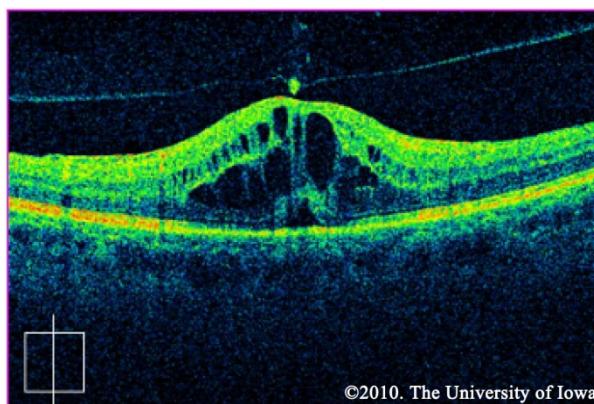
Fluorescein angiography (FA) may be used to definitively document retinal vessel occlusion and/or leakage. During an FA, a fluorescent dye is injected intravenously and a special camera takes fundus photos over several minutes while the vessels are being perfused. The test is best used to guide treatment of CSME, and not for diagnosis (AAO 2008).

Neovascularization in PDR can be seen on the slit lamp and dilated fundus exams and does not require any special testing.

Macular edema may be noted on fundus exam, but is much more easily appreciated using optical coherence tomography (OCT). OCT is a laser imaging technique which produces an image showing the individual layers of the retina and the shape of the retinal surface. Fluid accumulation between layers can be appreciated as black patches on the scan and irregular retinal surfaces may reflect the etiology behind a patient's visual abnormalities. It should be noted, however, that in the ETDRS (the study which is used to support the treatment for CSME), OCT was not used. CSME was diagnosed only by clinical appearance.



CSME OCT



Ultrasound is useful to detect retinal detachment when the fundus cannot be clearly seen on exam due to a dense cataract, vitreous hemorrhage, or other reasons.

WEB RESOURCES ON DIABETIC RETINOPATHY

Dr. Jon Walker's excellent textbook on diabetic retinopathy is available for free at
<http://www.drcobook.com/download.php>.

For a more detailed lesson on using the PASCAL laser system, check out Learning to Use the PASCAL Laser System. <http://www.eyerounds.org/tutorials/PASCAL-laser-tutorial.htm>

To watch focal laser, grid laser, and panretinal photocoagulation procedural videos, visit the OptiMedica website. <http://www.optimedica.com/pascal/video.aspx>

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Diabetic Retinopathy: Diabetic retinopathy

(pronounced *ret in OP uh thee*) is a complication of diabetes that causes damage to the blood vessels of the retina—the light-sensitive tissue that lines the back part of the eye, allowing you to see fine detail.

Diabetic retinopathy is the most common cause of irreversible blindness in working-age Americans. As many people with type 1 diabetes suffer blindness as those with the more common type 2 disease. Diabetic retinopathy occurs in more than half of the people who develop diabetes.

Causes: The primary cause of diabetic retinopathy is diabetes—a condition in which the levels of glucose (sugar) in the blood are too high. Elevated sugar levels from diabetes can damage the small blood vessels that nourish the retina and may, in some cases, block them completely.

When damaged blood vessels leak fluid into the retina it results in a condition known as **diabetic macular edema** which causes swelling in the center part of the eye (**macula**) that provides the sharp vision needed for reading and recognizing faces.

Prolonged damage to the small blood vessels in the retina results in poor circulation to the retina and macula prompting the development of growth factors that cause new abnormal blood vessels (**neovascularization**) and scar tissue to grow on the surface of the retina. This stage of the disease is known as **proliferative diabetic retinopathy (PDR)**.

New vessels may bleed into the middle of the eye, cause scar tissue formation, pull on the retina, cause **retinal detachment**, or may cause high pressure and pain if the blood vessels grow on the iris, clogging the drainage system of the eye—all of this can cause vision loss.

Risk Factors:

Anyone who has diabetes is at risk of developing diabetic retinopathy.

Additional factors can increase the risk:

- Disease duration: the longer someone has diabetes, the greater the risk of developing diabetic retinopathy.
- Poor control of blood sugar levels over time
- High blood pressure
- High cholesterol levels
- Pregnancy

Complications: The US Food and Drug Administration (FDA) has warned that taking some medicines could cause macular edema. People with type 2 diabetes who use certain prescription medicines, such as pioglitazone (Actos) and rosiglitazone (Avandia), to treat their diabetes have been reported to have a 3 to 6 times greater risk of macular edema.

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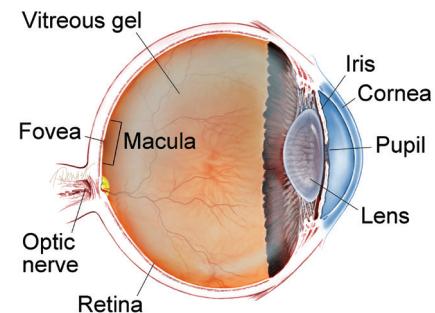
SYMPTOMS

It is possible to have diabetic retinopathy for a long time without noticing symptoms until substantial damage has occurred. Symptoms of diabetic retinopathy may occur in one or both eyes.

Symptoms may include:

- Blurred or double vision
- Difficulty reading
- The appearance of spots—commonly called “floaters”—in your vision
- A shadow across the field of vision
- Eye pain or pressure
- Difficulty with color perception

WHAT IS THE RETINA?



THE RETINA is a thin layer of light-sensitive nerve tissue that lines the back of the eye (or vitreous) cavity. When light enters the eye, it passes through the iris to the retina where images are focused and converted to electrical impulses that are carried by the optic nerve to the brain resulting in sight.

Diabetic Retinopathy

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Other medications have had rare reports of macular edema. These include:

- Prostaglandin analogs commonly used to treat glaucoma (Xalatan, Lumigan, and Travatan)
- Tamoxifen, taxanes, and interferon (used in some cancer treatments)
- Fingolimod (Gilenya) used in relapsing multiple sclerosis
- Various herbal and vitamin supplements that include high doses of niacin (vitamin B3)

Most people do not have eye side effects. Check with your physician for more information about prescription medications that could put you at risk.

Diagnostic Testing: The best way to diagnose diabetic retinopathy is a dilated eye exam. During this exam, the physician places drops in the eyes to make the pupils dilate (open widely) to allow a better view of the inside of the eye, especially the retinal tissue.

The physician will look for:

- Swelling in the retina that threatens vision (diabetic macular edema)
- Evidence of poor retina blood vessel circulation (retinal ischemia—pronounced *iss KEY me uh*)
- Abnormal blood vessels that may predict an increased risk of developing new blood vessels
- New blood vessels or scar tissue on the surface of the retina (proliferative diabetic retinopathy)

Regular dilated eye exams by an ophthalmologist are important, especially for those who are at a higher risk for diabetic retinopathy or diabetes. If you are over age 50, an exam every 1 to 2 years is a good idea so the physician can look for signs of diabetes or diabetic retinopathy before any vision loss has occurred.

In addition to checking for signs of diabetic eye disease, a comprehensive dilated eye exam will evaluate your vision/need for corrective lenses, eye pressure (looking for glaucoma), the “front” of the eye (eyelids, cornea, checking for dry eye), lens (looking for cataracts), as well as a complete exam of the retina and vitreous.

In addition to this exam, physicians use other tests to detect and manage diabetic retinopathy:

An **optical coherence tomography (OCT)** test provides highly detailed cross-sectional images of the retina that show its thickness, helping determine whether fluid has leaked into retinal tissue.

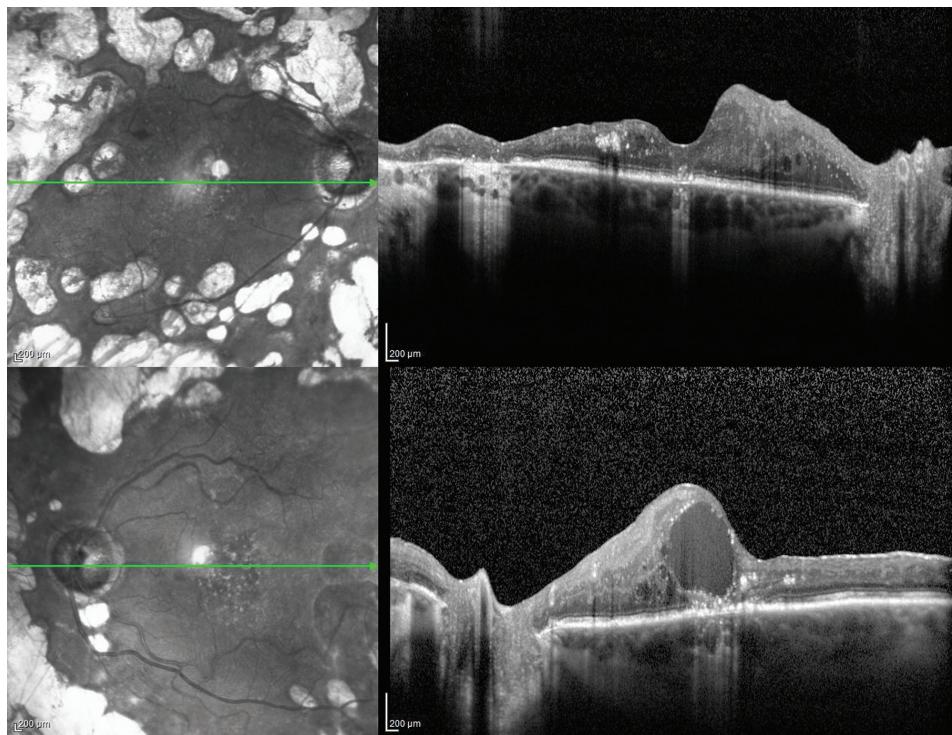


Figure 1

OCT of a patient with bilateral proliferative diabetic retinopathy with diabetic macular edema in the left eye. ©ASRS Retina Image Bank, May 2016. Image 26525. Olivia Rainey, Retina Specialists of Michigan.

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Diabetic Retinopathy

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The physician may take **fundus photographs** of the back of the eye to help detect and document diabetic retinopathy. These photos make it easier for the physician to monitor the disease on follow-up visits to determine if it is worsening.

To evaluate retina blood vessel circulation, the physician may conduct a retinal photography test called **fluorescein angiography (FA)**. After dilating the pupils, the physician will inject a dye into the patient's arm. The dye then circulates through the eyes and works like a food coloring; however, it does not affect the kidneys and is unlike the dye that is used with MRIs and CAT scans.

As the dye circulates, the physician takes pictures of the retina to accurately detect blood vessels that are closed, damaged, or leaking fluid. The pictures are black and white to help the doctor detect these changes more easily, but the process is not the same as having an x-ray. Prior to examination, ask your physician to discuss the risks and benefits of obtaining these images.

With proper examinations, diabetic retinopathy can be detected before vision loss begins. If the physician detects signs of diabetic retinopathy, she/he will determine how frequently follow-up examinations will be required to detect changes that would require treatment.

Treatment and Prognosis: As a result of major government- and industry-sponsored studies, there are many approved treatments for diabetic retinopathy, including **intravitreal injections** (small injections of medications into the middle cavity of the eye), laser treatments, and vitreous and retina surgery. These procedures can be done in an office or hospital setting to prevent, treat, or reverse damage from diabetes in the retina.

Research has shown that eye injections often result in better vision than laser treatment alone for patients with diabetic macular edema. The key to these treatments is their ability to block *vascular endothelial growth factor* (VEGF), a chemical signal that stimulates leakage and abnormal blood vessel growth. Repeated doses of anti-VEGF medications may be needed to prevent blood vessels from leaking fluid and causing vision loss.

Even if not all vision loss from diabetic retinopathy can be prevented or treated, patients usually are able to find resources to help them live with diminished vision. If you have been diagnosed with diabetic retinopathy or diabetes and have vision loss that cannot be reversed, a retina specialist can help you find access to rehabilitation with a variety of tools to make everyday living with this disease a little bit easier. A retina specialist can also help connect you with others who have similar limitations.

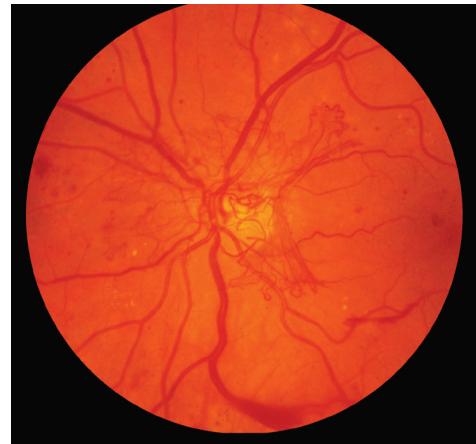


Figure 2

Retinal fundus photo of a patient with proliferative diabetic retinopathy. ©ASRS Retina Image Bank, 2012. Image 774. Michael P. Kelly, FOPS, Duke University Hospital.

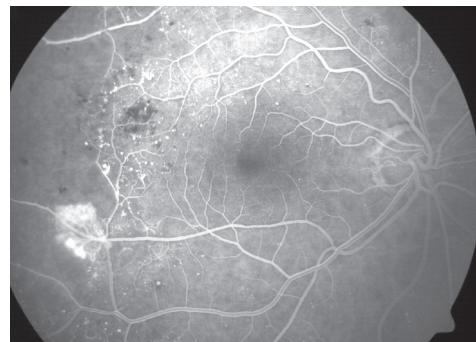


Figure 3

FA of a patient with proliferative diabetic retinopathy, retinal capillary nonperfusion, and neovascularization. ©ASRS Retina Image Bank, 2012. Image 2305. Sharon Fekrat, MD, FACS. Duke University Eye Center.

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Diabetic Retinopathy

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Prevention: Patients with diabetes frequently ask, "Is there anything I can do to keep from getting diabetic retinopathy or to prevent or treat vision loss once it occurs?"

If you have diabetes, the National Eye Institute suggests that you keep your health on **TRACK**:

- Take your medicines as prescribed by your doctor
- Reach and maintain a healthy weight
- Add physical activity to your day
- Control your ABCs—A1C, blood pressure, and cholesterol
- Kick the smoking habit

Regular dilated eye exams reduce the risk of developing more severe complications from the disease.

It is extremely important for diabetic patients to maintain the eye examination schedule put in place by the retina specialist. How often an examination is needed depends on the severity of your disease. Through early detection, the retina specialist can begin a treatment regimen to help prevent vision loss in almost all patients and preserve the activities you most enjoy. ●

Clinical Terms (appearing green within fact sheet text)

Diabetic macular edema (DME): The term used for swelling in the macula in eyes, or the center part of the retina which is responsible for providing the sharp, straight-ahead vision used for reading and recognizing faces as well as color vision.

Fluorescein angiography (FA): An imaging technique where a yellow dye called *sodium fluorescein* is injected into a vein in the arm. The dye allows a special camera to record circulation in the retina and *choroid* in the back of the eye. This test can be very useful in diagnosing a number of retinal disorders.

Fundus photography: Involves the use of specialized cameras equipped with lenses that capture images of the back of the eye where the retina, macula, vitreous, choroid and optic nerve are located.

Intravitreal injection: Treatment where a medication is injected into the vitreous cavity in the middle of the eye.

Macula: A small area at the center of the retina where light is sharply focused to produce the detailed color vision needed for tasks such as reading and driving.

Neovascularization: Excessive growth of new blood vessels on abnormal tissue as a result of oxygen deprivation that can cause vision loss.

Optical coherence tomography (OCT): A non-invasive imaging technique that uses light to create a 3-dimensional image of your eye for physician evaluation.

Proliferative diabetic retinopathy (PDR): An advanced stage of diabetic retinopathy in which new abnormal blood vessels and scar tissue form on the surface of the retina. The scar tissue can pull on the retina and cause retinal detachment and loss of vision. If blood vessels grow on the iris it can clog the drainage system of the eye causing glaucoma (high pressure in the eye), pain and vision loss.

Retinal detachment: A condition where the retina separates from the back of the eye cavity. This may be caused by vitreous gel or fluid leaking through a retinal tear or hole and collecting under the retina, causing it to separate from the tissue around it.

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Diabetic retinopathy

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Abstract

Diabetic retinopathy is a key cause of blindness in the working-age population. Despite the available treatments, some patients present late in the course of the disease when treatment is more difficult. If diabetic retinopathy is detected, tightening of modifiable risk factors (e.g. blood glucose, blood pressure) can slow disease progression. When sight-threatening retinopathy is detected, laser treatment and treatment with vascular endothelial growth factor inhibitors reduces the risk of visual loss. When a stage of advanced retinopathy is detected, vitrectomy operations with modern surgical techniques provide improving results for patients. Advances in optical coherence tomography technology have seen the development of high-definition three-dimensional imaging of the retina and of non-invasive, dye-free angiography, which has enhanced the understanding of and diagnostic capabilities within the field of diabetic retinopathy management.

Keywords Diabetic retinopathy; laser therapy; MRCP; optical coherence tomography; risk factors; screening; vascular endothelial growth factor

Definition and pathophysiology of diabetic retinopathy (DR)

DR refers to pathology of the capillaries, arterioles and venules in the retina, and the subsequent effects of leakage from or occlusion of the small vessels. Changes that occur within the retinal capillaries include:

- thickening of the basement membrane
- pericyte loss
- epithelial cell dysfunction (loss of epithelial tight junctions)
- loss of endothelial cells
- smooth muscle cell death
- capillary weakening
- increased capillary permeability
- capillary occlusion
- microaneurysm formation.

The microaneurysm is the hallmark of retinal microvascular disease in patients with diabetes mellitus. It has been suggested that microaneurysms may be asymmetrical dilatations of the capillary wall where it has been weakened or damaged by the loss of supporting pericytes and localized increases in hydrostatic pressure.

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Key points

- Diabetic retinopathy is still a key cause of blindness in the working population
- Screening and early treatment, with good blood pressure and glycaemic control, are effective in preventing visual loss
- VEGF inhibitors are successful in treating many patients with centre involving diabetic macular oedema
- Laser treatment is still the standard of care for treating proliferative diabetic retinopathy with vitrectomy operations for advanced disease

The Early Treatment Diabetic Retinopathy Study (ETDRS)

The ETDRS described the progression of DR in relation to the development of the following lesions (Figure 1):

- microaneurysms
- small retinal haemorrhages
- haemorrhage/microaneurysm (HMa)
- other larger retinal haemorrhages
 - flame haemorrhages
 - blot haemorrhages
- hard exudates (often just referred to as exudates)
- cotton wool spots (referred to in the ETDRS as soft exudates, although that term is now rarely used)
- intra-retinal microvascular abnormalities (IRMAs)
- venous abnormalities
- arteriolar abnormalities
- fibrous proliferation at the disc
- fibrous proliferation elsewhere
- new vessels at the disc (NVDs)
- new vessels elsewhere (NVEs)
- vitreous haemorrhage
- pre-retinal haemorrhage
- laser treatment – laser scars.

The ETDRS defined microaneurysm and haemorrhage as follows:

- A microaneurysm is defined as a red spot <125 micrometres in size (approximately the width of a vein at the disc margin) and with sharp margins.
- Haemorrhage is defined as a red spot that has irregular margins and/or uneven density, particularly when surrounding a smaller central lesion that is considered to be a microaneurysm. If a red lesion is >125 micrometres in its longest dimension, it is usually a haemorrhage unless features such as a round shape, smooth margins or central light reflex suggest it might be a microaneurysm.
- Because the ETDRS recognized that it was very difficult to differentiate between microaneurysms and small haemorrhages, the concept of 'HMa' was introduced, which is a small haemorrhage or microaneurysm.

The ETDRS defined hard exudates as small white or yellowish-white deposits with sharp margins, typically located in the outer layers of the retina.

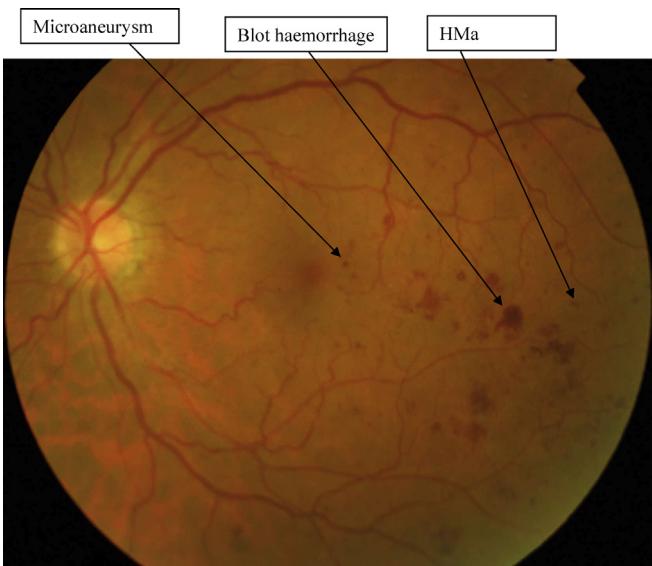


Figure 1 Microaneurysms, small HMAs and blot haemorrhages.

The ETDRS graded images from seven-field stereophotography (14 photographs of each eye), using these seven fields to describe the progression of retinopathy in the study. This level of detail can make this approach difficult to use in clinical practice, so there have been attempts to simplify it.

The ETDRS '4:2:1 rule', which is used in the simplified International Classification, defines severe non-proliferative DR as:

- extensive (>20) intra-retinal (blot) haemorrhages in four quadrants *or*
- definite venous beading in two or more quadrants *or*
- prominent IRMA in one or more quadrants
- *and* no signs of proliferative diabetic retinopathy.

Screening for DR

National screening programmes were announced in 2002–2003 in Scotland, Wales, England and Northern Ireland, all using digital photography.

The national screening programmes in England and Wales use two-field mydriatic digital photography, and the Scottish methodology involves one-field non-mydriatic digital photography with dilation and repeat photography for individuals with poor-quality images. In the Northern Ireland Screening Programme, patients <50 years of age do not routinely have their pupils dilated. A recent study has shown that, for the first time in at least five decades, DR/maculopathy is no longer the leading cause of certifiable blindness among working-age adults in England and Wales, having been overtaken by inherited retinal disorders.¹ This change may be related to factors including the introduction of nationwide DR screening programmes in England and Wales and improved glycaemic control.

English screening classification for DR progression

The classification used in England for progression and referral of DR is a simplified classification with a referral level that has been determined according to the need of a patient to be reviewed more than annually.

Each patient screened is given an R (retinopathy) level and an M (maculopathy) level, and the outcome depends on the grade of the worse eye (Table 1):

- R0M0 – no DR, no maculopathy
- R1M0 – background DR, no maculopathy
- R1M1 – background DR, maculopathy
- R2M0 – pre-proliferative DR, no maculopathy
- R2M1 – pre-proliferative DR, maculopathy
- R3M0 – proliferative DR, no maculopathy
- R3M1 – proliferative DR, maculopathy
- U – unassessable images.

People with diabetes who have unassessable images are referred for slit-lamp biomicroscopy investigation.

Treatment of associated risk factors

Systemic hypertension: good blood pressure control is crucial in terms of the progression of DR. Control of systemic hypertension has been shown to reduce the risk of new-onset DR and slow the progression of existing DR.

Glucose control: the importance of good blood glucose control in the progression of DR has been shown in both the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study.

Blood lipids: two studies have shown the importance of good blood lipid control in the progression of diabetic maculopathy.

Smoking: there is some evidence that smoking may be a risk factor in the progression of DR in type 1 diabetes as described by Muhlhauser and Karamanos (see Further reading). The evidence in type 2 disease is, however, controversial.

Non-modifiable risk factors for DR

The non-modifiable determinants of progression of DR include duration of diabetes, and a complex relationship with age, genetic predisposition and ethnicity.

The 'early worsening' phenomenon

In 1998, the DCCT described the effect of early worsening of DR at the 6- and/or 12-month visit in 13.1% of 711 patients assigned to intensive treatment. Early worsening led to high-risk proliferative retinopathy in two patients in the DCCT. The most important risk factors for early worsening were higher concentrations of glycated haemoglobin at screening and reduction of this concentration during the first 6 months after randomization. In the DCCT, the long-term benefits of intensive insulin treatment greatly outweighed the risks of early worsening.

Background DR

In the UK, patients who are screened and who show signs only of background DR are re-screened annually. For background DR with microaneurysms only, there is a 6.2% risk of progression to proliferative DR in 1 year. Microaneurysms in increasing numbers have been shown to be an important early measure of progression of DR.

English diabetic retinopathy screening classification

Retinopathy or R level	Maculopathy or M level
R0 Currently screen annually	M0 None of the features of M1 below
R1 Screen annually Background: <ul style="list-style-type: none"> • Microaneurysm(s) or HMAs • Retinal haemorrhage(s) • Venous loop • Any exudate or cotton wool spots in the presence of other non-referrable features of DR 	M1 Refer to ophthalmologist or surveillance clinic Exudate within one DD of the centre of the fovea
R2 Refer to ophthalmologist or surveillance clinic Pre-proliferative: <ul style="list-style-type: none"> • Venous beading • Venous reduplication • IRMAs • Multiple deep, round or blot haemorrhages 	M1 Refer to ophthalmologist Circinate or group of exudates within the macula (A circinate exudate needs to be at least one half of the disc area, which needs to be within the macular area)
R3A Urgent referral to ophthalmologist	M1 Refer to ophthalmologist or surveillance clinic Any microaneurysm or haemorrhage within 1 DD of the centre of the fovea but only if associated with a best visual acuity of $\leq 6/12$ (if no stereo)
R3A Proliferative: <ul style="list-style-type: none"> • NVDs • NVEs • Pre-retinal or vitreous haemorrhage • Pre-retinal fibrosis \pm tractional retinal detachment 	M1 Refer to ophthalmologist or surveillance clinic Retinal thickening within 1 DD of the centre of the fovea (if stereo available)

The macula is defined as that part of the retina which lies within a circle centred on the centre of the fovea whose radius is the distance between the centre of the fovea and the temporal margin of the disc.

DD, disc diameter.

Table 1

Cotton wool spots are fluffy white opaque areas caused by an arteriolar occlusion in an area of retina that results in an accumulation of axoplasm in the nerve fibre layer. These are not good signs in terms of the progression of DR as they are often associated with hypertension.

A venous loop is an abrupt curving deviation of a vein from its normal path. It is not considered to be associated with an increase in risk of progression over other features of background DR.

For the purposes of the English national screening programme, background DR is defined by the following lesions:

- one or more microaneurysm(s)
- one or more retinal haemorrhage(s)
- any exudate caused by DR.

Pre-proliferative DR

The main features that classify DR level in pre-proliferative DR are increasing signs of retinal ischaemia including venous beading, IRMAs and multiple blot haemorrhages:

- **Venous beading** is defined as a localized increase in calibre of the vein. The severity depends on the increase in calibre and the length of vein involved.

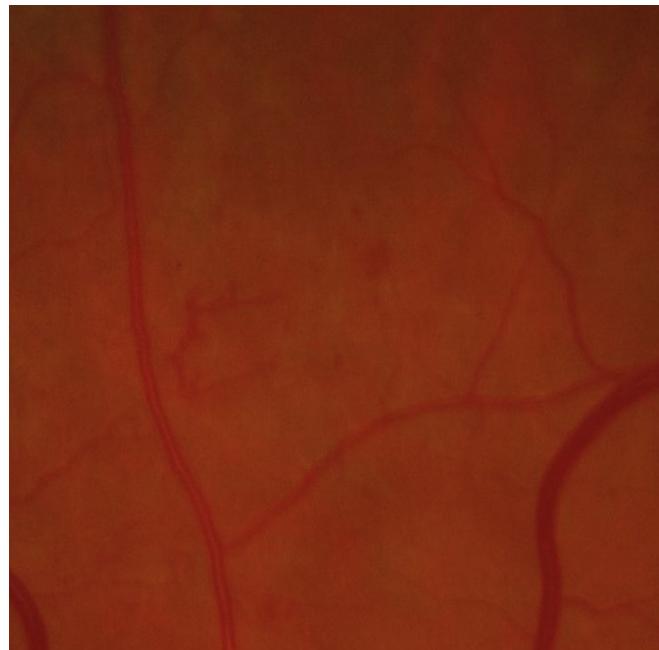


Figure 2 An example of an intra-retinal microvascular abnormality.



Figure 3 NVD formation.

- **IRMAs** are defined as tortuous intra-retinal vascular segments that vary in calibre (Figure 2). They derive from remodelling of the retinal capillaries and small collateral vessels in areas of microvascular occlusion.
- **Blot haemorrhages** are usually in a deeper retinal layer than more superficial dot haemorrhages and flame haemorrhages.

With increasing ischaemia, there is an increasing risk of progression to proliferative DR in 1 year. The risk increases from approximately 11.3% for the lower levels of pre-proliferative DR to 54.8% for the most severe DR level.

Proliferative DR

New vessels developing in DR are characterized according to whether they develop at or near the optic disc (NVDs) or elsewhere in the retina (NVEs):

- **NVDs** are defined as any new vessel developing at the optic disc (Figure 3) or within one disc diameter of the edge of the optic disc.
- **NVEs** are defined as any new vessel developing more than one disc diameter away from the edge of the optic disc (Figure 4).

They usually develop from the venous circulation and grow forwards in the vitreous gel, but they can also arise from the arterial circulation. New vessels growing into the vitreous are fragile and likely to bleed, causing significant floaters and blurring of the vision. In the more advanced stages, they can contract and cause retinal detachment.

The Diabetic Retinopathy Study (DRS) recommended prompt treatment in the presence of DRS high-risk characteristics, which reduced the 2-year risk of severe visual loss by 50% or more. These high-risk characteristics were defined as:

- the presence of pre-retinal or vitreous haemorrhage
- eyes with NVDs that equalled or exceeded one-quarter to one-third of the disc area in extent, with no haemorrhage

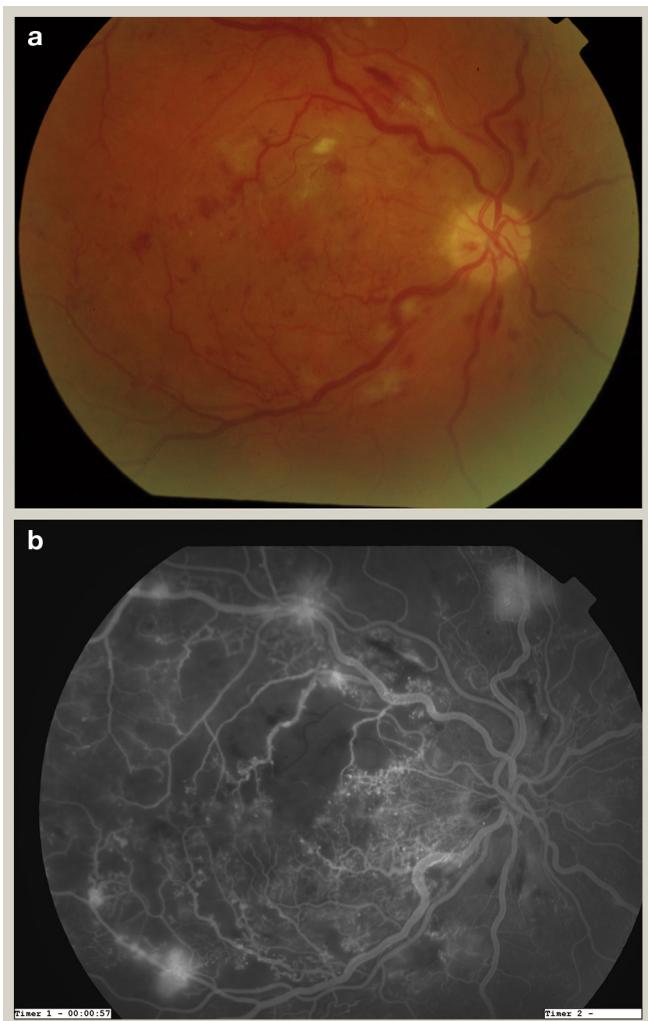


Figure 4 (a) Flame haemorrhages, cotton wool spots, IRMA and blot haemorrhages. (b) A mid-phase fluorescein angiogram showing IRMA ischaemic areas and early leakage from NVEs.

- NVE equalling more than half a disc area, with haemorrhage (from the NVEs).

Untreated, eyes with high-risk characteristics had a 25.6–36.9% chance of severe visual loss within 2 years.

Eyes with proliferative DR without high-risk characteristics showed the following risks of severe visual loss:

- untreated – 7.0% at 2 years, and 20.9% at 4 years
- treated – 3.2% at 2 years, and 7.4% at 4 years.

If a vitreous haemorrhage obscures the retinal view, it is usual to perform an ultrasound B-scan to check that the retina is flat. The vitreous haemorrhage often clears within 1 month, making laser treatment possible.

The adverse effects of laser treatment, particularly cystoid macular oedema and peripheral field loss related to laser treatment (as opposed to the disease process), have reduced since the early studies. Hence there has been an increasing tendency to treat eyes with proliferative DR and low-risk characteristics.

Advances in laser treatment have seen the introduction of multispot lasers, which allow multiple burns to be applied with

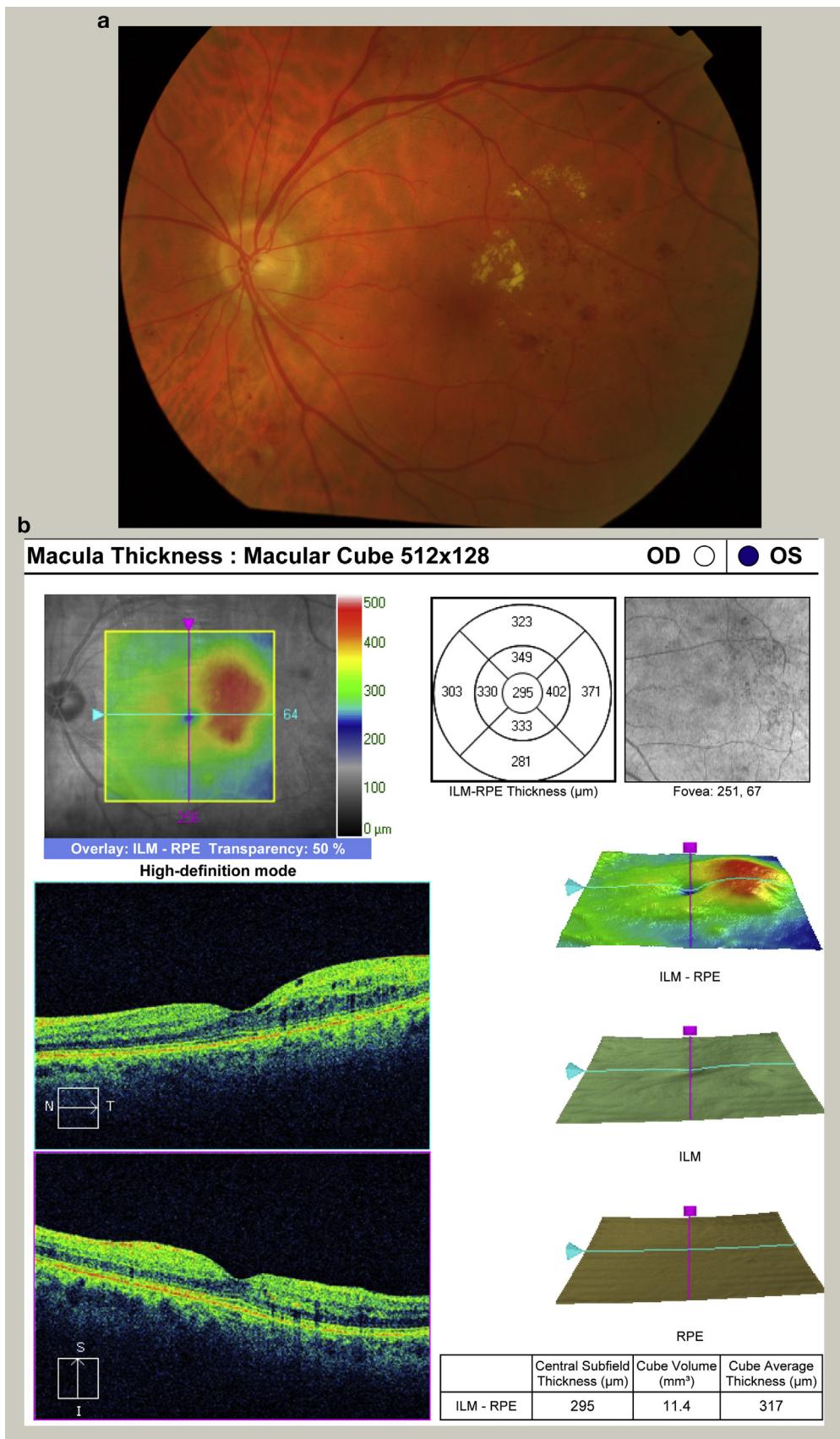


Figure 5 (a) Exudates in focal maculopathy. **(b)** OCT of the left macular area from **(a)**.

one depression of the foot pedal. Multispot lasers have the advantages of increased uniformity and precision of spot placement, reduced discomfort felt by the patient (probably related to the reduced burn duration) and reduced overall treatment time.

However, for the first time since 1976 an alternative treatment is being suggested – regular injections of vascular endothelial growth factor (VEGF) inhibitors. A study by the Diabetic Retinopathy Clinical Research Network assessed the non-inferiority of intravitreal ranibizumab compared with PRP for visual

acuity outcomes in patients with proliferative DR.² Among eyes with proliferative DR, treatment with ranibizumab resulted in visual acuity that was no worse than with panretinal photocoagulation (PRP) treatment at 2 years. A study from the UK found that patients with proliferative DR who were treated with intravitreal aflibercept had an improved outcome at 1 year compared with those treated with PRP standard care.³ However, the long-term requirements of a large number of injections to maintain this benefit and the economic costs are currently unknown, so PRP continues to be standard care for proliferative DR.

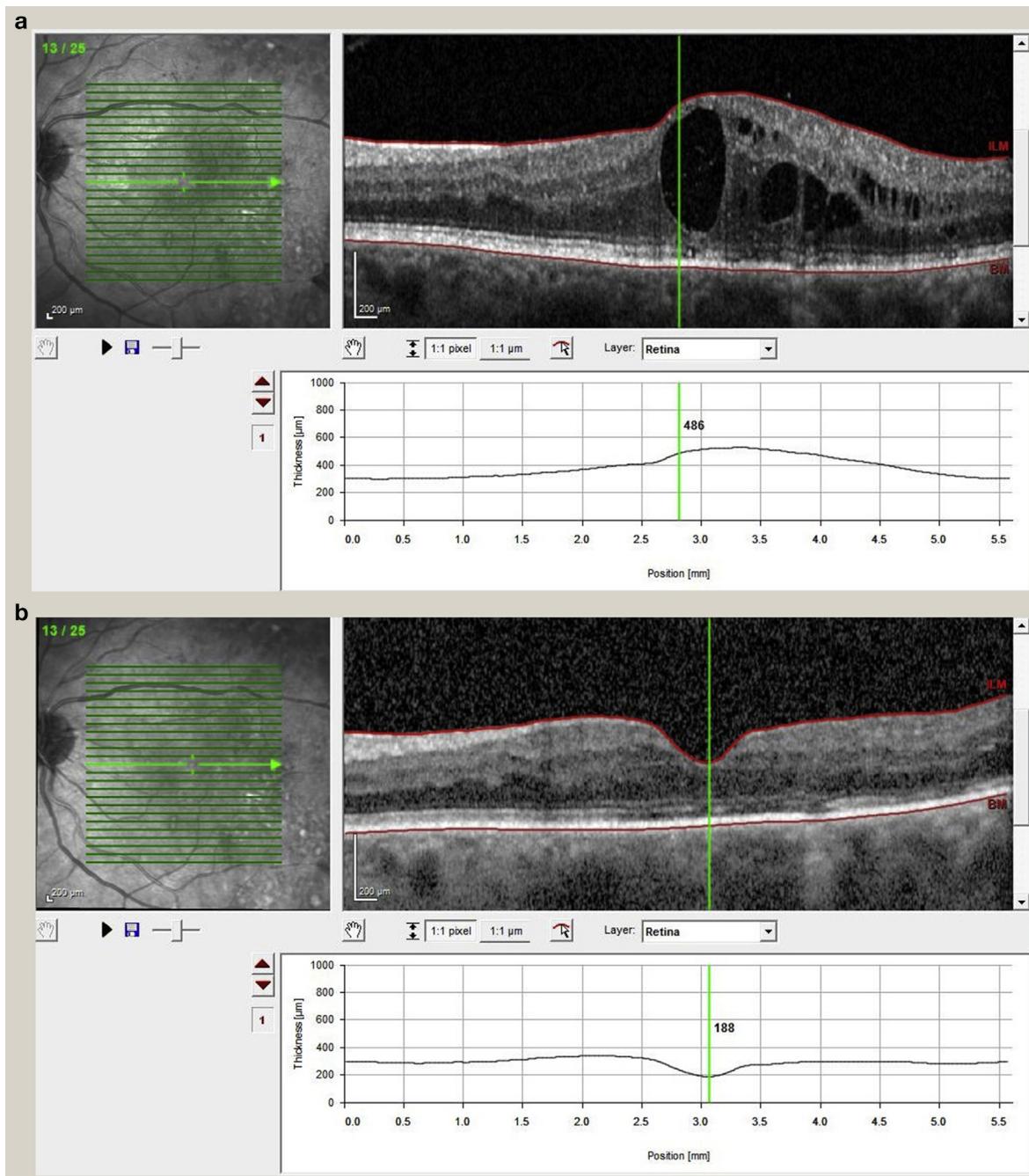


Figure 6 (a) Before treatment with a VEGF inhibitor, showing central oedema and a visual acuity of 6/24. (b) After treatment with a VEGF inhibitor, showing a normal appearance after clearing of central oedema; the visual acuity improved to 6/9.

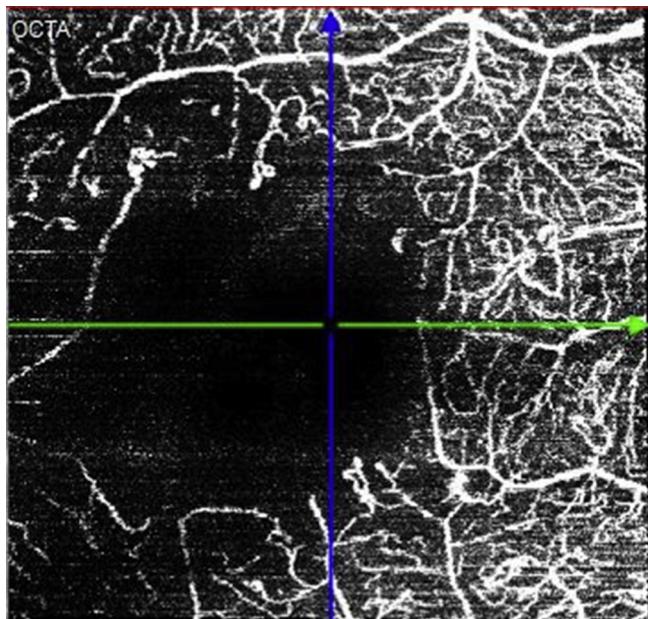


Figure 7 This patient's vision has dropped to 6/18 and she is complaining of blurred central vision. OCTA shows a poor blood supply in the macular area consistent with diabetic macular ischaemia.

Maculopathy

Diabetic maculopathy can be classified into the following types:

- focal (subdivided into focal exudates and focal/multifocal oedema)
- diffuse
- ischaemic.

In focal maculopathy, focal leakage tends to occur from microaneurysms, often with a circinate pattern of exudates around the focal leakage.

In the diffuse variety, there is a generalized breakdown of the blood–retina barrier and profuse early leakage from the entire capillary bed of the posterior pole, sometimes accompanied by cystoid macular changes.

In ischaemic maculopathy, enlargement of the foveal avascular zone caused by capillary closure is found, with variable degrees of visual loss.

Optical coherence tomography (OCT) is widely used in the assessment and monitoring of patients with diabetic macular oedema. It is an imaging technique that interprets the ‘time of flight’ and intensity of reflected optical waves using interferometry (Figure 5). As a result of the high level of resolution, OCT is particularly suitable for retinal thickness measurements, offering penetration to approximately 2–3 mm with micrometre-scale axial and lateral resolution.

The ETDRS reported that focal photocoagulation of ‘clinically significant’ diabetic macular oedema substantially reduced the risk of visual loss. Clinically significant’ macular oedema was defined as:

- thickening of the retina at or within 500 micrometres of the centre of the macula
- hard exudates at or within 500 micrometres of the centre of the fovea, if associated with thickening of the adjacent retina (not residual hard exudates remaining after the disappearance of retinal thickening)
- a zone or zones of retinal thickening one disc in area or larger, any part of which is within one disc diameter of the centre of the macula.

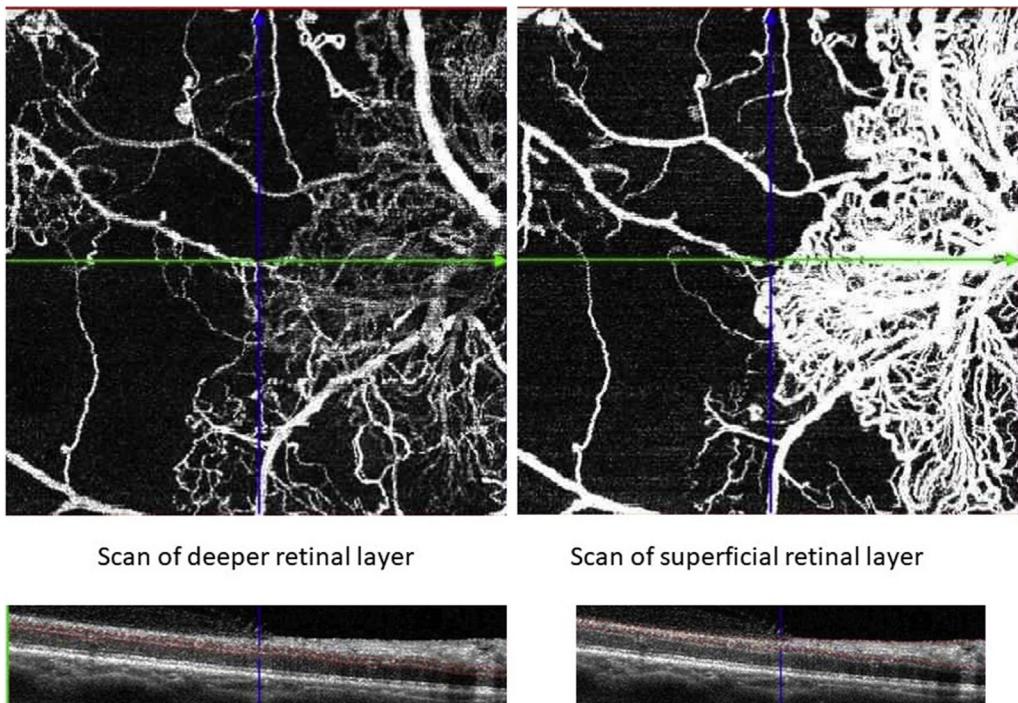


Figure 8 NVE in the supero-temporal area of the retina in a 26-year-old man. Superficial and deep OCTA demonstrates ischaemic areas with a poor vascular supply peripheral to the neovascular complex.

Treatment of diabetic maculopathy with VEGF inhibitors

Ocular neovascularization (angiogenesis) and increased vascular permeability have been associated with VEGF, which has provided a therapeutic rationale for targeting of VEGF DR.

Drugs have been developed that are given intravitreally, with an effect that lasts for approximately 1 month; therefore injections should be given as a course. There were concerns that, as VEGF has neuroprotective effects, there might be neurological or cardiovascular adverse effects with significant systemic absorption of anti-VEGF agents; however, these concerns do not appear to have been borne out in any trials or subsequent product evaluations. The main concern of any intravitreal treatment is the risk of endophthalmitis (infection being introduced into the eye at the time of the intravitreal injection; 0.04–0.06 per injection). There may also be a sustained elevation of intraocular pressure, which occurred in 9.5% of patients compared with 3.4% in a control group.

In England, National Institute for Health and Care Excellence guidelines restrict this treatment to patients with a disc centre thickness of 400 micrometres or more. A number of studies have shown that this treatment is beneficial in diabetic maculopathy when ranibizumab,⁴ afibercept⁵ or the off-label bevacizumab is used. In diabetic maculopathy, there tends to be a reduction in treatment frequency required over time, with an average of 7–9 anti-VEGF injections being required in the first year, 2–4 in the second year, 1–3 in the third year and approximately one injection per year in years 4 and 5.

It has been shown that inflammation plays a significant role in the development of macular oedema in some patients with diabetes. Dexamethasone implants, which last for approximately 3 months, are often given to patients who do not respond to VEGF inhibitors and are pseudophakic. If these are successful without significant elevation of the intraocular pressure, a longer lasting fluocinolone acetonide implant is available. The response to treatment varies, with some patients responding well, some responding slowly and some not at all. An example of a patient who responded after only one treatment is shown in Figure 6.

Advances in OCT have seen the development of non-invasive, dye-free angiography – OCT angiography (OCTA). Fluorescein angiography previously involved the intravenous injection of fluorescein, which is associated with a very small risk of anaphylaxis. Fluorescein angiography delineated the vasculature

as the fluorescein appeared in the choroidal, arterial, arteriovenous and venous phases, and fluorescein leakage from blood vessels was apparent. OCTA, however, detects movement of blood cells within retinal vasculature and does not detect leakage. Therefore apparent absence of a blood vessel on OCTA can just represent slow blood flow, and reading OCTA is very different from reading fluorescein angiograms. Examples of OCTA are shown in Figures 7 and 8. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online [here](#).

Question 1

A 24-year-old woman presented with a 2-hour history of a shower of floaters in her right eye and blurring of her right vision that came on after coughing. She was able to see movement, but nothing was clear. She had type 1 diabetes but had been a regular non-attender at clinic appointments and had been running her blood sugars high because in this way she managed to retain a slim figure.

What is the most likely diagnosis?

- A. Muscae volitantes
- B. Diabetic macular oedema
- C. Branch retinal vein occlusion
- D. Retinal detachment
- E. Vitreous haemorrhage

Question 2

A 45-year-old woman was being reviewed for possible eye complications. She had a 30-year history of type 1 diabetes.

Which one of the following retinal changes is most predictive of proliferative diabetic retinopathy?

- A Multiple flame haemorrhages
- B Exudates
- C Cotton wool spots
- D Venous beading
- E Microaneurysms

Question 3

A 56-year-old man presented with a 3-week history of decreased vision in the right eye. There was no pain. He had had type 2 diabetes for 20 years.

On clinical examination, the retina appeared normal. Optical coherence tomography angiography examination was performed.

What is this technique most likely to demonstrate?

- A Whether blood vessels are present
- B Whether there is a reasonable flow of blood within a vessel
- C Whether there is leakage from a vessel
- D Whether haemorrhages are present
- E Whether diabetic macular oedema is present

PREFERRED PRACTICE PATTERN®



Diabetic Retinopathy

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RETINA/VITREOUS PREFERRED PRACTICE PATTERN® DEVELOPMENT PROCESS AND PARTICIPANTS

The **Retina/Vitreous Preferred Practice Pattern® Panel** members wrote the Diabetic Retinopathy Preferred Practice Pattern® (“PPP”) guidelines. The PPP Panel members discussed and reviewed successive drafts of the document, meeting in person twice and conducting other review by e-mail discussion, to develop a consensus over the final version of the document.

Retina/Vitreous Preferred Practice Pattern Panel 2013–2014

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The **Preferred Practice Patterns Committee** members reviewed and discussed the document during a meeting in March 2014. The document was edited in response to the discussion and comments.

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The Diabetic Retinopathy PPP was then sent for review to additional internal and external groups and individuals in June 2014. All those returning comments were required to provide disclosure of relevant relationships with industry to have their comments considered. Members of the Retina/Vitreous Preferred Practice Pattern Panel reviewed and discussed these comments and determined revisions to the document.

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In compliance with the Council of Medical Specialty Societies' Code for Interactions with Companies (available at www.cmss.org/codeforinteractions.aspx), relevant relationships with industry are listed. The Academy has Relationship with Industry Procedures to comply with the Code (available at www.aao.org/about-preferred-practice-patterns). A majority (86%) of the members of the Retina/Vitreous Preferred Practice Pattern Panel 2013–2014 had no financial relationship to disclose.

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The disclosures of relevant relationships to industry of other reviewers of the document from January to August 2014 are available online at www.aao.org/ppp.



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OBJECTIVES OF PREFERRED PRACTICE PATTERN® GUIDELINES

As a service to its members and the public, the American Academy of Ophthalmology has developed a series of Preferred Practice Pattern® guidelines that **identify characteristics and components of quality eye care**. Appendix 1 describes the core criteria of quality eye care.

The Preferred Practice Pattern® guidelines are based on the best available scientific data as interpreted by panels of knowledgeable health professionals. In some instances, such as when results of carefully conducted clinical trials are available, the data are particularly persuasive and provide clear guidance. In other instances, the panels have to rely on their collective judgment and evaluation of available evidence.

These documents provide guidance for the pattern of practice, not for the care of a particular individual. While they should generally meet the needs of most patients, they cannot possibly best meet the needs of all patients. Adherence to these PPPs will not ensure a successful outcome in every situation. These practice patterns should not be deemed inclusive of all proper methods of care or exclusive of other methods of care reasonably directed at obtaining the best results. It may be necessary to approach different patients' needs in different ways. The physician must make the ultimate judgment about the propriety of the care of a particular patient in light of all of the circumstances presented by that patient. The American Academy of Ophthalmology is available to assist members in resolving ethical dilemmas that arise in the course of ophthalmic practice.

Preferred Practice Pattern® guidelines are not medical standards to be adhered to in all individual situations. The Academy specifically disclaims any and all liability for injury or other damages of any kind, from negligence or otherwise, for any and all claims that may arise out of the use of any recommendations or other information contained herein.

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Innovation in medicine is essential to ensure the future health of the American public, and the Academy encourages the development of new diagnostic and therapeutic methods that will improve eye care. It is essential to recognize that true medical excellence is achieved only when the patients' needs are the foremost consideration.

All Preferred Practice Pattern® guidelines are reviewed by their parent panel annually or earlier if developments warrant and updated accordingly. To ensure that all PPPs are current, each is valid for 5 years from the "approved by" date unless superseded by a revision. Preferred Practice Pattern guidelines are funded by the Academy without commercial support. Authors and reviewers of PPPs are volunteers and do not receive any financial compensation for their contributions to the documents. The PPPs are externally reviewed by experts and stakeholders, including consumer representatives, before publication. The PPPs are developed in compliance with the Council of Medical Specialty Societies' Code for Interactions with Companies. The Academy has Relationship with Industry Procedures (available at www.aao.org/about-preferred-practice-patterns) to comply with the Code.

Appendix 2 contains the International Statistical Classification of Diseases and Related Health Problems (ICD) codes for the disease entities that this PPP covers. The intended users of the Diabetic Retinopathy PPP are ophthalmologists.



METHODS AND KEY TO RATINGS

Preferred Practice Pattern® guidelines should be clinically relevant and specific enough to provide useful information to practitioners. Where evidence exists to support a recommendation for care, the recommendation should be given an explicit rating that shows the strength of evidence. To accomplish these aims, methods from the Scottish Intercollegiate Guideline Network¹ (SIGN) and the Grading of Recommendations Assessment, Development and Evaluation² (GRADE) group are used. GRADE is a systematic approach to grading the strength of the total body of evidence that is available to support recommendations on a specific clinical management issue. Organizations that have adopted GRADE include SIGN, the World Health Organization, the Agency for Healthcare Research and Policy, and the American College of Physicians.³

- ◆ All studies used to form a recommendation for care are graded for strength of evidence individually, and that grade is listed with the study citation.
- ◆ To rate individual studies, a scale based on SIGN¹ is used. The definitions and levels of evidence to rate individual studies are as follows:

I++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
I+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
I-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
II++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
II+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
II-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
III	Nonanalytic studies (e.g., case reports, case series)

- ◆ Recommendations for care are formed based on the body of the evidence. The body of evidence quality ratings are defined by GRADE² as follows:

Good quality	Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Insufficient quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate Any estimate of effect is very uncertain

- ◆ Key recommendations for care are defined by GRADE² as follows:

Strong recommendation	Used when the desirable effects of an intervention clearly outweigh the undesirable effects or clearly do not
Discretionary recommendation	Used when the trade-offs are less certain—either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced

- ◆ The Highlighted Findings and Recommendations for Care section lists points determined by the PPP Panel to be of particular importance to vision and quality of life outcomes.
- ◆ All recommendations for care in this PPP were rated using the system described above. To locate ratings for specific recommendations, see Appendix 3 for additional information.
- ◆ A literature search to update the PPP was undertaken in June 2013 in PubMed and the Cochrane Library. Complete details of the literature search are available at www.aao.org/ppp.



HIGHLIGHTED FINDINGS AND RECOMMENDATIONS FOR CARE

The prevalence of diabetes, both worldwide and in the United States, is increasing; as such, the prevalence of diabetic retinopathy and vision-threatening diabetic retinopathy (VTDR) is also expected to increase dramatically.

Currently, only about 60% of people with diabetes have yearly screenings for diabetic retinopathy.

People with Type 1 diabetes should have annual screenings for diabetic retinopathy beginning 5 years after the onset of their disease, whereas those with Type 2 diabetes should have a prompt examination at the time of diagnosis and at least yearly examinations thereafter.

Maintaining near-normal glucose levels and near-normal blood pressure lowers the risk of retinopathy developing and/or progressing, so patients should be informed of the importance of maintaining good glycosylated hemoglobin levels, serum lipids, and blood pressure.

Patients with diabetes may use aspirin for other medical indications without an adverse effect on their risk of diabetic retinopathy.

Women who develop gestational diabetes do not require an eye examination during pregnancy and do not appear to be at increased risk of developing diabetic retinopathy during pregnancy. However, patients with diabetes who become pregnant should be examined early in the course of the pregnancy.

Referral to an ophthalmologist is required when there is any nonproliferative diabetic retinopathy, proliferative retinopathy, or macular edema.

Ophthalmologists should communicate both ophthalmologic findings and level of retinopathy to the primary care physician. They should emphasize to the patient the need to adhere to the primary care physician's guidance to optimize metabolic control.

Intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents have been shown to be an effective treatment for center-involving diabetic macular edema and also as an alternative therapy for proliferative diabetic retinopathy.

At this time, laser photocoagulation remains the preferred treatment for non-center-involving diabetic macular edema.



INTRODUCTION

DISEASE DEFINITION

Diabetic retinopathy is a leading cause of visual impairment in working-age adults. Although defects in neurosensory function have been demonstrated in patients with diabetes mellitus prior to the onset of vascular lesions, the most common early clinically visible manifestations of diabetic retinopathy include microaneurysm formation and intraretinal hemorrhages. Microvascular damage leads to retinal capillary nonperfusion, cotton wool spots, increased numbers of hemorrhages, venous abnormalities, and intraretinal microvascular abnormalities (IRMA). During this stage, increased vasopermeability can result in retinal thickening (edema) and/or exudates that may lead to a loss in central visual acuity. The proliferative stage results from closure of arterioles and venules with secondary proliferation of new vessels on the disc, retina, iris, and in the filtration angle. These new vessels then lead to traction retinal detachments and neovascular glaucoma, respectively. Vision can be lost in this stage as a result of capillary nonperfusion or edema in the macula, vitreous hemorrhage, and distortion or traction retinal detachment.

A description of the fundus findings in various stages of diabetic retinopathy is included in the Natural History section, and important terms are defined in the Glossary.

PATIENT POPULATION

The patient population includes all patients with diabetes mellitus.

CLINICAL OBJECTIVES

- ◆ Identify patients at risk of developing diabetic retinopathy.
- ◆ Encourage a collaborative approach between the patient, the primary care physician, and subspecialists in the management of the patient's systemic disorder, with specific attention to control of blood sugar (hemoglobin A_{1c} [HbA_{1c}]), blood pressure, serum lipids, body weight, and management of renal disease, coronary artery disease,⁴ and neuropathy.
- ◆ Encourage and provide lifelong monitoring of retinopathy progression.
- ◆ Treat patients with visual loss or those at risk for visual loss from diabetic retinopathy.
- ◆ Minimize the side effects of treatment that might adversely affect the patient's vision and/or vision-related quality of life.
- ◆ Provide or refer for visual rehabilitation services when a patient has visual impairment from the disease.



BACKGROUND

INTRODUCTION

Two forms of diabetes mellitus are recognized. Type 1, previously called juvenile-onset or insulin-dependent diabetes, is characterized by cellular-mediated autoimmune destruction of the beta-cells in the pancreas and usually leads to severe insulin deficiency. Type 2 diabetes was previously referred to as adult-onset or noninsulin-dependent diabetes. Type 2 is characterized by a range of disease from insulin resistance with relative insulin deficiency to predominately an insulin secretory defect combined with insulin resistance. Type 2 patients usually have a relative rather than an absolute insulin deficiency, may take insulin, yet typically do not need insulin for survival. Many patients with Type 2 diabetes are obese, and obesity itself causes relative insulin resistance. Between 90% and 95% of all patients with diabetes have Type 2 diabetes.⁵ Because of the disproportionately large number of patients with Type 2 diabetes, this group comprises a larger proportion of the disease burden in patients with visual impairment from diabetic retinopathy, even though Type 1 diabetes is associated with more frequent and more severe ocular complications.^{6,7}

Diabetic Retinopathy PPP: Risk Factors

Prevalence of Diabetes

An estimated 25.6 million Americans aged 20 years or older have either been diagnosed or remain undiagnosed with diabetes mellitus (11% of people in this age group),⁸ and about one-third are not aware that they have the disease.⁹ An additional 79 million persons have impaired fasting blood glucose levels (based on both fasting blood glucose levels and HbA_{1c} levels).⁹ In the United States, an estimated three out of five people with diabetes have one or more of the complications associated with the disease.¹⁰ Americans of African descent or Hispanic ethnicity have a disproportionately high prevalence of diabetes compared with Americans of European descent (12.6%, 11.8%, 7.0%, respectively), whereas Asian Americans have only a slightly higher prevalence (8.4%).⁹ Native Americans and Alaskan Natives have an approximate diabetes prevalence of 9%, with a 46% increase between 1990 and 1998 among this group under age 35.^{11, 12} Other research suggests a high prevalence of diabetes in Asia.^{13, 14} In addition, there is evidence suggesting that diabetes develops at earlier ages and carries a higher incidence of complications among ethnic minorities.¹⁵⁻¹⁷

According to estimates based from the United States Census Bureau data, approximately one-third of Americans are at risk of developing diabetes mellitus during their lifetime.¹⁸ With increasing industrialization and globalization, there is a concomitant increasing prevalence of diabetes that is leading to a worldwide epidemic.¹⁹ An alarming increase in the frequency of Type 2 diabetes in the pediatric age group has been noted in several countries,^{7, 20-24} including in the United States, and has been associated with the increased frequency of childhood obesity.²⁵ Diabetes is one of the most common diseases in school-aged children. Clearly, these trends predict an increase in the number of individuals with diabetes as well as the associated increased costs for health care and the burdens of disability associated with diabetes and its complications.

Prevalence of Diabetic Retinopathy

Diabetic retinopathy is a leading cause of new cases of legal blindness among working-age Americans and represents a leading cause of blindness in this age group worldwide.²⁶ The prevalence rate for retinopathy for all adults with diabetes aged 40 and older in the United States is 28.5% (4.2 million people); worldwide, the prevalence rate has been estimated at 34.6% (93 million people). An estimate of the prevalence rate for vision-threatening diabetic retinopathy (VTDR) in the United States is 4.4% (0.7 million people). Worldwide, this prevalence rate has been estimated at 10.2% (28 million people).^{27, 28} Assuming a similar prevalence of diabetes mellitus, the projected prevalence of individuals with any diabetic retinopathy in the United States by the year 2020 is 6 million persons, and 1.34 million persons will have VTDR.

RISK FACTORS

Duration of diabetes is a major risk factor associated with the development of diabetic retinopathy. After 5 years, approximately 25% of Type 1 patients will have retinopathy. After 10 years, almost 60% have retinopathy, and after 15 years, 80% have retinopathy.^{29, 30} In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) for patients ages 30 and younger, proliferative diabetic retinopathy (PDR), the most vision-threatening form of the disease, was present in approximately 50% of Type 1 patients who had the disease for 20 years.³¹ In the Los Angeles Latino Eye Study (LALES) and in Proyecto VER (Vision, Evaluation and Research), 18% of participants with diabetes of more than 15 years' duration had PDR, with no difference in the percentage with PDR between those with Type 1 versus Type 2 diabetes.^{30, 32}

Of Type 2 patients over the age of 30 who have a known duration of diabetes of less than 5 years, 40% of those patients taking insulin and 24% of those not taking insulin have retinopathy. These rates increase to 84% and 53%, respectively, when the duration of diabetes has been documented for up to 19 years. Proliferative diabetic retinopathy develops in 2% of Type 2 patients who have diabetes for less than 5 years and in 25% of patients who have diabetes for 25 years or more.³³ Comparisons of information from WESDR and more recent population-based studies such as Proyecto VER and LALES may account for differences in blood glucose and hypertension management that have occurred over time.

Glycemic control is the key modifiable risk factor associated with the development of diabetic retinopathy. Support for this association is based on both clinical trials and epidemiologic studies.³⁴⁻⁴¹ There is general agreement that duration of diabetes and severity of hyperglycemia are the major risk factors for developing retinopathy. Once retinopathy is present, duration of diabetes appears to be a less important factor than glycemic control in forecasting progression from earlier to later stages of retinopathy.^{42, 43} It is recommended that a HbA_{1c} of 7% or lower is the target for glycemic control in most patients, whereas in selected patients, there may be some benefit to setting a lower target of 6.5%.⁴⁴ Intensive management of hypertension may slow retinopathy progression, yet the data remain inconclusive.^{45, 46} Large studies have suggested that management of serum lipids may reduce retinopathy progression and the need for treatment.⁴⁷⁻⁵⁰ There is less agreement among studies concerning the importance of other factors such as age, type of diabetes, clotting factors, renal disease, physical inactivity, inflammatory biomarkers, and use of angiotensin-converting enzyme inhibitors.^{42, 48, 51-54} Many of these factors are associated with substantial cardiovascular morbidity and mortality and other complications associated with diabetes. Thus, ophthalmologists should encourage patients with diabetes to be as compliant as possible with therapy of all medical aspects of their disease.⁵⁵

NATURAL HISTORY

Diabetic retinopathy progresses in an orderly fashion from mild to more severe stages when there is not appropriate intervention. It is important to recognize the stages when treatment may be most beneficial. Several decades of clinical research have provided excellent data on the natural course of the disease and on treatment strategies that are 90% effective in preventing the occurrence of severe vision loss.⁵⁶ The outcomes of key clinical trials form a solid foundation in support of treating diabetic retinopathy. The results of these studies are summarized in Appendices 4 and 5. Major studies include the following (see Glossary):

- ◆ Diabetes Control and Complications Trial (DCCT)^{36, 57, 58}
- ◆ Follow-up study to the DCCT titled Epidemiology of Diabetes Interventions and Complications (EDIC)^{35, 37, 49, 59, 60}
- ◆ Diabetic Retinopathy Study (DRS)^{61, 62}
- ◆ Early Treatment Diabetic Retinopathy Study (ETDRS)⁶³⁻⁶⁵
- ◆ Diabetic Retinopathy Vitrectomy Study (DRVS)⁶⁶
- ◆ Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR)⁶⁷
- ◆ Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study⁶⁸
- ◆ Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial⁶⁹
- ◆ Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol I study⁷⁰
- ◆ United Kingdom Prospective Diabetes Study (UKPDS)^{38, 45, 71}

The nonproliferative stages of diabetic retinopathy are characterized by retinal vascular related abnormalities, such as microaneurysms, intraretinal hemorrhages, venous dilation, and cotton-wool spots. Increased retinal vascular permeability that occurs at these or later stages of retinopathy may result in retinal thickening (edema) and lipid deposits (hard exudates). Clinically significant macular edema (CSME) is a term commonly used to describe retinal thickening and/or adjacent hard exudates that either involve the center of the macula or threaten to involve it. Patients with CSME should be considered for prompt treatment, particularly when the center of the macula is already involved or if retinal thickening and/or hard exudates are very close to the center (see Care Process). Clinically significant macular edema can be divided into center-involving and non-center-involving macular edema. (See Glossary.)

As diabetic retinopathy progresses, there is a gradual closure of retinal vessels that results in impaired perfusion and retinal ischemia. Signs of increasing ischemia include venous abnormalities (e.g., dilation, beading, loops), IRMA, and more severe and extensive vascular leakage characterized by increasing retinal hemorrhages and exudation. When these signs progress beyond certain defined thresholds, severe nonproliferative diabetic retinopathy (NPDR) is diagnosed. Such patients should be considered candidates for treatment with panretinal (scatter) photocoagulation (see Care Process).

Diabetic Retinopathy PPP: Disease Severity Scale

The more advanced stage, PDR, is characterized by the onset of neovascularization at the inner surface of the retina induced by more global retinal ischemia. New vessels on or near the optic disc (NVD) and new vessels elsewhere in the retina (NVE) are prone to bleed, resulting in vitreous hemorrhage. These new vessels may undergo fibrosis and contraction; this and other fibrous proliferation may result in epiretinal membrane formation, vitreoretinal traction bands, retinal tears, and traction or rhegmatogenous retinal detachments. When new vessels are accompanied by vitreous hemorrhage, or when new vessels at the optic disc occupy greater than or equal to about one-quarter to one-third disc area, even in the absence of vitreous hemorrhage, PDR is considered high-risk. (See Glossary.) Neovascular glaucoma can result from new vessels growing on the iris (NVI) and anterior chamber angle structures. Patients with neovascular glaucoma or high-risk PDR should receive prompt panretinal photocoagulation, and their treating ophthalmologist should also consider initiating anti-vascular endothelial growth factor (VEGF) therapy (see Care Process and Glossary).

Table 1 classifies diabetic retinopathy by severity based on clinical findings. In an attempt to improve communication worldwide between ophthalmologists and primary care physicians caring for patients with diabetes, an international clinical disease severity scale has been developed for diabetic retinopathy and macular edema⁷² (See Tables 1 and 2.) This scale is based on the ETDRS classification of diabetic retinopathy and on the data collected from clinical trials and epidemiologic studies of diabetic retinopathy. (See Appendix 6.)

TABLE 1 DIABETIC RETINOPATHY DISEASE SEVERITY SCALE AND INTERNATIONAL CLINICAL DIABETIC RETINOPATHY DISEASE SEVERITY SCALE

Disease Severity Level	Findings Observable upon Dilated Ophthalmoscopy
No apparent retinopathy	No abnormalities
Mild NPDR (see Glossary)	Microaneurysms only
Moderate NPDR (see Glossary)	More than just microaneurysms but less than severe NPDR
Severe NPDR	<p>U.S. Definition</p> <p>Any of the following (4-2-1 rule) and no signs of proliferative retinopathy:</p> <ul style="list-style-type: none"> • Severe intraretinal hemorrhages and microaneurysms in each of four quadrants • Definite venous beading in two or more quadrants • Moderate IRMA in one or more quadrants <p>International Definition</p> <p>Any of the following and no signs of proliferative retinopathy:</p> <ul style="list-style-type: none"> • More than 20 intraretinal hemorrhages in each of four quadrants • Definite venous beading in two or more quadrants • Prominent IRMA in one or more quadrants
PDR	<p>One or both of the following:</p> <ul style="list-style-type: none"> • Neovascularization • Vitreous/preretinal hemorrhage

IRMA = intraretinal microvascular abnormalities; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy

NOTE:

- Any patient with two or more of the characteristics of severe NPDR is considered to have very severe NPDR.
- PDR may be classified as high-risk and non-high-risk. See Table 6 for more information.

Adapted with permission from Wilkinson CP, Ferris FL III, Klein RE, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology* 2003;110:1679.

TABLE 2 INTERNATIONAL CLINICAL DIABETIC MACULAR EDEMA DISEASE SEVERITY SCALE

Proposed Disease Severity Level	Findings Observable upon Dilated Ophthalmoscopy
Diabetic macular edema apparently absent	No apparent retinal thickening or hard exudates in posterior pole
Diabetic macular edema apparently present	Some apparent retinal thickening or hard exudates in posterior pole
If diabetic macular edema is present, it can be categorized as follows:	
Proposed Disease Severity Level	Findings Observable upon Dilated Ophthalmoscopy*
Diabetic macular edema present	<ul style="list-style-type: none"> • Mild diabetic macular edema: some retinal thickening or hard exudates in posterior pole but distant from the center of the macula • Moderate diabetic macular edema: retinal thickening or hard exudates approaching the center of the macula but not involving the center • Severe diabetic macular edema: retinal thickening or hard exudates involving the center of the macula

Reproduced with permission from Wilkinson CP, Ferris FL III, Klein RE, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology* 2003;110:1680.

* Hard exudates are a sign of current or previous macular edema. Diabetic macular edema is defined as retinal thickening; this requires a three-dimensional assessment that is best performed by dilated examination using slit-lamp biomicroscopy and/or stereoscopic fundus photography. Optical coherence tomography may supplement the fundus evaluation for determining the presence of diabetic macular edema.



CARE PROCESS

The care process for diabetic retinopathy includes a medical history, a regular ophthalmologic examination or screening of high-quality retinal photographs of patients who have not had previous treatment for diabetic retinopathy or other eye disease, and regular follow-up. The purpose of an effective screening program is to determine who needs to be referred to an ophthalmologist for close follow-up and possible treatment, and who may simply be screened annually. Early detection of retinopathy depends on educating patients who have diabetes, as well as their family, friends, and health care providers, about the importance of regular eye examination even though the patient may be asymptomatic. In lay terms, patients must be informed that they may have good vision and no ocular symptoms but that they may still have significant disease that needs treatment. They should be educated that early treatment works best and that is why they need to return for an annual eye examination, even when their vision is good. Individuals with Type 2 diabetes mellitus without diabetic retinopathy should be encouraged to have an annual dilated eye examination to detect the onset of diabetic retinopathy.^{29, 33, 73-90} Individuals with Type 1 diabetes mellitus without diabetic retinopathy should have annual dilated eye examinations beginning 5 years after the onset of diabetes.^{29, 91} The recommended timing of the first ophthalmic examination and subsequent follow-up examinations for patients with diabetes is listed in Table 3 and described in the Management section.

TABLE 3 RECOMMENDED EYE EXAMINATIONS FOR PATIENTS WITH DIABETES MELLITUS AND NO DIABETIC RETINOPATHY

Diabetes Type	Recommended Initial Evaluation	Recommended Follow-up*
Type 1	5 years after diagnosis ²⁹	Yearly ²⁹
Type 2	At time of diagnosis ^{33, 92}	Yearly ^{33, 92}
Pregnancy [†] (Type 1 or Type 2)	Soon after conception and early in the first trimester ⁹³⁻⁹⁵	<ul style="list-style-type: none"> • No retinopathy to mild or moderate NPDR: every 3–12 months⁹³⁻⁹⁵ • Severe NPDR or worse: every 1–3 months⁹³⁻⁹⁵

NPDR = nonproliferative diabetic retinopathy

* Abnormal findings may dictate frequent follow-up examinations.

[†] Women who develop gestational diabetes do not require an eye examination during pregnancy and do not appear to be at increased risk for diabetic retinopathy during pregnancy.

Diabetic Retinopathy PPP: Patient Outcome Criteria

Maintaining near-normal glucose levels and near-normal blood pressure lowers the risk of retinopathy developing and/or progressing,^{35, 36, 38, 45, 96} so patients should be informed of the importance of maintaining good glycosylated hemoglobin levels, serum lipids, and blood pressure. Aspirin may be used by diabetic patients for other medical indications without concern that the aspirin therapy will worsen diabetic retinopathy.^{97, 98}

PATIENT OUTCOME CRITERIA

Patient outcome criteria include the following:

- ◆ Improvement or stabilization of visual function
- ◆ Improvement or stabilization of vision-related quality of life
- ◆ Optimal control of glucose, blood pressure, and other risk factors through close communication with the patient's primary care physician regarding the status of the diabetic retinopathy and the need for optimal metabolic control

DIAGNOSIS

The initial examination for a patient with diabetes mellitus includes all features of the comprehensive adult medical eye evaluation,⁹⁹ with particular attention to those aspects relevant to diabetic retinopathy.

History

An initial history should consider the following elements:

- ◆ Duration of diabetes^{29, 42, 100}
- ◆ Past glycemic control (HbA_{1c})^{42, 58, 100}
- ◆ Medications
- ◆ Medical history (e.g., obesity, renal disease,^{29, 33} systemic hypertension,^{29, 33} serum lipid levels,¹⁰¹ pregnancy,^{93, 94} neuropathy)
- ◆ Ocular history (e.g., trauma, other eye diseases, ocular injections, surgery, including retinal laser treatment and refractive surgery)

Physical Examination

The initial examination should include the following elements:

- ◆ Visual acuity¹⁰²
- ◆ Slit-lamp biomicroscopy
- ◆ Intraocular pressure (IOP)
- ◆ Gonioscopy before dilation, when indicated. Iris neovascularization is best recognized prior to dilation. When neovascularization of the iris is present or suspected, or if the IOP is elevated, undilated gonioscopy can be used to detect neovascularization in the anterior chamber angle.
- ◆ Pupillary assessment for optic nerve dysfunction
- ◆ Thorough funduscopic examination of the posterior pole⁶⁵
- ◆ Examination of the peripheral retina and vitreous

A dilated pupil is preferred to ensure optimal examination of the retina, because only 50% of eyes are correctly classified for the presence and severity of retinopathy through undilated pupils.¹⁰³ Slit-lamp biomicroscopy is the recommended method to evaluate retinopathy in the posterior pole and midperipheral retina.⁶⁵ Examination of the peripheral retina is best performed using indirect ophthalmoscopy or slit-lamp biomicroscopy.

Because treatment is effective in reducing the risk of visual loss, a detailed examination is indicated to assess for the following features that often lead to visual impairment:

- ◆ Macular edema
- ◆ Signs of severe NPDR (extensive retinal hemorrhages/microaneurysms, venous beading, and IRMA)
- ◆ Optic nerve head neovascularization and/or neovascularization elsewhere
- ◆ Vitreous or preretinal hemorrhage

Examination Schedule

Type 1 Diabetes

Many studies of patients with Type 1 diabetes have reported a direct relationship between the prevalence and severity of retinopathy and the duration of diabetes.^{33, 104, 105} The development of vision-threatening retinopathy is rare in children prior to puberty.^{104, 106} Among patients with Type 1 diabetes, substantial retinopathy may become apparent as early as 6 to 7 years after onset of the disease.²⁹ Ophthalmic examinations are recommended beginning 5 years after the diagnosis of Type 1 diabetes and annually thereafter, which will detect the vast majority of Type 1 patients who require therapy.^{29, 91} Patient education about the visual impact of early glucose control is important and should begin with the onset of disease.

Type 2 Diabetes

The time of onset of Type 2 diabetes is often difficult to determine and may precede the diagnosis by a number of years.¹⁰⁷ Up to 3% of patients whose diabetes is first diagnosed at age 30 or later will have CSME or high-risk features at the time of the initial diagnosis of diabetes.²⁹ About 30% of patients will have some manifestation of diabetic retinopathy at diagnosis. Therefore, the patient should be referred for ophthalmologic evaluation at the time of diagnosis.^{33, 92}

Diabetes Associated with Pregnancy

Diabetic retinopathy can worsen during pregnancy due to the physiologic changes of pregnancy itself or changes in overall metabolic control.⁹³⁻⁹⁵ Patients with diabetes who plan to become pregnant should have an ophthalmologic examination prior to pregnancy and counseled about the risk of development and/or progression of diabetic retinopathy. The obstetrician or primary care physician should carefully guide the management of the pregnant patient with diabetes' blood glucose, blood pressure, as well as other issues related to pregnancy.⁹³⁻⁹⁵ During the first trimester, an eye examination should be performed with repeat and follow-up visits scheduled depending on the severity of retinopathy. (See Table 3.) Women who develop gestational diabetes¹⁰⁸ do not require an eye examination during pregnancy and do not appear to be at increased risk for diabetic retinopathy during pregnancy.

After the examination, the ophthalmologist should discuss the results and their implications with the patient. Both eyes should be classified according to the categories of diabetic retinopathy and macular edema discussed in the Natural History and Treatment sections. Each category has an inherent risk for progression and is dependent upon adherence to overall diabetes control. Thus, the diagnostic category, combined with the level of diabetes control, determines the timing for both the intervention and follow-up examination.

Ancillary Tests

If used appropriately, a number of tests ancillary to the clinical examination may enhance patient care. The most common tests include the following:

- ◆ Color and red-free fundus photography
- ◆ Optical coherence tomography (OCT)
- ◆ Fluorescein angiography (FA)
- ◆ Ultrasonography

Color Fundus Photography

Fundus photography is a reproducible technique for detecting diabetic retinopathy and has been used in large clinical research studies. Fundus photography is also useful for documenting the severity of the diabetes, the presence of NVE and NVD, the response to treatment, and the need for additional treatment at future visits.

Optical Coherence Tomography

Optical coherence tomography provides high-resolution imaging of the vitreoretinal interface, neurosensory retina, and subretinal space. Optical coherence tomography can be used to quantify retinal thickness, monitor macular edema, identify vitreomacular traction, and detect other forms of macular disease in patients with diabetic macular edema.¹⁰⁹⁻¹¹⁴ (See Table 4.) Large clinical trials testing anti-VEGF treatment have utilized OCT rather than stereoscopic photographs or clinical examination to evaluate and follow macular edema status because it allows an objective, accurate assessment of the amount and location of retinal thickening.^{70, 115-117} In clinical practice, decisions are often based on OCT findings. For example, the decision to repeat anti-VEGF injections, change therapeutic agents (e.g., intraocular corticosteroids), initiate laser treatment, or even consider vitrectomy surgery is often based in part on OCT findings. Nevertheless, retinal thickness, even when measured by OCT, is not always consistently correlated with visual acuity.^{118, 119}

TABLE 4 USE OF OPTICAL COHERENCE TOMOGRAPHY FOR DIABETIC RETINOPATHY

Situation	Usually	Occasionally	Never
To evaluate unexplained visual acuity loss	•		
To identify areas of vitreomacular traction	•		
To evaluate patients with difficult and/or questionable examinations for DME	•		
To investigate other causes of macular swelling		•	
To screen a patient with no or minimal diabetic retinopathy			•

DME = diabetic macular edema

Fluorescein Angiography

Routine FA is not indicated as a part of the regular examination of patients with diabetes. Macular edema and PDR are best diagnosed by means of clinical examination and/or FA. As the use of anti-VEGF agents and intraocular corticosteroids has increased for the treatment of macular edema, the use of focal laser surgery has decreased. Therefore, the need for angiography that localizes leaking microaneurysms or areas of capillary dropout has also declined.

Nevertheless, FA is useful to differentiate diabetic macular swelling from other macular disease or for a patient with unexplained vision loss. (See Table 5.) Angiography can identify macular capillary nonperfusion¹²⁰ in the foveal or even in the entire macular region as an explanation for vision loss that is unresponsive to therapy. Fluorescein angiography may also detect areas of untreated retinal capillary nonperfusion that could explain persistent retinal or disc neovascularization after previous scatter laser surgery. Thus, FA remains a valuable tool, and facilities for conducting FA should be available to physicians who diagnose and treat patients with diabetic retinopathy.

TABLE 5 USE OF FLUORESCEIN ANGIOGRAPHY FOR DIABETIC RETINOPATHY

Situation	Usually	Occasionally	Never
To guide laser treatment of CSME	•		
To evaluate unexplained visual loss	•		
To identify suspected but clinically obscure retinal neovascularization	•		
To identify areas of vitreomacular traction		•	
To rule out other causes of macular swelling		•	
To identify large areas of capillary nonperfusion		•	
To evaluate patients with difficult and/or questionable examinations for DME		•	
To screen a patient with no or minimal diabetic retinopathy			•

CSME = clinically significant macular edema; DME = diabetic macular edema

An ophthalmologist who orders FA must be aware of the potential risks associated with the procedure, because severe medical complications may occur, including death in about 1/200,000 patients.¹²¹ Each angiography facility should have in place an emergency care plan and a clear protocol to minimize the risks and to manage complications. Fluorescein dye crosses the placenta into the fetal circulation,¹²² but detrimental effects of fluorescein dye on a fetus have not been documented.

Ultrasonography

Ultrasonography is an extremely valuable diagnostic tool that enables assessment of the status of the retina in the presence of a vitreous hemorrhage or other media opacity. Furthermore, B-scan ultrasonography may be helpful to define the extent and severity of vitreoretinal traction, especially on the macula of diabetic eyes. Currently, ultrasonography is used secondary to OCT testing when there is clear media.

MANAGEMENT

A healthy diet and lifestyle that includes exercise and weight control may decrease the risk of developing diabetes in some patients;^{123, 124} however, diabetes complications simply cannot be prevented in all cases. Nevertheless, the visual complications of diabetes mellitus can at least be moderated by a healthy lifestyle. When visual complications occur, treatment is believed to yield a substantial cost savings when compared with the direct costs for individuals disabled by vision loss (see Socioeconomic Considerations section). According to the National Committee for Quality Assurance's Health Plan Employers Data Information Set System, national monitoring of quality data has shown a slow but definite trend toward improving rates of screening examinations and blood glucose control.¹²⁵ Still, screening rates remain lower than ideal in spite of evidence supporting the effectiveness of treatment. Physicians who care for patients with diabetes, and patients themselves, need to be educated about indications for ophthalmologic referral. (See Table 6.)

Prevention and Early Detection of Diabetic Retinopathy

Analyses from two clinical trials show that treatment for diabetic retinopathy may be 90% effective in preventing severe vision loss (visual acuity <5/200) using current therapeutic treatment strategies.⁵⁶ Although effective treatment is available, fewer patients with diabetes are referred by their primary care physicians for ophthalmic care than would be expected according to guidelines by the American Diabetes Association and the American Academy of Ophthalmology.¹²⁶ In two community-based studies, 43% to 65% of participants had not received a dilated eye examination at the time of enrollment.^{125, 127}

The purpose of an effective screening program for diabetic retinopathy is to determine who needs to be referred to an ophthalmologist for close follow-up and possible treatment and who may simply be screened annually. Some studies have shown that screening programs using digital retinal images taken with or without dilation may enable early detection of diabetic retinopathy along with an appropriate referral.⁷³⁻⁸¹ Digital cameras with stereoscopic capabilities are useful for identifying subtle neovascularization and macular edema.^{82, 83} Optical coherence tomography appears to be an effective and sensitive imaging tool for detecting diabetic macular edema as long as there are no other causes for cystoid macular edema.^{113, 128}

Studies have found a positive association between participating in a photographic screening program and subsequent adherence to receiving recommended comprehensive dilated eye examinations by a clinician.^{84, 85} Of course, such screening programs are more relevant when access to ophthalmic care is limited.⁸⁶⁻⁸⁹ Screening programs should follow established guidelines.⁹⁰ Given the known gap in accessibility of direct ophthalmologic screening, fundus photographic screening programs may help increase the chances that at-risk individuals will be promptly referred for more detailed evaluation and management.

Secondary Prevention

The DCCT showed that the development and progression of diabetic retinopathy in patients with Type 1 diabetes can be delayed when the HbA_{1c} is optimized.³⁶ (See Appendix 5.) Establishing a close partnership with the ophthalmologist and the primary care physician is an

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important step to ensure optimal patient care. Furthermore, it is important to help educate patients with diabetes as well as their primary care physician about the ophthalmologic implications of controlling blood glucose (as monitored by HbA_{1c}) to as near normal as is safely possible. Results from multiple studies have demonstrated the value of controlling blood glucose, serum lipid levels, and blood pressure in patients with Type 2 diabetes. (See Appendix 5 for further information.)

Aspirin therapy has been evaluated for use in the management of diabetic retinopathy. The ETDRS found that aspirin therapy at a dose of 650 mg per day does not slow the progression of diabetic retinopathy.⁹⁷ Also, aspirin therapy did not cause more severe, more frequent, or longer-lasting vitreous hemorrhages in patients with PDR.⁹⁸ As such, aspirin appears to be neither helpful nor harmful in the management of diabetic retinopathy. Therefore, no recommended changes in medically administered aspirin therapy are indicated in the setting of diabetic retinal disease.

Medical and Surgical Management

Management recommendations for patients with diabetes are summarized in Table 6 and are described according to severity of the retinopathy. Given the recent evidence on the efficacy of anti-VEGF therapies in patients with center-involved CSME, the population may be further distinguished as having center-involving or non-center-involving diabetic macular edema. The table provides guidance for a preferred practice pattern for the general population of patients with diabetes; however, specific needs may vary on a case-by-case basis. Table 7 lists side effects and complications of treatment.

TABLE 6 MANAGEMENT RECOMMENDATIONS FOR PATIENTS WITH DIABETES

Severity of Retinopathy	Presence of Macular Edema	Follow-up (Months)	Panretinal Photocoagulation (Scatter) Laser	Focal and/or Grid Laser*	Intravitreal Anti-VEGF Therapy
Normal or minimal NPDR	No	12	No	No	No
Mild NPDR	No	12	No	No	No
	ME	4–6	No	No	No
	CSME [†]	1*	No	Sometimes	Sometimes
Moderate NPDR	No	12 [‡]	No	No	No
	ME	3–6	No	No	No
	CSME [†]	1*	No	Sometimes	Sometimes
Severe NPDR	No	4	Sometimes	No	Sometimes
	ME	2–4	Sometimes	No	Sometimes
	CSME [†]	1*	Sometimes	Sometimes	Sometimes
Non-high-risk PDR	No	4	Sometimes	No	Sometimes
	ME	2–4	Sometimes	No	Sometimes
	CSME [†]	1*	Sometimes	Sometimes	Sometimes
High-risk PDR	No	4	Recommended	No	Alternative ^{129, 130}
	ME	4	Recommended	Sometimes	Usually
	CSME [†]	1*	Recommended	Sometimes	Usually

Anti-VEGF = anti-vascular endothelial growth factor; CSME = clinically significant macular edema; ME = non-clinically significant macular edema; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy

* Adjunctive treatments that may be considered include intravitreal corticosteroids or anti-VEGF agents (off-label use, except afibbercept and ranibizumab). Data from the Diabetic Retinopathy Clinical Research Network in 2011 demonstrated that, at two years of follow-up, intravitreal ranibizumab with prompt or deferred laser resulted in greater visual acuity gain and intravitreal triamcinolone acetonide plus laser also resulted in greater visual gain in pseudophakic eyes compared with laser alone.¹³¹ Individuals receiving the intravitreal injections of anti-VEGF agents may be re-examined as early as one month following injection.

† Exceptions include hypertension or fluid retention associated with heart failure, renal failure, pregnancy, or any other causes that may aggravate macular edema. Deferral of photocoagulation for a brief period of medical treatment may be considered in these cases.¹³² Also, deferral of CSME treatment is an option when the center of the macula is not involved, visual acuity is excellent, close follow-up is possible, and the patient understands the risks.

‡ Or at shorter intervals if signs approaching those of severe NPDR appear.

TABLE 7 SIDE EFFECTS AND COMPLICATIONS OF TREATMENT FOR DIABETIC RETINOPATHY

Treatment	Side Effect/Complication
Focal laser photocoagulation for diabetic macular edema	<ul style="list-style-type: none"> Possible transient initial decrease in central vision Paracentral scotomas if laser burns have been placed close to the fovea, especially large or confluent burns¹³³ Permanent central scotoma from inadvertent foveal burns Expansion of laser scar area (over many years)
Panretinal photocoagulation (scatter) for severe NPDR or PDR	<ul style="list-style-type: none"> Transient central vision loss from macular edema¹⁰² Peripheral visual field constriction with delayed dark adaptation Vitreous hemorrhage if neovascularization is present Reduced or compromised accommodation¹³⁴ Pupillary dilation (mydriasis)
Vitrectomy	<ul style="list-style-type: none"> Recurrent vitreous hemorrhage^{135, 136} Retinal tear or detachment¹³⁷ Vision loss^{137, 138} Infectious endophthalmitis¹³⁹ Cataract¹⁴⁰
Intravitreal injections	<ul style="list-style-type: none"> Cataract^{141, 142} Elevated intraocular pressure (i.e., corticosteroids)^{141, 142} Infectious endophthalmitis Noninfectious inflammatory reactions Possible systemic effect from intravitreal medication Increased retinal traction

NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy

Normal or Minimal NPDR

The patient with a normal retinal examination or minimal NPDR (i.e., with rare microaneurysms) should be re-examined annually,²⁹ because within 1 year 5% to 10% of patients without retinopathy will develop diabetic retinopathy. Existing retinopathy will worsen by a similar percentage.^{51, 52, 57} Laser surgery, color fundus photography, and FA are not necessarily indicated.

Mild to Moderate NPDR without Macular Edema

Patients with retinal microaneurysms and occasional blot hemorrhages or hard exudates should be re-examined within 6 to 12 months, because disease progression is common.⁵¹ The natural history of Type 1 diabetic patients suggests that approximately 16% of patients with mild retinopathy (hard exudates and microaneurysms only) will progress to proliferative stages within 4 years.⁵¹

Laser surgery and FA are not indicated for this group of patients. Color fundus photography and OCT imaging of the macula may occasionally be helpful to establish a baseline for future comparison and for patient education. (See Ancillary Tests section.)

For patients with mild NPDR, the 4-year incidence of either CSME or macular edema that is not clinically significant is approximately 12%. For moderate NPDR, the risk increases to 23% for patients with either Type 1 or 2 diabetes.¹⁰² Patients with macular edema that is not clinically significant should be re-examined within 3 to 4 months, because they are at significant risk of developing CSME.⁶⁵

Mild to Moderate NPDR with CSME

Clinically significant macular edema is defined by the ETDRS to include any of the following features:

- ◆ Thickening of the retina at or within 500 µm of the center of the macula
- ◆ Hard exudates at or within 500 µm of the center of the macula, when associated with adjacent retinal thickening. (This criteria does not apply to residual hard exudates that remain after successful treatment of prior retinal thickening.)
- ◆ A zone or zones of retinal thickening one disc area or larger, where any portion of the thickening is within one disc diameter of the center of the macula

It is now appropriate to subdivide diabetic macular edema according to involvement at the center of the macula, because the risk of visual loss and the need for treatment is greater when the center is involved. The diagnosis of diabetic macular edema can be difficult.

Macular edema is best evaluated by dilated examination using slit-lamp biomicroscopy, OCT, and/or stereoscopic fundus photography. An ophthalmologist who treats patients for this condition should be familiar with relevant studies and techniques as described in the ETDRS and subsequent studies, such as the DRCR.net Protocol trial⁷⁰ and other studies involving anti-VEGF treatment.^{65, 120} Fluorescein angiography prior to laser surgery for CSME is often helpful for identifying treatable lesions. Fluorescein angiography is less relevant when there are circinate lipid exudates and the leaking lesions are clearly detected within the lipid ring. Fluorescein angiography is also useful for detecting capillary dropout and pathologic enlargement of the foveal avascular zone, a feature that may be useful when planning treatment.⁶⁵ Color fundus photography is often helpful to document the status of the retina even if laser surgery is not performed. (See Ancillary Tests section.) Optical coherence tomography is also a helpful screening tool that is able to detect subtle edema and also to follow the course of edema after treatment.

The traditional treatment for CSME has been laser surgery. However, current data from multiple well-designed studies demonstrate that intravitreal anti-VEGF agents provide a more effective treatment for center-involved CSME than monotherapy with laser surgery.^{65, 70, 116, 120, 131, 143-149} The visual acuity gain and reduction in macular thickness following the administration of the combination of intravitreal ranibizumab, with prompt or deferred laser surgery, had better outcomes than laser alone after 2 years of follow-up.¹³¹ Recent clinical trials have divided clinically significant diabetic macular edema into center-involving (ci-CSME) and non-center-involving (nci-CSME). Enrollment in these recent clinical trials included only subjects with ci-CSME. When ci-CSME is present, the anti-VEGF therapies provide a better visual acuity and anatomic (less macular edema) outcome than focal/grid laser surgery alone. (See Glossary.) Deferred laser surgery may ultimately decrease the need for repeat anti-VEGF injections. For nci-CSME, the role of laser surgery is guided by the ETDRS. The ETDRS demonstrated a definite benefit in favor of laser photocoagulation surgery in both ci-CSME and nci-CSME. Therefore, both anti-VEGF and laser remain effective treatment options for CSME as outlined above.

Anti-VEGF Therapy

Multiple studies have demonstrated the benefit of anti-VEGF therapy in cases of center-involving diabetic macular edema. (See Appendix 4.) At the present time, anti-VEGF therapy is the initial treatment choice for center-involving macular edema, with possible subsequent or deferred focal laser treatment. The Ranibizumab for Edema of the mAcula in Diabetes (READ-2) study involved 126 patients randomized to either anti-VEGF therapy (in this case ranibizumab alone), laser alone, or focal/grid laser combined with anti-VEGF therapy. (See Glossary.) The group that received anti-VEGF therapy alone or with laser treatment did better than the group treated with laser alone.¹⁵⁰ The Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol I also showed that anti-VEGF with either prompt or deferred laser photocoagulation was better than either laser alone or laser combined with triamcinolone acetonide.⁷⁰ (See Glossary.) These referenced studies used ranibizumab, while the Bevacizumab or Laser Treatment (BOLT) study also showed

favorable outcomes for bevacizumab use over macular laser treatment in eyes with ci-CSME.¹⁵¹ (See Glossary.) The DME and VEGF Trap-Eye: Investigation of Clinical Impact (DA VINCI) study demonstrated better outcomes using aflibercept over laser treatment for ci-CSME.¹⁵² (See Glossary.) The DRCR.net protocol T demonstrated that anti-VEGF therapy using bevacizumab, ranibizumab, or aflibercept is an effective treatment for center-involving CSME.¹⁵³ The two-year results did not reveal a statistical difference among the three drugs in serious adverse events or visual acuity improvement, except for aflibercept's greater visual acuity improvement over bevacizumab during year 1 in eyes with 20/50 or worse baseline vision.¹⁵⁴ In the second year, the average number of injections decreased to about half of the number in the first year.

The DRCR.net protocol S was a randomized controlled trial that compared panretinal or scatter photocoagulation to ranibizumab in patients primarily with PDR with and without diabetic macular edema, and approximately 11 percent had mild to severe NPDR.^{129,130} The patients receiving ranibizumab received a baseline 0.5 mg intravitreal injection, followed by an injection every month for 3 months and then received treatment as per a specified protocol. The study concluded that ranibizumab resulted in not more than 5 letters worse VA than panretinal or scatter photocoagulation at 2 years. The ranibizumab group did appear to have better average visual acuity, less visual field loss, fewer number of vitrectomies, but did involve a higher number of treatments and visits than the group receiving panretinal or scatter photocoagulation. In April, 2017, the FDA approved ranibizumab for all stages of diabetic retinopathy, based on the Protocol S, RIDE and RISE studies. A follow up of patients from RIDE and RISE studies found that more patients receiving ranibizumab treatment had a ≥ 2 or a ≥ 3 step DR improvement, compared with the sham crossover group at a median level of moderate NPDR.¹⁵⁵ It would be reasonable to consider use of ranibizumab in severe NPDR patients in settings where laser surgery would be considered. The clinical situation dictates when an intravitreal injection would be more appropriate for the patient. Also, a key clinical consideration for determining the use of anti-VEGF and/or laser treatment is the reliability of patient follow-up. Furthermore, the long-term role for supplementing anti-VEGF with pan-retinal photoagulation is yet to be determined. The clinical indications for use in patients with moderate NPDR and mild NPDR also depend upon other factors such as systemic blood glucose control, compliance with follow-up examinations, and clinical judgment is important for guiding therapy.

Treating physicians should note that the use of betadine antiseptic drops and a lid speculum is recommended during intravitreal injections. The use of routine antibiotic eye drops is not recommended before or following intravitreal injection procedures.¹⁵⁶ Individuals receiving the intravitreal injections of anti-VEGF agents may be examined at 1 month following therapy. (See Table 6.) Uncommon, yet severe, adverse side effects are associated with intravitreal injections. These include infectious endophthalmitis, cataract formation, retinal detachment, and elevated IOP, particularly for the corticosteroids such as triamcinolone. (See Table 7.)

Laser Photocoagulation

Effective laser treatment and retreatment protocols have been detailed in the DRS and the ETDRS.^{61, 157, 158} With the advent of anti-VEGF therapy for macular edema, many retina specialists prefer to use a modified ETDRS treatment approach. This includes a less intense laser treatment, greater spacing, directly targeting microaneurysms, and avoiding foveal vasculature within at least 500 μm of the center of the macula.¹⁵⁹ Preoperatively, the ophthalmologist should discuss with the patient the side effects and risks of treatment.^{65, 120} A follow-up examination for individuals with CSME should be scheduled within 3 to 4 months of laser surgery.⁶⁵ Rarely, focal laser photocoagulation may induce subretinal fibrosis with choroidal neovascularization, a complication that may be associated with permanent central vision loss.¹⁶⁰⁻¹⁶² Other than choroidal neovascularization, the most important factor associated with the development of subretinal fibrosis includes both the more severe levels of subretinal hard exudates and elevated serum lipids prior to laser photocoagulation.¹⁶³ Approximately 8% of cases of subretinal fibrosis can be directly related to focal laser photocoagulation.

Effects Related to Other Treatments

There have been case reports of idiosyncratic macular edema that is temporally associated with use of the glitazone class of oral antihyperglycemic agents.^{164, 165} When substantial vitreomacular traction is present, pars plana vitrectomy may improve visual acuity in selected patients who have diffuse CSME that is unresponsive to previous macular laser photocoagulation and/or anti-VEGF therapy.¹⁶⁶⁻¹⁶⁸ However, the value of vitrectomy in CSME is difficult to study in a randomized clinical trial, as there are many variables. (See DRCR.net protocol D.¹⁶⁹)

Treatment Deferral

When treatment for macular edema is deferred, the patient should be observed closely (at least every 3 to 4 months) for signs of progression.

Severe NPDR and Non-High-Risk PDR

Severe NPDR and non-high-risk PDR are discussed together because the ETDRS data showed that they have a similar clinical course and subsequent recommendations for treatment are similar. In eyes with severe NPDR, the risk of progression to proliferative disease is high. Half of patients with severe NPDR will develop PDR within 1 year, and 15% will have high-risk PDR.¹⁰² For patients with very severe NPDR, the risk of developing PDR within 1 year is 75%. Furthermore, 45% will become high-risk PDR in this same time frame. Therefore, these patients should be re-examined within 2 to 4 months.^{102, 170} Refer to Table 1 for the definition of severe NPDR and very severe NPDR.

The ETDRS compared early panretinal photocoagulation with deferral of photocoagulation with careful follow-up (at 4-month intervals) and prompt panretinal photocoagulation if progression to high-risk PDR occurred. (See Appendix 4.) Although the study did not provide definitive guidelines, the ETDRS suggested that panretinal photocoagulation should not be recommended for eyes with mild or moderate NPDR, provided that follow-up could be maintained. When retinopathy is more severe, panretinal photocoagulation should be considered and should not be delayed when the eye reaches the high-risk proliferative stage.¹⁰² (See Appendix 4.) Careful follow-up at 3 to 4 months is important: if the patient will not or cannot be followed closely or if there are associated medical conditions such as impending cataract surgery or pregnancy, early laser panretinal photocoagulation may be warranted.^{102, 170} Laser photocoagulation may be indicated, particularly when access to health care is difficult. If laser surgery is elected, full panretinal photocoagulation is a proven treatment approach. Partial or limited panretinal photocoagulation treatment is not recommended.⁶¹

Additional analyses of visual outcome in ETDRS patients with severe NPDR to non-high-risk PDR suggest that the recommendation to consider panretinal photocoagulation before the development of high-risk PDR is particularly appropriate for patients with Type 2 diabetes. The risk of severe vision loss or vitrectomy was reduced by 50% (2.5% vs. 5%, $P=0.0001$) in patients with Type 2 diabetes who were treated early when compared with deferral panretinal photocoagulation until high-risk PDR developed.¹⁷⁰ For patients with Type 1 diabetes, the timing of the panretinal photocoagulation depends on the patient's compliance with follow-up and the status and response to treatment of the fellow eye. For both patients with Type 1 and Type 2 diabetes, impending or recent cataract surgery or pregnancy may increase the risk of progression and may influence the decision to perform panretinal photocoagulation.

The goal of laser surgery is to reduce the risk of vision loss. Preoperatively, the ophthalmologist should assess for the presence of macular edema, discuss side effects of treatment and risks of visual loss with the patient, and obtain informed consent.^{157, 158}

When panretinal photocoagulation for severe NPDR or non-high-risk PDR is to be performed on eyes with macular edema, many experts think that it is preferable to perform focal photocoagulation and/or anti-VEGF therapy prior to panretinal photocoagulation.

(See Glossary.) There is evidence based on clinical trials that panretinal photocoagulation, as used in the DRS and ETDRS, may exacerbate macular edema and may increase the rate of moderate visual loss (i.e., doubling of the visual angle) compared with untreated control eyes.¹⁰² (See Glossary.) However, panretinal photocoagulation surgery should not be delayed when PDR is at the high-risk stage (i.e., if NVD is extensive or vitreous/preretinal hemorrhage has occurred recently). In such cases, anti-VEGF therapy and panretinal photocoagulation may be performed concomitantly. Currently, the role of anti-VEGF therapy in the management of severe NPDR and non-high-risk PDR is under investigation.

Fluorescein angiography may be helpful to determine the presence or absence of areas of nonperfusion and/or clinically undetected areas of retinal neovascularization and to establish the cause for a loss in visual acuity.

High-Risk PDR

The presence of any three of the following four features characterizes DRS high-risk PDR:

- ◆ Neovascularization (at any location)
- ◆ Neovascularization at the optic disc
- ◆ Severe neovascularization:
 - ◆ New vessels within one disc diameter of the optic nerve head that are larger than one-quarter to one-third disc area in size
 - ◆ New vessels elsewhere that are at least one-half disc area in size
- ◆ Vitreous or preretinal hemorrhage

The risk of severe visual loss among patients with high-risk PDR is reduced substantially by treatment using panretinal photocoagulation as described in the DRS and ETDRS. (See Glossary.) Most patients with high-risk PDR should receive panretinal photocoagulation surgery expeditiously.^{61, 171} Panretinal photocoagulation usually induces regression of retinal neovascularization. This technique has been fully described^{61, 157} and the results are summarized in Appendix 4.

Very recently, the DRCR.net study protocol S has demonstrated that alternative use of anti-VEGF agents (ranibizumab was used in this protocol), may be an alternative to panretinal laser photocoagulation.¹²⁹ However, many feel that panretinal photocoagulation remains the first choice for management of PDR. The anti-VEGF alternative could be considered for patients who can follow-up regularly. Further studies are required to determine the long-term implications of using anti-VEGF agents alone.¹³⁰ Additional panretinal photocoagulation, anti-VEGF therapy, or vitrectomy surgery may be necessary to address increasing neovascularization of the iris and should be considered for the following situations:

- ◆ Failure of the neovascularization to regress
- ◆ Increasing neovascularization of the retina or iris
- ◆ New vitreous hemorrhage
- ◆ New areas of neovascularization

For patients who have CSME in addition to high-risk PDR, combined anti-VEGF therapy and panretinal photocoagulation at the first treatment session and in the early stages of such higher risk eyes could also be considered. Fluorescein angiography does not usually need to be performed in order to apply the panretinal photocoagulation effectively. However, a fluorescein angiogram may be used to guide focal photocoagulation. In some cases, vitreous hemorrhage may recur in patients who have had extensive panretinal photocoagulation. These hemorrhages may be due to traction on pre-existing or involved neovascularization. They may clear spontaneously and do not necessarily require additional panretinal laser surgery.

Some patients with previously untreated PDR who have vitreous opacities and active neovascular or fibrovascular proliferation should be considered as candidates for pars plana vitrectomy.^{66, 172-174} The value of early vitrectomy tends to increase with the increasing severity of neovascularization. (See Appendix 4.) The role of anti-VEGFs in these later stages of proliferative retinopathy is under investigation.

High-Risk PDR Not Amenable to Photocoagulation

In some patients with severe vitreous or preretinal hemorrhage, it may not be possible to deliver laser photocoagulation adequately. Furthermore, advanced active PDR may persist despite extensive panretinal photocoagulation. In such cases, vitrectomy surgery may be indicated. Vitreous surgery is frequently indicated in patients with macula-threatening traction retinal detachment (particularly of recent onset), combined traction-rhegmatogenous retinal detachment, and vitreous hemorrhage precluding panretinal photocoagulation. Patients with vitreous hemorrhage and rubeosis iridis also should be considered for prompt vitrectomy and intraoperative panretinal photocoagulation surgery. The role of anti-VEGFs in treatment of these cases is under investigation.

Other Treatments

Several studies have evaluated the use of intravitreal administration of short- and long-acting corticosteroids for the treatment of diabetic macular edema and the use of anti-VEGF agents in the treatment of PDR. An earlier DRCR.net study evaluated the role of intravitreal triamcinolone acetonide compared with focal laser photocoagulation. Treatment with intravitreal triamcinolone acetonide resulted in an early decrease in retinal thickness at 4 months, yet by 24 months those patients randomized to focal/grid laser photocoagulation had better mean visual acuity and fewer adverse effects of cataract development and elevation of IOP.¹⁷⁵ At 3 years, these results were largely unchanged.¹⁷⁶ However, this study did not evaluate the role of intravitreal corticosteroids plus standard focal/grid laser photocoagulation compared with laser photocoagulation alone. A subsequent study showed increased visual gain in pseudophakic eyes that were given the combination of the intravitreal triamcinolone acetonide and laser; however, even in this group the eyes treated with anti-VEGF agents tended to do better overall.^{131, 144} Future studies will help define the role of corticosteroids in the treatment strategies for persons with diabetic macular edema.

Micropulse laser treatment as well as FA-guided therapy have also been advocated. Studies suggest that micropulse laser induces less damage to the macula, and several studies using this method have shown encouraging results. This method has not been compared with standard or modified ETDRS laser surgery in randomized clinical trials.¹⁷⁷

Follow-Up Evaluation

The follow-up evaluation includes a history and examination.

History

A follow-up history should include changes in the following:

- ◆ Symptoms
- ◆ Systemic status (pregnancy, blood pressure, serum cholesterol, renal status)
- ◆ Glycemic status (HbA_{1c})^{42, 58, 100}

Examination

A follow-up examination should include the following elements:

- ◆ Visual acuity¹⁰²
- ◆ Slit-lamp biomicroscopy with iris examination¹⁷⁸
- ◆ Intraocular pressure
- ◆ Gonioscopy (preferably before dilation when iris neovascularization is suspected or if IOP is elevated)¹⁷⁸
- ◆ Stereoscopic examination of the posterior pole after dilation of the pupils⁶⁵
- ◆ OCT imaging, when appropriate
- ◆ Peripheral retina and vitreous examination, when indicated⁶⁴

Recommended intervals for follow-up are given in Table 6.

PROVIDER AND SETTING

Although the ophthalmologist will perform most of the examination and all surgery, certain aspects of data collection may be performed by trained individuals under the ophthalmologist's supervision and

review. Because of the complexities of the diagnosis and treatment for diabetic retinopathy, the ophthalmologist caring for patients with this condition should be familiar with the specific recommendations of relevant clinical trials.^{37, 70, 101, 102, 117, 150-152, 158, 179-186}

PHYSICIAN QUALITY REPORTING SYSTEM

The Physician Quality Reporting System (PQRS) program, initially launched by the Centers for Medicare and Medicaid Services in July 2007, encourages quality improvement through the use of clinical performance measures on a variety of clinical conditions. Measures in the 2014 program for diabetic eye care include an annual dilated eye examination for patients with diabetes, documentation of the level of severity of retinopathy and the presence or absence of macular edema, and communication of examination results to the physician managing ongoing diabetes care for patients with diabetic retinopathy.¹⁸⁷

COUNSELING AND REFERRAL

The ophthalmologist should refer patients with diabetes to a primary care physician for appropriate management of their systemic condition and should communicate examination results to the physician managing the patient's ongoing diabetes care. An Eye MD Examination Report Form is available from the American Academy of Ophthalmology.¹⁸⁸

Some patients with diabetic retinopathy will lose substantial vision despite being treated according to the recommendations in this document.¹⁷⁰ Patients whose conditions fail to respond to surgery and those for whom further treatment is unavailable should be provided with proper professional support and offered referral for counseling, vision rehabilitation, or social services as appropriate.¹⁸⁹ Vision rehabilitation restores functional ability,¹⁹⁰ and patients with functionally limiting postoperative visual impairment should be referred for vision rehabilitation and social services.¹⁸⁹ More information on vision rehabilitation, including materials for patients, is available at www.aao.org/smart-sight-low-vision.

SOCIOECONOMIC CONSIDERATIONS

One analysis of medical and economic effects of diabetic retinopathy control predicted that over their lifetime, 72% of patients with Type 1 diabetes would eventually develop PDR requiring panretinal photocoagulation and that 42% will develop macular edema.¹⁹¹ If treatments are delivered as recommended in the clinical trials, the model predicted a cost of \$966 per person-year of vision saved for patients with PDR and \$1120 per person-year of central visual acuity saved for patients with macular edema. These costs are less than the cost of a year of Social Security disability payments for patients disabled by vision loss. Therefore, treatment yields a substantial savings compared with the direct cost to society of untreated PDR in a Type 1 diabetic patient.¹⁹² The indirect costs in lost productivity and human suffering are even greater.

Another analysis estimated that screening and treatment of eye disease in patients with diabetes costs, on average, \$3190 per quality adjusted life year (QALY) saved.¹⁹³ For patients with Type 1 diabetes, it costs \$1996 per QALY saved; for patients with Type 2 diabetes who use insulin, it costs \$2933 per QALY saved; and for patients with Type 2 diabetes who do not use insulin, it costs \$3530 per QALY saved. Insofar as patients with Type 2 diabetes not using insulin represent the largest subset of the patient population, most of the economic benefits of screening and treatment are realized among these patients.

A recent (2013) cost-effectiveness analysis of various interventions for diabetic macular edema evaluated the cost effectiveness of anti-VEGF therapies for CSME. Compared with laser alone, the incremental cost-effectiveness of laser plus bevacizumab is \$11,138/QALY and thus seems to confer the greatest value among the various treatment options for CSME.¹⁹⁴ By comparison, the cost-utility of laser photocoagulation for diabetic macular edema is \$3101/QALY,¹⁹⁵ whereas laser photocoagulation for extrafoveal choroidal neovascularization is \$23,640/QALY.¹⁹⁶ Finally, a cost-utility analysis of detection and treatment of diabetic retinopathy in patients with Type 1 and Type 2 diabetes demonstrates that provision of recommended ophthalmic care would reduce the prevalence of blindness by 52% and that the direct costs of care would be less than the losses in productivity and the costs of facilities provided for disability.¹⁹⁷



APPENDIX 1. QUALITY OF OPHTHALMIC CARE CORE CRITERIA

*Providing quality care
is the physician's foremost ethical obligation, and is
the basis of public trust in physicians.*

AMA Board of Trustees, 1986

Quality ophthalmic care is provided in a manner and with the skill that is consistent with the best interests of the patient. The discussion that follows characterizes the core elements of such care.

The ophthalmologist is first and foremost a physician. As such, the ophthalmologist demonstrates compassion and concern for the individual, and utilizes the science and art of medicine to help alleviate patient fear and suffering. The ophthalmologist strives to develop and maintain clinical skills at the highest feasible level, consistent with the needs of patients, through training and continuing education. The ophthalmologist evaluates those skills and medical knowledge in relation to the needs of the patient and responds accordingly. The ophthalmologist also ensures that needy patients receive necessary care directly or through referral to appropriate persons and facilities that will provide such care, and he or she supports activities that promote health and prevent disease and disability.

The ophthalmologist recognizes that disease places patients in a disadvantaged, dependent state. The ophthalmologist respects the dignity and integrity of his or her patients, and does not exploit their vulnerability.

Quality ophthalmic care has the following optimal attributes, among others.

- ◆ The essence of quality care is a meaningful partnership relationship between patient and physician. The ophthalmologist strives to communicate effectively with his or her patients, listening carefully to their needs and concerns. In turn, the ophthalmologist educates his or her patients about the nature and prognosis of their condition and about proper and appropriate therapeutic modalities. This is to ensure their meaningful participation (appropriate to their unique physical, intellectual, and emotional state) in decisions affecting their management and care, to improve their motivation and compliance with the agreed plan of treatment, and to help alleviate their fears and concerns.
- ◆ The ophthalmologist uses his or her best judgment in choosing and timing appropriate diagnostic and therapeutic modalities as well as the frequency of evaluation and follow-up, with due regard to the urgency and nature of the patient's condition and unique needs and desires.
- ◆ The ophthalmologist carries out only those procedures for which he or she is adequately trained, experienced, and competent, or, when necessary, is assisted by someone who is, depending on the urgency of the problem and availability and accessibility of alternative providers.
- ◆ Patients are assured access to, and continuity of, needed and appropriate ophthalmic care, which can be described as follows.
 - ◆ The ophthalmologist treats patients with due regard to timeliness, appropriateness, and his or her own ability to provide such care.
 - ◆ The operating ophthalmologist makes adequate provision for appropriate pre- and postoperative patient care.
 - ◆ When the ophthalmologist is unavailable for his or her patient, he or she provides appropriate alternate ophthalmic care, with adequate mechanisms for informing patients of the existence of such care and procedures for obtaining it.
 - ◆ The ophthalmologist refers patients to other ophthalmologists and eye care providers based on the timeliness and appropriateness of such referral, the patient's needs, the competence and qualifications of the person to whom the referral is made, and access and availability.

Diabetic Retinopathy PPP:
Appendix 1. Quality of Ophthalmic Care Core Criteria

- ◆ The ophthalmologist seeks appropriate consultation with due regard to the nature of the ocular or other medical or surgical problem. Consultants are suggested for their skill, competence, and accessibility. They receive as complete and accurate an accounting of the problem as necessary to provide efficient and effective advice or intervention, and in turn they respond in an adequate and timely manner. The ophthalmologist maintains complete and accurate medical records.
- ◆ On appropriate request, the ophthalmologist provides a full and accurate rendering of the patient's records in his or her possession.
- ◆ The ophthalmologist reviews the results of consultations and laboratory tests in a timely and effective manner and takes appropriate actions.
- ◆ The ophthalmologist and those who assist in providing care identify themselves and their profession.
- ◆ For patients whose conditions fail to respond to treatment and for whom further treatment is unavailable, the ophthalmologist provides proper professional support, counseling, rehabilitative and social services, and referral as appropriate and accessible.
- ◆ Prior to therapeutic or invasive diagnostic procedures, the ophthalmologist becomes appropriately conversant with the patient's condition by collecting pertinent historical information and performing relevant preoperative examinations. Additionally, he or she enables the patient to reach a fully informed decision by providing an accurate and truthful explanation of the diagnosis; the nature, purpose, risks, benefits, and probability of success of the proposed treatment and of alternative treatment; and the risks and benefits of no treatment.
- ◆ The ophthalmologist adopts new technology (e.g., drugs, devices, surgical techniques) in judicious fashion, appropriate to the cost and potential benefit relative to existing alternatives and to its demonstrated safety and efficacy.
- ◆ The ophthalmologist enhances the quality of care he or she provides by periodically reviewing and assessing his or her personal performance in relation to established standards, and by revising or altering his or her practices and techniques appropriately.
- ◆ The ophthalmologist improves ophthalmic care by communicating to colleagues, through appropriate professional channels, knowledge gained through clinical research and practice. This includes alerting colleagues of instances of unusual or unexpected rates of complications and problems related to new drugs, devices, or procedures.
- ◆ The ophthalmologist provides care in suitably staffed and equipped facilities adequate to deal with potential ocular and systemic complications requiring immediate attention.
- ◆ The ophthalmologist also provides ophthalmic care in a manner that is cost effective without unacceptably compromising accepted standards of quality.

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APPENDIX 2. INTERNATIONAL STATISTICAL CLASSIFICATION OF DISEASES AND RELATED HEALTH PROBLEMS (ICD) CODES

Diabetic retinopathy, which includes entities with the following ICD-9 and ICD-10 classifications (see Glossary):

	ICD-9 CM	ICD-10 CM
Diabetic retinopathy:		
background	362.01	<ul style="list-style-type: none"> • E10.311 Type 1 with macular edema • E10.319 Type 1 without macular edema • E11.311 Type 2 with macular edema • E11.319 Type 2 without macular edema • E13.311 other specified types of diabetes mellitus with unspecified diabetic retinopathy with macular edema • E13.319 other specified types of diabetes mellitus with unspecified diabetic retinopathy without macular edema
proliferative	362.02	<ul style="list-style-type: none"> • E10.351 Type 1 with macular edema • E10.359 Type 1 without macular edema • E11.351 Type 2 with macular edema • E11.359 Type 2 without macular edema • E13.351 other specified diabetes mellitus with proliferative diabetic retinopathy with macular edema • E13.359 other specified diabetes mellitus with proliferative diabetic retinopathy without macular edema
nonproliferative, NOS	362.03	<ul style="list-style-type: none"> • E10.321 Type 1 with macular edema • E10.329 Type 1 without macular edema • E11.321 Type 2 with macular edema • E11.329 Type 2 without macular edema • E13.321 other specified types of diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema • E13.329 other specified types of diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema
nonproliferative, mild	362.04	
nonproliferative, moderate	362.05	<ul style="list-style-type: none"> • E10.331 Type 1 with macular edema • E10.339 Type 1 without macular edema • E11.331 Type 2 with macular edema • E11.339 Type 2 without macular edema • E13.331 other specified types of diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema • E13.339 other specified types of diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema

**Diabetic Retinopathy PPP:
Appendix 2. ICD Codes**

ICD-9 CM	ICD-10 CM
Diabetic retinopathy (continued):	
nonproliferative, severe	362.06 <ul style="list-style-type: none"> • E10.341 Type 1 with macular edema • E10.349 Type 1 without macular edema • E11.341 Type 2 with macular edema • E11.349 Type 2 without macular edema • E13.341 other specified types of diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema • E13.349 other specified types of diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema
Diabetic macular edema	362.07 <ul style="list-style-type: none"> • E10.321 Type 1 mild nonproliferative diabetic retinopathy • E10.331 Type 1 moderate nonproliferative diabetic retinopathy • E10.341 Type 1 severe nonproliferative diabetic retinopathy • E10.351 Type 1 proliferative diabetic retinopathy • E11.321 Type 2 mild nonproliferative diabetic retinopathy • E11.331 Type 2 moderate nonproliferative diabetic retinopathy • E11.341 Type 2 severe nonproliferative diabetic retinopathy • E11.351 Type 2 proliferative diabetic retinopathy • E13.321 other specified diabetes mellitus with mild nonproliferative diabetic retinopathy • E13.331 other specified diabetes mellitus with moderate nonproliferative diabetic retinopathy

ICD = International Classification of Diseases; CM = Clinical Modification used in the United States; NOS = not otherwise specified

Additional information for ICD-10 codes:

- Certain ICD-10 CM categories have applicable 6th characters. In the diabetic retinopathy series, indicate "with or without" macular edema. Laterality indicators are not required in this series.
 - 1 = with macular edema
 - 9 = without macular edema
- For bilateral sites, the final character of the codes in the ICD-10 CM indicates laterality. If no bilateral code is provided and the condition is bilateral, separate codes for both the left and right side should be assigned. *Unspecified codes should only be used when there is no other code option available.*



APPENDIX 3. PREFERRED PRACTICE PATTERN RECOMMENDATION GRADING

The grades herein report the SIGN grade associated with the included studies supporting each recommendation (I++; I+; I-; II++; II+; II-; III), the GRADE evaluation of the body of evidence (Good, Moderate, Insufficient), and the GRADE assessment of the strength of the recommendation (Strong, Discretionary). Details of these grading systems are reported in the Methods and Key to Ratings section.

Highlighted Findings and Recommendations for Care

Page 4: People with Type 1 diabetes should have annual screenings for diabetic retinopathy beginning 5 years after the onset of their disease, while those with Type 2 diabetes should have yearly screening for diabetic retinopathy beginning immediately following their diagnosis: II+; Good; Strong

Page 4: Patients with diabetes may use aspirin for other medical indications without an adverse effect on their risk of diabetic retinopathy: I++; Good; Discretionary

Page 4: Women who develop gestational diabetes do not require an eye examination during pregnancy, and do not appear to be at increased risk of developing diabetic retinopathy during pregnancy. However, diabetics who become pregnant should be examined early in the course of the pregnancy: II+; Good; Strong

Page 4: Referral to an ophthalmologist is required when there is any non-proliferative diabetic retinopathy, proliferative retinopathy or macular edema: III; Good; Strong

Page 4: Ophthalmologists should communicate the ophthalmologic findings and level of retinopathy with the primary care physician as well as the need for optimizing metabolic control: III; Good; Strong

Page 4: Intravitreal injections of anti- vascular endothelial growth factor (VEGF) agents have been shown to be an effective treatment for center-involving diabetic macular edema: I++; Good; Strong

Page 4: At this time, laser photocoagulation remains the preferred treatment for non-center-involving diabetic macular edema: I++; Good; Strong

Introduction

Page 7: It is recommended that an HbA_{1c} of 7.0% or lower is the target for glycemic control in most patients while in selected patients, there may be some benefit to setting a target of 6.5%: I++; Good; Strong

Page 8: Intensive management of hypertension may slow retinopathy progress, but the data are inconclusive: II++; Moderate; Discretionary

Page 8: Management of serum lipids may reduce retinopathy progression and the need for treatment: II+; Moderate; Discretionary

Page 8: It is reasonable to encourage patients with diabetes to be as compliant as possible with therapy of all medical aspects of their disease: II++; Good; Strong

Care Process

Page 9: The care process for diabetic retinopathy includes a medical history, a regular ophthalmologic examination or screening of high quality retinal photographs of patients who have not had previous treatment for diabetic retinopathy or other eye disease and regular follow-up: III; Good; Strong

Page 9: Patients must be informed that they may have good vision and no ocular symptoms, yet may still have significant disease that needs treatment. They should be educated that early treatment works best and is why they need to return for an annual eye examination, even when their vision is good: III; Good; Strong

**Diabetic Retinopathy PPP:
Appendix 3. PPP Recommendation Grading**

Page 9: Individuals with Type 2 diabetes mellitus without diabetic retinopathy should be encouraged to have an annual dilated eye exam or screenings using fundus photography to detect the onset of diabetic retinopathy: II++; Good; Strong

Page 9: Those with Type 1 diabetes mellitus without diabetic retinopathy should have annual dilated eye examinations or screenings beginning 5 years after the onset of diabetes: II++; Good; Strong

Page 9: Table 3, Recommended initial evaluation for Type 1 diabetes: 5 years after diagnosis: II++; Good; Strong

Page 9: Table 3: Recommended follow-up evaluation for Type 1 diabetes: Yearly: III; Good; Strong

Page 9: Table 3: Recommended initial evaluation for Type 2 diabetes: At time of diagnosis: II+; Good; Strong

Page 9: Table 3: Recommended follow-up evaluation for Type 2 diabetes: Yearly: III; Good; Strong

Page 9: Table 3: Recommended initial evaluation for pregnant women with diabetes (Type 1 or Type 2): Soon after conception and early in first trimester: III; Good; Strong

Page 9: Table 3: Recommended follow-up evaluation for pregnant women with diabetes (Type 1 or Type 2), no retinopathy to mild or moderate NPDR: Every 3–12 months: III; Good; Strong

Page 9: Table 3: Recommended follow-up evaluation for pregnant women with diabetes (Type 1 or Type 2), severe NPDR or worse: Every 1–3 months: III; Good; Strong

Page 10: Patients should be informed of the importance of maintaining good glycosylated hemoglobin levels, serum lipids, and blood pressure: III; Good; Strong

Page 10: Aspirin may be used by diabetic patients for other medical indications without concern that the aspirin therapy will worsen diabetic retinopathy: III; Moderate; Discretionary

Page 10: The initial examination for a patient with diabetes mellitus includes all features of the comprehensive adult medical eye evaluation, with particular attention to those aspects relevant to diabetic retinopathy: II++; Good; Strong

Page 10: An initial history should consider duration of diabetes: II++; Good; Strong

Page 10: An initial history should consider past glycemic control: II++; Good; Strong

Page 10: An initial history should consider medications: III; Good; Strong

Page 10: An initial history should consider medical history: II++; Good; Strong

Page 10: An initial history should consider ocular history: III; Good; Strong

Page 10: The initial physical examination should include visual acuity: III; Good; Strong

Page 10: The initial physical examination should include slit-lamp biomicroscopy: III; Good; Strong

Page 10: The initial physical examination should include intraocular pressure: III; Good; Strong

Page 10: The initial physical examination should include gonioscopy before dilation, when indicated: III; Good; Strong

Page 10: The initial physical examination should include thorough fundoscopy, including stereoscopic examination of the posterior pole: III; Good; Strong

Page 10: The initial physical examination should include examination of the peripheral retina and vitreous: III; Good; Strong

Page 10: Slit-lamp biomicroscopy is the recommended method to evaluate retinopathy in the posterior pole and midperipheral retina: III; Good; Strong

Page 10: Examination of the peripheral retina is best performed with indirect ophthalmoscopy or with slit-lamp biomicroscopy: III; Good; Strong

Page 10: A detailed examination is indicated to assess for macular edema: III; Good; Strong

Page 10: A detailed examination is indicated to assess for signs of severe NPDR: III; Good; Strong

Page 10: A detailed examination is indicated to assess for optic nerve head neovascularization and/or neovascularization elsewhere: III; Good; Strong

Page 10: A detailed examination is indicated to assess for vitreous or preretinal hemorrhage: III; Good; Strong

Page 11: Ophthalmic examinations are recommended beginning 5 years after the diagnosis of Type I diabetes and annually thereafter: II++; Good; Strong

Page 11: The patient with Type 2 diabetes should be referred for ophthalmologic evaluation at the time of diagnosis: II+; Good; Strong

Page 11: Patients with diabetes who plan to become pregnant should have an ophthalmologic examination prior to pregnancy and should be counseled about the risk of development and/or progression of diabetic retinopathy: III; Good; Strong

Page 11: The obstetrician or primary care physician should carefully guide the management of the pregnant diabetic's blood glucose as well as other issues related to pregnancy: III; Good; Strong

Page 11: During the first trimester, an eye examination should be performed with repeat and follow-up visits scheduled depending on the severity of retinopathy: III; Good; Strong

Page 11: Women who develop gestational diabetes¹⁰⁸¹⁰⁸¹⁰⁸ do not require an eye examination during pregnancy and do not appear to be at increased risk for diabetic retinopathy during pregnancy: II+; Good; Strong

Page 11: After the first-trimester eye examination, the ophthalmologist should discuss the results and their implications with the patient: III; Good; Strong

Page 11: Both eyes should be classified according to the categories of diabetic retinopathy and macular edema discussed in the Natural History and Treatment sections: III; Good; Strong

Page 11: If used appropriately, color and red-free fundus photography ancillary to the clinical examination may enhance patient care: III; Insufficient; Discretionary

Page 11: If used appropriately, optical coherence tomography ancillary to the clinical examination may enhance patient care: III; Insufficient; Discretionary

Page 11: If used appropriately, fluorescein angiography ancillary to the clinical examination may enhance patient care: III; Insufficient; Discretionary

Page 11: If used appropriately, ultrasonography ancillary to the clinical examination may enhance patient care: III; Insufficient; Discretionary

Page 12: Table 4: OCT is usually used to evaluate unexplained visual acuity loss: III; Insufficient; Discretionary

Page 12: Table 4: OCT is usually used to identify areas of vitreomacular traction: III; Insufficient; Discretionary

**Diabetic Retinopathy PPP:
Appendix 3. PPP Recommendation Grading**

Page 12: Table 4: OCT is usually used to evaluate patients with difficult and/or questionable examinations for DME: III; Insufficient; Discretionary

Page 12: Table 4: OCT is occasionally used to investigate other causes of macular swelling: III; Insufficient; Discretionary

Page 12: Table 4: OCT is never used to screen a patient with no or minimal diabetic retinopathy: III; Good; Strong

Page 12: Routine fluorescein angiography is not indicated as a part of the regular examination of patients with diabetes: III; Good; Strong

Page 12: Facilities for fluorescein angiography should be available to physicians who diagnose and treat patients with diabetic retinopathy: II++; Good; Discretionary

Page 12: Table 5: Fluorescein angiography is usually used to guide laser treatment of CSME: III; Insufficient; Discretionary

Page 12: Table 5: Fluorescein angiography is usually used to evaluate unexplained visual loss: III; Insufficient; Discretionary

Page 12: Table 5: Fluorescein angiography is usually used to identify suspected but clinically obscure retinal neovascularization: III; Insufficient; Discretionary

Page 12: Table 5: Fluorescein angiography is occasionally used to identify areas of vitreomacular traction: III; Insufficient; Discretionary

Page 12: Table 5: Fluorescein angiography is occasionally used to rule out other causes of macular swelling: III; Insufficient; Discretionary

Page 12: Table 5: Fluorescein angiography is occasionally used to identify large areas of capillary nonperfusion: III; Insufficient; Discretionary

Page 12: Table 5: Fluorescein angiography is occasionally used to evaluate patients with difficult and/or questionable examinations for DME: III; Insufficient; Discretionary

Page 12: Table 5: Fluorescein angiography is never used to screen a patient with no or minimal diabetic retinopathy: III; Good; Strong

Page 13: Each angiography facility should have in place an emergency care plan and a clear protocol to minimize the risks and to manage complications: III; Good; Strong

Page 13: Ultrasonography is an extremely valuable diagnostic tool that enables assessment of the status of the retina in the presence of a vitreous hemorrhage or other media opacity: III; Good; Strong

Page 13: Physicians who care for patients with diabetes, and patients themselves, need to be educated about indications for ophthalmologic referral: III; Good; Strong

Page 13: Screening programs should follow established guidelines: III; Good; Strong

Page 13: Close partnership with the primary care physician is important to make sure that the care of the patient is optimized: III; Good; Strong

Page 14: It is important to educate patients with diabetes, in conjunction with their primary care physician, on the importance of optimizing control of blood glucose to as near normal as is safely possible: III; Good; Strong

Page 14: Aspirin appears to be neither helpful nor harmful in the management of diabetic retinopathy: I++; Good; Discretionary

Page 14: Table 6: Follow-up for patients with normal or minimal NPDR and no DME: 12 months: III; Good; Strong

Page 14: Table 6: Follow-up for patients with mild NPDR and no DME: 12 months: III; Good; Strong

Page 14: Table 6: Follow-up for patients with mild NPDR and ME: 4–6 months: III; Good; Strong

Page 14: Table 6: Follow-up for patients with mild NPDR and CSME: 1 month: III; Good; Strong

Page 14: Table 6: Panretinal photocoagulation laser treatment not recommended for patients with normal or minimal NPDR: III; Good; Strong

Page 14: Table 6: Panretinal photocoagulation laser treatment not recommended for patients with mild NPDR and no DME: III; Good; Strong

Page 14: Table 6: Panretinal photocoagulation laser treatment not recommended for patients with mild NPDR and ME: III; Good; Strong

Page 14: Table 6: Panretinal photocoagulation laser treatment not recommended for patients with mild NPDR and CSME: III; Good; Strong

Page 14: Table 6: Focal and/or grid laser treatment not recommended for patients with normal or minimal NPDR: III; Good; Strong

Page 14: Table 6: Focal and/or grid laser treatment not recommended for patients with mild NPDR and no DME: III; Good; Strong

Page 14: Table 6: Focal and/or grid laser treatment not recommended for patients with mild NPDR and ME: III; Good; Strong

Page 14: Table 6: Focal and/or grid laser treatment sometimes recommended for patients with mild NPDR and CSME: I++; Good; Strong

Page 14: Table 6: Intravitreal anti-VEGF treatment sometimes recommended for patients with mild NPDR and CSME: I++; Good; Strong

Page 14: Table 6: Follow-up for patients with moderate NPDR and no DME: 6–12 months: III; Good; Strong

Page 14: Table 6: Follow-up for patients with moderate NPDR and ME: 3–6 months: III; Good; Strong

Page 14: Table 6: Follow-up for patients with moderate NPDR and CSME: 1 month: III; Good; Strong

Page 14: Table 6: Panretinal photocoagulation laser treatment not recommended for patients with moderate NPDR and no DME: III; Good; Strong

Page 14: Table 6: Panretinal photocoagulation laser treatment not recommended for patients with moderate NPDR and ME: III; Good; Strong

Page 14: Table 6: Panretinal photocoagulation laser treatment not recommended for patients with moderate NPDR and CSME: III; Good; Strong

Page 14: Table 6: Focal and/or grid laser treatment not recommended for patients with moderate NPDR and no DME: III; Good; Strong

Page 14: Table 6: Focal and/or laser treatment not recommended for patients with moderate NPDR and ME: III; Good; Strong

Page 14: Table 6: Focal and/or grid laser treatment sometimes recommended for patients with moderate NPDR and CSME: I++; Good; Strong

Page 14: Table 6: Intravitreal anti-VEGF treatment sometimes recommended for patients with moderate NPDR and CSME: I++; Good; Strong

Page 14: Table 6: Follow-up for patients with severe NPDR and no DME: 4 months: III; Good; Strong

Page 14: Table 6: Follow-up for patients with severe NPDR and ME: 2–4 months: III; Good; Strong

Page 14: Table 6: Follow-up for patients with severe NPDR and CSME: 1 month: III; Good; Strong

Page 14: Table 6: Panretinal photocoagulation laser treatment sometimes recommended for patients with severe NPDR and no DME: I++; Good; Strong

Page 14: Table 6: Panretinal photocoagulation laser treatment sometimes recommended for patients with severe NPDR and ME: I++; Good; Strong

Page 14: Table 6: Panretinal photocoagulation laser treatment sometimes recommended for patients with severe NPDR and CSME: I++; Good; Strong

Page 14: Table 6: Focal and/or grid laser treatment not recommended for patients with severe NPDR and no DME: III; Good; Strong

Page 14: Table 6: Focal and/or grid laser treatment not recommended for patients with severe NPDR and ME: III; Good; Strong

Page 14: Table 6: Focal and/or grid laser treatment sometimes recommended for patients with severe NPDR and CSME: III; Good; Strong

Page 14: Table 6: Intravitreal anti-VEGF treatment not recommended for patients with severe NPDR and no DME: III; Good; Strong

Page 14: Table 6: Intravitreal anti-VEGF treatment not recommended for patients with severe NPDR and ME: III; Good; Strong

Page 14: Table 6: Intravitreal anti-VEGF treatment sometimes recommended for patients with severe NPDR and CSME: III; Insufficient; Discretionary

Page 14: Table 6: Follow-up for patients with non-high-risk PDR and no DME: 4 months: III; Good; Strong

Page 14: Table 6: Follow-up for patients with non-high-risk PDR and ME: 4 months: III; Good; Strong

Page 14: Table 6: Follow-up for patients with non-high-risk PDR and CSME: 1 month: III; Good; Strong

Page 14: Table 6: Panretinal photocoagulation laser treatment sometimes recommended for patients with non-high-risk PDR and no DME: I++; Good; Strong

Page 14: Table 6: Panretinal photocoagulation laser treatment sometimes recommended for patients with non-high-risk PDR and ME: I++; Good; Strong

Page 14: Table 6: Panretinal photocoagulation laser treatment sometimes recommended for patients with non-high-risk PDR and CSME: I++; Good; Strong

Page 14: Table 6: Focal and/or grid laser treatment not recommended for patients with non-high-risk PDR and no DME: III; Good; Strong

Page 14: Table 6: Focal and/or grid laser treatment not recommended for patients with non-high-risk PDR and ME: III; Good; Strong

Page 14: Table 6: Focal and/or grid laser treatment sometimes recommended for patients with non-high-risk PDR and CSME: III; Good; Strong

Page 14: Table 6: Intravitreal anti-VEGF treatment not recommended for patients with non-high-risk PDR and no DME: III; Good; Strong

Page 14: Table 6: Intravitreal anti-VEGF treatment not recommended for patients with non-high-risk PDR and ME: III; Good; Strong

Page 14: Table 6: Intravitreal anti-VEGF treatment sometimes recommended for patients with non-high-risk PDR and CSME: III; Insufficient; Discretionary

Page 14: Table 6: Follow-up for patients with high-risk PDR and no DME: 4 months: III; Good; Strong

Page 14: Table 6: Follow-up for patients with high-risk PDR and ME: 4 months: III; Good; Strong

Page 14: Table 6: Follow-up for patients with high-risk PDR and CSME: 1 month: III; Good; Strong

Page 14: Table 6: Panretinal photocoagulation laser treatment recommended for patients with high-risk PDR and no DME: I++; Good; Strong

Page 14: Table 6: Panretinal photocoagulation laser treatment recommended for patients with high-risk PDR and ME: I++; Good; Strong

Page 14: Table 6: Panretinal photocoagulation laser treatment usually recommended for patients with high-risk PDR and CSME: I++; Good; Strong

Page 14: Table 6: Focal and/or grid laser treatment not recommended for patients with high-risk PDR and no DME: III; Good; Strong

Page 14: Table 6: Focal and/or grid laser treatment sometimes recommended for patients with high-risk PDR and ME: III; Good; Strong

Page 14: Table 6: Focal and/or grid laser treatment sometimes recommended for patients with high-risk PDR and CSME: III; Good; Strong

Page 14: Table 6: Intravitreal anti-VEGF treatment considered for patients with high-risk PDR and no DME: III; Good; Strong

Page 14: Table 6: Intravitreal anti-VEGF treatment usually recommended for patients with high-risk PDR and ME: III; Good; Strong

Page 14: Table 6: Intravitreal anti-VEGF treatment usually recommended for patients with high-risk PDR and CSME: III; Good; Strong

Page 15: The patient with a normal retinal exam or minimal NPDR should be re-examined annually: III; Good; Strong

Page 15: Laser surgery, color fundus photography, and fluorescein angiography are not indicated for patients with normal retinal examinations or minimal NPDR: III; Good; Strong

Page 15: Patients with retinal microaneurysms and occasional blot hemorrhages or hard exudates should be re-examined within 6 to 12 months: III; Good; Strong

Page 15: Laser surgery and fluorescein angiography are not indicated for mild to moderate NPDR without macular edema: III; Good; Strong

Page 15: Color fundus photography and OCT imaging of the macular may occasionally be helpful to establish a baseline for future comparison: III; Insufficient; Discretionary

Page 15: Patients with mild or moderate NPDR and non-clinically significant macular edema should be re-examined within 3 to 4 months: III; Good; Strong

**Diabetic Retinopathy PPP:
Appendix 3. PPP Recommendation Grading**

Page 16: Macular edema is best evaluated by dilated examination using slit-lamp biomicroscopy, optical coherence tomography, and/or stereoscopic fundus photography: III; Good; Strong

Page 16: An ophthalmologist who treats patients for macular edema should be familiar with relevant studies and techniques as described in the ETDRS: III; Good; Strong

Page 16: Fluorescein angiography prior to laser surgery for CSME is often helpful for identifying treatable lesions: III; Good; Discretionary

Page 16: Fluorescein angiography is useful for identifying capillary dropout and pathologic enlargement of the foveal avascular zone, a feature that may be useful when planning treatment: III; Good; Discretionary

Page 16: Color fundus photography is often helpful to document the status of the retina even if laser surgery is not performed: III; Good; Discretionary

Page 16: Optical coherence tomography is a helpful screening tool to detect subtle edema and to follow the course of edema after treatment: III; Good; Discretionary

Page 16: The treatment of CMSE has traditionally been laser surgery; however, current data demonstrates that intravitreal anti-VEGF agents are effective treatments for center-involving CSME: I++; Good; Strong

Page 16: The ETDRS demonstrated a benefit of laser photocoagulation in both ci-CSME and nci-CSME: I++; Good; Strong

Page 16: Anti-VEGF therapy is the treatment of choice for macular edema with or without focal laser treatment: I++; Good; Strong

Page 17: Treating physicians should note that the use of betadine antiseptic drops is recommended during intravitreal injections: III; Good; Strong

Page 17: The use of routine antibiotic eye drops is not recommended before or following intravitreal injection procedures: III; Insufficient; Discretionary

Page 17: Many retina specialists prefer a less intense laser treatment, greater spacing, directly targeting microaneurysms, and avoiding foveal vasculature within at least 500 µm of the center of the macula: I++; Good; Discretionary

Page 17: Preoperatively, the ophthalmologist should discuss with the patient the side effects and risks of treatment: III; Good; Strong

Page 17: A follow-up examination for individuals with CSME should be scheduled within 3 to 4 months of laser surgery: III; Good; Strong

Page 17: Individuals receiving the intravitreal injections of anti-VEGF agents may be examined at 1 month following therapy: III; Good; Strong

Page 17: When treatment for macular edema is deferred, the patient should be observed closely (at least every 3 to 4 months) for signs of progression: III; Good; Strong

Page 17: Patients with very severe NPDR should be re-examined within 2 to 4 months: III; Good; Strong

Page 17: Panretinal photocoagulation should not be recommended for eyes with mild or moderate NPDR, provided that follow-up [can] be maintained: I++; Good; Strong

Page 17: When retinopathy is more severe, panretinal photocoagulation should be considered and should not be delayed when the eye reaches the high-risk proliferative stage: I++; Good; Strong

Page 18: Careful follow-up at 3 to 4 months is important: if the patient will not or cannot be followed closely or if there are associated medical conditions such as impending cataract surgery or pregnancy, then early laser photocoagulation may be warranted: III; Good; Strong

Page 18: Laser photocoagulation may be indicated particularly when access to health care is difficult: III; Insufficient; Discretionary

Page 18: If laser surgery is elected, full panretinal photocoagulation is a proven surgical technique: I++; Good; Strong

Page 18: Partial panretinal photocoagulation treatment is not recommended: III; Good; Strong

Page 18: The recommendation to consider panretinal photocoagulation before the development of high-risk PDR is particularly appropriate for patients with Type 2 diabetes and severe to non-high-risk NPDR: II++; Moderate; Strong

Page 18: For patients with Type 1 diabetes, the timing of the panretinal photocoagulation depends on the compliance with follow-up and the status and response to treatment of the fellow eye: III; Insufficient; Discretionary

Page 18: Preoperatively [to laser surgery], the ophthalmologist should assess macular edema, discuss side effects of treatment and risks of visual loss with the patient, and obtain informed consent: III; Good; Strong

Page 18: When panretinal photocoagulation for severe NPDR or non-high-risk PDR is to be performed on eyes with macular edema, many experts think that it is preferable to perform focal photocoagulation and/or anti-VEGF therapy prior to panretinal photocoagulation: III; Good; Strong

Page 18: Panretinal photocoagulation surgery should not be delayed when PDR is at the high-risk stage: III; Good; Strong

Page 18: When PDR is at the high-risk stage, anti-VEGF therapy and panretinal photocoagulation may be performed concomitantly: III; Good; Strong

Page 18: Fluorescein angiography may be helpful to determine the presence or absence of areas of nonperfusion and/or clinically undetected areas of retinal neovascularization and to establish the cause for a loss in visual acuity: III; Moderate; Discretionary

Page 18: The risk of severe visual loss among patients with high-risk PDR is reduced substantially by treatment using panretinal photocoagulation as described in the DRS and ETDRS: I++; Good; Strong

Page 18: Most patients with high-risk PDR should receive panretinal photocoagulation surgery expeditiously: II++; Good; Strong

Page 19: Additional panretinal photocoagulation or vitrectomy may be required for increasing neovascularization of the iris and may be considered for the following indications: failure of the neovascularization to regress; increasing neovascularization of the retina or iris; new vitreous hemorrhage; new areas of neovascularization: III; Insufficient; Discretionary

Page 19: For patients who have CSME in addition to high-risk PDR, combined anti-VEGF therapy and panretinal photocoagulation at the first treatment session should be considered: III; Insufficient; Discretionary

Page 19: Fluorescein angiography does not usually need to be performed in order to apply the panretinal photocoagulation effectively. If CSME is present, however, a fluorescein angiogram may be used to guide focal photocoagulation: III; Insufficient; Discretionary

Page 19: Vitreous hemorrhages following extensive panretinal photocoagulation may clear spontaneously and do not necessarily require additional laser surgery: III; Insufficient; Discretionary

Page 19: Some patients with previously untreated PDR who have vitreous opacities and active neovascular or fibrovascular proliferation should be considered candidates for pars plana vitrectomy: I++; Good; Strong

**Diabetic Retinopathy PPP:
Appendix 3. PPP Recommendation Grading**

Page 19: In some patients with severe vitreous or preretinal hemorrhage, in which advanced, active PDR persists despite extensive panretinal photocoagulation, vitrectomy surgery may be indicated: III; Insufficient; Discretionary

Page 19: Vitreous surgery is frequently indicated in patients with traction macular detachment (particularly of recent onset), combined traction–rhegmatogenous retinal detachment, and vitreous hemorrhage precluding panretinal photocoagulation: III; Insufficient; Discretionary

Page 19: Patients with vitreous hemorrhage and rubeosis iridis also should be considered for prompt vitrectomy and intraoperative panretinal photocoagulation surgery: III; Insufficient; Discretionary

Page 20: A follow-up history should include changes in symptoms: III; Good; Strong

Page 20: A follow-up history should include changes in systemic status: III; Good; Strong

Page 20: A follow-up history should include changes in glycemic status: III; Good; Strong

Page 20: A follow-up examination should include visual acuity: III; Good; Strong

Page 20: A follow-up examination should include slit-lamp biomicroscopy with iris examination: III; Good; Strong

Page 20: A follow-up examination should include intraocular pressure: III; Good; Strong

Page 20: A follow-up examination should include gonioscopy (preferably before dilation when iris neovascularization is suspected or if IOP is elevated): III; Good; Strong

Page 20: A follow-up examination should include stereoscopic examination of the posterior pole after dilation of the pupils: III; Good; Strong

Page 20: A follow-up examination should include OCT imaging, when appropriate: III; Good; Strong

Page 20: A follow-up examination should include peripheral retina and vitreous examination, when indicated: III; Good; Strong

Page 20: Although the ophthalmologist will perform most of the examination and all surgery, certain aspects of data collection may be performed by trained individuals under the ophthalmologist’s supervision and review: III; Good; Strong

Page 20: Because of the complexities of the diagnosis and treatment for diabetic retinopathy, the ophthalmologist caring for patients with this condition should be familiar with the specific recommendations of relevant clinical trials: III; Good; Strong

Page 20: The ophthalmologist should refer patients with diabetes to a primary care physician for appropriate management of their systemic condition, and should communicate examination results to the physician managing the patient’s ongoing diabetes care: III; Good; Strong

Page 20: Those whose conditions fail to respond to surgery and those for whom further treatment is unavailable should be provided with proper professional support and offered referral for counseling, vision rehabilitation, or social services as appropriate: III; Good; Strong

Page 20: Patients with functionally limiting postoperative visual impairment should be referred for vision rehabilitation and social services: III; Good; Strong

APPENDIX 5

Page 40: Frequent ophthalmologic monitoring is important when patients are being brought under better control: III; Good; Strong

Page 40: Diabetes mellitus education and regular reinforcement should be provided by diabetes nurses and dietitian educators and may help minimize the risk of hypoglycemia: III; Good; Strong



APPENDIX 4. MAJOR STUDY RESULTS

DIABETIC RETINOPATHY STUDY (1972–1979)

The Diabetic Retinopathy Study (DRS) was designed to investigate the value of laser photocoagulation surgery for patients with severe NPDR and PDR.⁶¹ The results are shown in Table A4-1.

TABLE A4-1 VISUAL OUTCOME FOR LASER PHOTOCOAGULATION FROM THE DIABETIC RETINOPATHY STUDY

Baseline Severity of Retinopathy	Duration of Follow-up (Years)	Control Patients (% with Severe Visual Loss)	Treated Patients (% with Severe Visual Loss)
Severe nonproliferative	2	3	3
	4	13	4
Mild proliferative	2	7	3
	4	21	7
High-risk proliferative	2	26	11
	4	44	20

NOTE: Severe visual loss was defined as worse than 5/200 visual acuity at two or more consecutive completed visits (scheduled at 4-month intervals).

WISCONSIN EPIDEMIOLOGIC STUDY OF DIABETIC RETINOPATHY (1979)

The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) began in 1979. It was initially funded by the National Eye Institute, which is part of the National Institutes of Health. The purpose of the WESDR is to describe the frequency and incidence of complications associated with diabetes (eye complications such as diabetic retinopathy and visual loss, kidney complications such as diabetic nephropathy, and amputations), and to identify risk factors (such as poor glycemic control, smoking, and high blood pressure) that may contribute to the development of these complications.⁶⁷

EARLY TREATMENT DIABETIC RETINOPATHY STUDY (1985–1990)

The Early Treatment Diabetic Retinopathy Study (ETDRS) investigated the value of photocoagulation surgery for patients with NPDR or PDR without high-risk characteristics.^{65, 102} The results for eyes with macular edema are shown in Table A4-2. Visual loss was defined as at least doubling of the visual angle (e.g., 20/20 to 20/40, or 20/50 to 20/100).

TABLE A4-2 VISUAL OUTCOME FOR LASER PHOTOCOAGULATION TREATMENT FROM THE EARLY TREATMENT DIABETIC RETINOPATHY STUDY

Extent of Macular Edema	Duration of Follow-up (Years)	Control Patients (% with Visual Loss)	Treated Patients (% with Visual Loss)
CSME (center of macula not involved)	1	8	1
	2	16	6
	3	22	13
CSME (center of macula involved)	1	13	8
	2	24	9
	3	33	14

CSME = clinically significant macular edema

NOTE: Visual loss was defined as at least doubling of the visual angle.

Results of Early Scatter Laser Treatment in ETDRS

In eyes with NPDR or non-high-risk PDR, early panretinal photocoagulation was compared with deferral of photocoagulation, and although there was a beneficial treatment effect, the outlook for maintaining vision was good in both groups. The 5-year rates of severe visual loss or vitrectomy ranged from 2% to 6% in eyes assigned to early photocoagulation and from 4% to 10% in eyes assigned to deferral. Early panretinal photocoagulation was associated with side effects (small decreases in visual acuity and visual field) in some eyes, and the ETDRS concluded that deferral of photocoagulation was preferable at least until retinopathy was approaching the high-risk stage. Eyes approaching that stage had a 50% risk of reaching it within 12 to 18 months. Eyes in this category had very severe NPDR or non-high-risk PDR characterized by NVD less than one-quarter to one-third disc area and/or NVE, without vitreous or preretinal hemorrhage.

Recent additional analyses of visual outcome in ETDRS patients with severe NPDR to non-high-risk PDR suggest that the recommendation to consider panretinal photocoagulation before the development of high-risk PDR is particularly appropriate for patients with Type 2 diabetes.¹⁷⁰ The risk of severe vision loss or vitrectomy was reduced by 50% in patients who were treated early compared with those who deferred treatment until high-risk PDR developed.

For patients with Type 1 diabetes, the timing of the panretinal photocoagulation will depend on the compliance with follow-up, status and response to treatment of the fellow eye, impending cataract surgery, and/or pregnancy status.

DIABETIC RETINOPATHY VITRECTOMY STUDY (1983–1987)

The Diabetic Retinopathy Vitrectomy Study (DRVS) investigated the role of vitrectomy in managing eyes with very severe PDR.^{66, 172-174} The benefit of early vitrectomy for severe vitreous hemorrhage (defined as hemorrhage obscuring the macula or major retinal vessels for three disc diameters from the macular center) was seen in Type 1 patients, but no such advantage was found in Type 2 patients, who did not benefit from earlier surgery. Early vitrectomy was beneficial among patients with visual acuity of 5/200 or worse and severe vitreous hemorrhage with reduced vision for at least 1 month and without previous treatment or complications such as retinal detachment or neovascularization of the iris. Overall, at 2 years after surgery, 25% of the early vitrectomy group and 15% of the deferral group had visual acuity of 20/40 or better. The advantage was most pronounced in patients with Type 1 diabetes (36% vs. 12% for early vitrectomy versus deferral of vitrectomy, respectively) and was not statistically significant for patients with Type 2 diabetes.

The DRVS showed that early vitrectomy was beneficial for patients with visual acuity of 20/400 or better plus one of the following: (1) severe neovascularization and fibrous proliferation; (2) fibrous proliferation and moderate vitreous hemorrhage; or (3) moderate neovascularization, severe fibrous proliferation, and moderate vitreous hemorrhage. Among such patients, 44% with early vitrectomy and 28% in the observation group had visual acuity of 20/40 or better at 4 years of follow-up.

The results of the DRVS should be interpreted in light of subsequent advances in vitreoretinal surgery, such as the introduction of small-gauge vitrectomy technology, endoscopic and indirect ophthalmoscopic laser photocoagulation, and advanced instrumentation. The use of long-acting intraocular gases such as sulfur hexafluoride and perfluoropropane, the use of viscodissection, and the use of heavier-than-water liquids such as perfluoro-octane are advances in vitreoretinal surgery that developed after the DRVS. Thus, the results may actually be better than those reported in the DRVS.^{136, 198} Early vitrectomy should be considered for selected patients with Type 2 diabetes, particularly those in whom severe vitreous hemorrhage prohibits laser therapy photocoagulation of active neovascularization.

FENOFIBRATE INTERVENTION AND EVENT LOWERING IN DIABETES (FIELD) STUDY (2005)

The FIELD study was a randomized controlled trial that evaluated long-term fenofibrate therapy for the reduction of cardiovascular events in 9795 patients with Type 2 diabetes mellitus. Fenofibrate did not significantly reduce the risk of the primary outcome of coronary events. It did reduce total cardiovascular events, mainly due to fewer nonfatal myocardial infarctions and revascularizations. The higher rate of starting statin therapy in patients allocated to receive placebo might have masked a moderately larger treatment benefit.

DIABETIC RETINOPATHY CLINICAL RESEARCH NETWORK (DRCR.NET) (2002–PRESENT)

The Diabetic Retinopathy Clinical Research Network (DRCR.net) is a collaborative network dedicated to facilitating multicenter clinical research of diabetic retinopathy, diabetic macular edema, and associated conditions. The DRCR.net supports the identification, design, and implementation of multicenter clinical research initiatives focused on diabetes-induced retinal disorders. Principal emphasis is placed on clinical trials, but epidemiologic outcomes and other research may be supported as well.

The DRCR.net was formed in 2002 and currently includes over 109 participating sites (offices) with over 320 physicians throughout the United States. The DRCR.net is funded by the National Eye Institute (NEI), which is a part of the National Institutes of Health, the branch of government that funds medical research.

The DRCR.net has completed multiple clinical trials evaluating the role of anti-VEGF, laser treatment, and corticosteroids in diabetic macular edema. One of the most important is Protocol I: Intravitreal Ranibizumab for Diabetic Macular Edema with Prompt vs. Deferred Laser Treatment. Three-year results were reported in 2012. The study utilized ranibizumab monthly until improvement no longer occurred (with resumption if the condition worsened) and random assignment to focal/grid laser treatment promptly or deferred (≥ 24 weeks). The 3-year results suggest that focal/grid laser treatment at the initiation of intravitreal ranibizumab is no better, and possibly worse for vision outcomes, than deferring laser treatment for ≥ 24 weeks in eyes with DME involving the fovea and with vision impairment.⁷⁰

A previous publication from Protocol I results confirmed the 1 year results that intravitreal ranibizumab with prompt or deferred laser was more effective through 2 years compared with prompt laser alone for the treatment of DME involving the central macula. Laser was not associated with endophthalmitis, the rare but potentially devastating complication of injecting ranibizumab. In pseudophakic eyes, results with intravitreal triamcinolone plus prompt laser appeared similar to results in the ranibizumab arms and were more effective than laser alone, but the triamcinolone plus prompt laser arm had an increased risk of IOP elevation.¹³¹

STUDY OF RANIBIZUMAB INJECTION IN SUBJECTS WITH CSDME WITH CENTER INVOLVEMENT SECONDARY TO DIABETES MELLITUS (RISE AND RIDE)

The RISE and RIDE trials were parallel phase III multicenter double-masked sham injection-controlled randomized studies conducted at private and university-based retina specialty clinics in the United States and South America. (See Glossary.)

The phase III results for both studies were published in 2012. The studies utilized monthly intravitreal ranibizumab (0.5 or 0.3 mg) or sham injections, with macular laser available if needed. The study concluded that ranibizumab rapidly and sustainably improved vision, reduced the risk of further vision loss, and improved macular edema in patients with DME, with low rates of ocular and nonocular side effects.¹⁴⁷

RANIBIZUMAB FOR EDEMA OF THE MACULA IN DIABETES (READ-2)

READ-2 was a phase II multicenter randomized controlled trial that compared 0.5 mg injections of ranibizumab versus focal laser treatment over 2 years in patients with Type 1 or Type 2 diabetes mellitus and DME. Patients randomized to one arm of the trial received ranibizumab at baseline, and at 1, 3 and 5 months after baseline; a second arm received laser treatment at baseline and at 3 months (if needed); the third arm received both ranibizumab and laser treatment at baseline and 3 months. From month 5, all subjects received ranibizumab every 2 months and/or maintenance laser treatment every 3 months.

At 24 months, differences between the groups were not statistically significant, and all groups experienced improved visual acuity. Patients receiving combined ranibizumab and laser treatment required fewer injections than patients receiving ranibizumab alone.¹⁵⁰

BEVACIZUMAB OR LASER THERAPY (BOLT) STUDY

BOLT was a phase II 2-year randomized controlled trial that compared intravitreal 1.25 mg bevacizumab injections and focal laser treatment in patients with persistent DME and visual impairment. Bevacizumab patients received an injection every 6 weeks, whereas laser patients were treated every 4 weeks.

At 2 years, visual acuity results were substantially better in the bevacizumab group compared with the laser group, with significant differences in the proportions of patients gaining 10 letters and 15 letters. No patients lost 10 or more letters in the bevacizumab group, compared with 14% of patients treated with laser.¹⁵¹

DME AND VEGF TRAP-EYE: INVESTIGATION OF CLINICAL IMPACT (DA VINCI) STUDY

DA VINCI was an active-controlled phase II randomized controlled trial that compared various doses of aflibercept and focal laser treatment in patients with CSME. At 1 year, patients receiving aflibercept had greater gains in visual acuity (averaging 9.7–12.0 letters gained) compared with patients receiving laser treatment (averaging -1.3 letters lost). Aflibercept patients were also more likely to gain 10 or more letters and 15 or more letters than patients in the laser treatment arm.¹⁵²



APPENDIX 5. GLYCEMIC CONTROL

The Diabetes Control and Complications Trial (DCCT) was a multicenter, randomized controlled trial designed to study the connection between glycemic control and retinal, renal, and neurologic complications of Type 1 diabetes mellitus. Published results from this trial demonstrated that improved blood sugar control can delay the onset and slow the progression of diabetic retinopathy, nephropathy, and neuropathy in Type 1 patients.⁵⁷ The DCCT showed a strong exponential relationship between the risk of diabetic retinopathy and the mean hemoglobin A_{1c} (HbA_{1c}) level. For each 10% decrease in the HbA_{1c} (e.g., from 9% to 8.1%), there was a 39% decrease in the risk of progression of retinopathy over the range of HbA_{1c} values. There was no glycemic threshold when the risk of retinopathy was eliminated above the nondiabetic range of HbA_{1c} (4% to 6.05%).

After 6.5 years of follow-up, the DCCT ended, and all patients were encouraged to pursue strict control of blood sugar. Most of these patients are being followed in the Epidemiology of Diabetes Interventions and Complications (EDIC) study, which includes 95% of the DCCT subjects. A total of 1294 to 1335 patients have been examined annually in the EDIC study. Further progression of diabetic retinopathy during the first 4 years of the EDIC study was 66% to 77% less in the former intensive treatment group than in the former conventional treatment group.³⁵ The benefit persisted even at 7 years. This benefit included an effect on severe diabetic retinopathy, including severe NPDR, PDR, CSME, and the need for focal/grid or panretinal laser photocoagulation.³⁷ The decrease in HbA_{1c} from 9% to approximately 8% did not drastically reduce the progression of diabetic retinopathy in the former conventional treatment group, nor did the increase in HbA_{1c} from approximately 7% to approximately 8% drastically accelerate diabetic retinopathy in the former intensive treatment group.³⁵ Thus, it takes time for improvements in control to negate the long-lasting effects of prior prolonged hyperglycemia, and once the biological effects of prolonged improved control are manifest, the benefits are long-lasting. Furthermore, the total glycemic exposure of the patient (i.e., degree and duration) determines the degree of retinopathy observed at any one time.

A positive relationship between the 4-year incidence and progression of retinopathy and glycosylated hemoglobin remains after controlling for other risk factors, such as duration of diabetes and severity of retinopathy at a baseline examination.^{51, 52, 100} Extrapolation of pathologic and clinical experience strongly suggests that poor levels of control contribute to microangiopathy, including retinopathy.¹⁹⁹ The development of PDR parallels an increased risk of nephropathy, myocardial infarction, and/or cerebral vascular accidents.

Although good glycemic control is advised, there is some evidence that rapid improvement of long-standing poor control may increase the risk of retinopathy progression over the first year for some patients. About 10% of Type 1 patients who had initial retinopathy at the beginning of the DCCT had increased retinopathy progression.²⁰⁰ Specifically, there may be a transient increase in the number of cotton-wool spots seen on retinal examination. Frequent ophthalmologic monitoring is important when diabetic patients are being brought under better metabolic control.²⁰⁰

In the DCCT there was a threefold increase in severe hypoglycemic events and excess weight gain among patients using intensive treatment regimens. Increased risk of hypoglycemia is a consequence of strict blood glucose control. Irregular food intake, failure to check blood glucose before planned or unplanned vigorous exercise or before operating a motor vehicle, and excess alcohol are risk factors for hypoglycemia. Diabetes mellitus education and regular reinforcement should be provided by diabetes nurses and dietitian educators and may help minimize the risk of hypoglycemia.

The United Kingdom Prospective Diabetes Study (UKPDS),^{38, 96} a randomized controlled clinical trial of blood glucose control, enrolled 3867 patients with newly diagnosed Type 2 diabetes. Intensive blood glucose control by either the sulfonylureas or insulin decreased the risk of microvascular complications but not the risk of macrovascular disease. There were no adverse effects of the individual drugs on the cardiovascular outcome. In this study, there was a 29% reduction in the need for retinal photocoagulation in the group that had intensive glucose therapy compared with those that had conventional treatment (relative risk, 0.71; 95% confidence interval, 0.53–0.96; $P=0.003$).

The ACCORD (Action to Control Cardiovascular Risk in Diabetes) study (www.accordtrial.org) was a large clinical trial of adults with established Type 2 diabetes who are at especially high risk of cardiovascular disease (CVD). Type 2 diabetes increases the risk of a number of complications, especially CVD, which is the leading cause of early death in people with diabetes.

The ACCORD study consisted primarily of three clinical trials that tested treatment approaches to determine the best ways to decrease the high rate of major CVD events—heart attack, stroke, or death from CVD—among people with Type 2 diabetes who are at especially high risk of having such a CVD event. These three treatment approaches were intensive lowering of blood sugar levels compared with a more standard blood sugar treatment; intensive lowering of blood pressure compared with standard blood pressure treatment; and treatment of multiple blood lipids with two drugs—a fibrate plus a statin—compared with one drug, a statin alone.²⁰¹

The study began enrolling participants in 2001 and took place in 77 clinical sites across the United States and Canada. A total of 10,251 adults with established Type 2 diabetes participated in ACCORD. At enrollment, study participants were between age 40 and 79 (average age 62), had diabetes for an average of 10 years, and were at especially high risk for CVD events because they already had pre-existing CVD, evidence of subclinical CVD, or at least two CVD risk factors in addition to Type 2 diabetes. The other CVD risk factors could be high low-density lipoprotein (LDL) cholesterol, high blood pressure, smoking, or obesity.

The primary outcome measure for all three trials was the first occurrence after randomization of a major CVD event, specifically nonfatal heart attack, nonfatal stroke, or CVD death. Secondary outcomes include total mortality (death), microvascular outcomes (e.g., eye, kidney, and nerve complications), health-related quality of life, and cost-effectiveness.

All three ACCORD clinical trials have ended. The National Heart, Lung, and Blood Institute (NHLBI) stopped the intensive blood sugar lowering strategy in 2008 due to safety concerns. Participants in the intensive blood sugar treatment strategy group were transitioned to the standard treatment strategy. The blood pressure and lipid treatment trials continued until the planned end of the study in 2009. In its regular review of the available study data, the ACCORD Data and Safety Monitoring Board (DSMB) noticed an unexpected increase in total deaths from any cause among participants who had been randomly (by chance) assigned to the intensive lowering of blood sugar levels group compared with those assigned to the standard blood sugar treatment group. The data analyses showed that over an average of 3.5 years of treatment (ranging from about 2 years to about 7 years), 257 participants in the intensive group died compared with 203 in the standard group—a difference of 54 deaths, or an excess of about 3 deaths per 1,000 participants treated for a year. This translates to a statistically significant 22% higher rate of death in the intensive group than in the standard group.

There was a trend toward lower (10% lower) rate of primary outcome events, primarily nonfatal heart attacks, in the intensive group compared with the standard treatment group. However, the DSMB recommended discontinuing intensive blood sugar treatment because the harm of the intensive strategy outweighed the potential benefit. The NHLBI accepted the DSMB's recommendation and decided to transition all participants to the standard blood sugar strategy.

The results of the blood sugar trial were published in 2008.²⁰² There was no significant difference in the primary study outcome between the intensive and standard blood pressure treatment groups. The primary outcome was the time to first occurrence after randomization of a heart attack, a stroke, or a cardiovascular death. Thus, the primary hypothesis of the ACCORD BP trial was not supported. There was, however, a significant reduction in the rate of strokes, although the numbers were relatively small. This reduction in stroke was consistent with previous blood pressure lowering trials. Overall, however, the findings from the ACCORD blood pressure trial suggest that, on average, the standard treatment for lowering blood pressure was just as good as the intensive lowering treatment for cardiovascular outcomes.

The results of the lipid²⁰³ and the blood pressure²⁰⁴ trials were published in 2010. Overall, the fibrate and the placebo groups did not differ in the rates of the combined outcome of heart attacks, strokes, or cardiovascular death. The results, however, suggest that men may benefit from this treatment, but there was a trend toward more cardiovascular problems in women receiving the combination therapy compared with those who received statins only. Also, the group of patients who at the start of the trial had the lowest level of HDL cholesterol combined with the highest level of triglycerides (which represented only 17% of the ACCORD participants) may have benefitted from this combined drug treatment.



APPENDIX 6. CLASSIFICATION OF DIABETIC RETINOPATHY IN THE EARLY TREATMENT OF DIABETIC RETINOPATHY STUDY

The Early Treatment of Diabetic Retinopathy Study (ETDRS) classification of diabetic retinopathy and definitions of macular edema are in Tables A6-1 and A6-2.

TABLE A6-1 CLASSIFICATION OF DIABETIC RETINOPATHY IN THE EARLY TREATMENT OF DIABETIC RETINOPATHY STUDY

Disease Severity Level	Findings Observable upon Dilated Ophthalmoscopy
Mild nonproliferative retinopathy	At least one microaneurysm, and definition not met for moderate nonproliferative retinopathy, severe nonproliferative retinopathy, early proliferative retinopathy, or high-risk proliferative retinopathy (see below)
Moderate nonproliferative retinopathy	Hemorrhages and/or microaneurysms \geq standard photograph 2A*; and/or soft exudates, venous beading, or intraretinal microvascular abnormalities definitely present; and definition not met for severe nonproliferative retinopathy, early proliferative retinopathy, or high-risk proliferative retinopathy (see below)
Severe nonproliferative retinopathy	Cotton-wool spots, venous beading, and intraretinal microvascular abnormalities all definitely present in at least two of fields four through seven; or two of the preceding three lesions present in at least two of fields four through seven and hemorrhages and microaneurysms present in these four fields, \geq standard photo 2A in at least one of them; or intraretinal microvascular abnormalities present in each of fields four through seven and \geq standard photograph 8A in at least two of them; and definition not met for early proliferative retinopathy or high-risk proliferative retinopathy (see below)
Early proliferative retinopathy (i.e., proliferative retinopathy without Diabetic Retinopathy Study high-risk characteristics) (see Glossary)	New vessels; and definition not met for high-risk proliferative retinopathy (see below)
High-risk proliferative retinopathy (i.e., proliferative retinopathy with Diabetic Retinopathy Study high-risk characteristics) (see Glossary)	New vessels on or within one disc diameter of the optic disc (NVD) \geq standard photograph 10A* (about one-quarter to one-third disc area), with or without vitreous or preretinal hemorrhage; or vitreous and/or preretinal hemorrhage accompanied by new vessels, either NVD $<$ standard photograph 10A or new vessels elsewhere (NVE) \geq one-quarter disc area

Adapted with permission from the Early Treatment Diabetic Retinopathy Study Research Group. Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics: ETDRS report number 7. *Ophthalmology* 1991;98:742.

* Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs--an extension of the modified Airlie House classification: ETDRS report number 10. *Ophthalmology* 1991;98:786-806.

TABLE A6-2 DIABETIC MACULAR EDEMA DISEASE DEFINITIONS IN THE EARLY TREATMENT OF DIABETIC RETINOPATHY STUDY

Disease Severity Level	Findings Observable upon Dilated Ophthalmoscopy
Diabetic macular edema apparently absent	No apparent retinal thickening or hard exudates in posterior pole
Diabetic macular edema apparently present	Thickening of retina within one disc diameter of the center of the macula; and/or hard exudates \geq standard photograph 3* in a standard 30° photographic field centered on the macula (field 2), with some hard exudates within one disc diameter of the center of the macula
Clinically significant macular edema	Retinal thickening at or within 500 μm of the center of the macula; and/or hard exudates at or within 500 μm of the center of the macula, if associated with thickening of the adjacent retina; and/or a zone or zones of retinal thickening one disc area in size at least part of which was within one disc diameter of the center

Adapted with permission from the Early Treatment Diabetic Retinopathy Study Research Group. Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics: ETDRS report number 7. *Ophthalmology* 1991;98:742.

* Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs--an extension of the modified Airlie House classification: ETDRS report number 10. *Ophthalmology* 1991;98:786-806.



GLOSSARY

Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: A large multicenter clinical trial that evaluated intensive control of blood sugar, intensive control of blood pressure, and statin therapy (with or without fibrate treatment) for the prevention of cardiovascular disease events among high-risk patients with Type 2 diabetes.

ACCORD: See Action to Control Cardiovascular Risk in Diabetes trial.

Anti-VEGF: See Anti-vascular endothelial growth factor.

Anti-vascular endothelial growth factor (VEGF): Substances that inhibit the action of vascular endothelial growth factor protein.

Bevacizumab or Laser Treatment (BOLT) study: A randomized trial that evaluated intravitreal bevacizumab or conventional laser treatment for center-involving diabetic macular edema.

BOLT: See Bevacizumab or Laser Treatment study.

Clinically significant macular edema (CSME): Retinal thickening at or within 500 µm of the center of the macula; and/or hard exudates at or within 500 µm of the center of the macula, if associated with thickening of the adjacent retina; and/or a zone or zones of retinal thickening one disc area in size, any part of which is within one disc diameter of the center of the macula.

CSME: See Clinically significant macular edema.

ci-CSME: Center-involving CSME.

DA VINCI: See DME and VEGF Trap-Eye: Investigation of Clinical Impact study.

DCCT: See Diabetes Control and Complications Trial.

Diabetes Control and Complications Trial (DCCT): A multicenter randomized controlled trial designed to study the connection between glycemic control and retinal, renal, and neurologic complications of Type 1 diabetes mellitus. (See Appendix 5.)

Diabetes mellitus: According to the American Diabetes Association Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, the criteria for the diagnosis of diabetes mellitus are as follows.

- ◆ Fasting plasma glucose equal to or exceeding 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours.
or
- ◆ Symptoms of hyperglycemia and a casual plasma glucose concentration equal to or exceeding 200 mg/dL (11.1 mmol/L). “Casual” is defined as any time of day without regard to time since last meal. The classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss.
or
- ◆ A plasma glucose measurement at 2 hours postload equal to or exceeding 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. However, the expert committee has recommended against oral glucose tolerance testing for routine clinical use. (Source: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2008;31 (suppl):55-60.)

Diabetic Retinopathy Clinical Research Network (DRCR.net): A multicenter trial that is evaluating different treatment modalities for diabetic retinopathy.

Diabetic Retinopathy Study (DRS): A study designed to investigate the value of xenon arc and argon photocoagulation surgery for patients with severe NPDR and PDR. (See Appendix 4.)

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Diabetic Retinopathy Vitrectomy Study (DRVS): A study that investigated the role of vitrectomy in managing eyes with very severe PDR. (See Appendix 4.)

DME and VEGF Trap-Eye: Investigation of Clinical Impact (DA VINCI) study: A randomized trial of the use of afibbercept for diabetic macular edema.

DRCR.net: See Diabetic Retinopathy Clinical Research Network.

DRS: See Diabetic Retinopathy Study.

DRVS: See Diabetic Retinopathy Vitrectomy Study.

Early Treatment Diabetic Retinopathy Study (ETDRS): A study that investigated the value of photocoagulation surgery for patients with NPDR or PDR who did not have high-risk characteristics. (See Appendix 4.)

Early proliferative diabetic retinopathy (i.e., proliferative retinopathy without DRS high-risk characteristics): New vessels that do not meet the criteria of high-risk proliferative retinopathy.

EDIC: See Epidemiology of Diabetes Interventions and Complications study.

Epidemiology of Diabetes Interventions and Complications (EDIC) study: An observational study following 95% of the DCCT subjects. (See Appendix 5.)

ETDRS: See Early Treatment Diabetic Retinopathy Study.

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study: A large randomized controlled trial that evaluated long-term fenofibrate therapy for prevention of cardiovascular events in patients with Type 2 diabetes mellitus.

FIELD study: See Fenofibrate Intervention and Event Lowering in Diabetes study.

Focal photocoagulation: A laser technique directed to abnormal blood vessels with specific areas of focal leakage (i.e., microaneurysms) to reduce chronic fluid leakage in patients with macular edema.

Grid photocoagulation: A laser technique in which a grid pattern of scatter burns is applied in areas of diffuse macular edema and nonperfusion. Typically, fluorescein angiograms of these areas show a diffuse pattern rather than focal leakage.

High-risk proliferative diabetic retinopathy (PDR): New vessels on or within one disc diameter of the optic disc equaling or exceeding standard photograph 10A (about one-quarter to one-third disc area), with or without vitreous or preretinal hemorrhage; or vitreous and/or preretinal hemorrhage accompanied by new vessels either on the optic disc less than standard photograph 10A or new vessels elsewhere equaling or exceeding one-quarter disc area.



Standard photograph 10A defines the lower border of moderate NVD. NVD covers approximately one-third the area of the standard disc. This extent of NVD alone would constitute PDR with high-risk characteristics.

Reprinted with permission from the Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House classification: ETDRS report number 10. Ophthalmology 1991;98:786-806.

ICD-9: International Statistical Classification of Diseases and Related Health Problems, Ninth Edition.

ICD-10: International Statistical Classification of Diseases and Related Health Problems, Tenth Edition.

Intraretinal microvascular abnormalities (IRMA): Tortuous intraretinal vascular segments, varying in caliber from barely visible to 31 µm in diameter (one-quarter the width of a major vein at the disc margin); they occasionally can be larger. IRMA may be difficult to distinguish from neovascularization.

IRMA: See Intraretinal microvascular abnormalities.

Macular edema: Thickening of the retina within one or two disc diameters of the center of the macula. (See Clinically significant macular edema.) Any other thickening of the macula not within this area is non-CSME.

Mild nonproliferative diabetic retinopathy (NPDR): At least one microaneurysm and less than moderate nonproliferative diabetic retinopathy.

Moderate nonproliferative diabetic retinopathy (NPDR): Hemorrhages and/or microaneurysms greater than standard photograph 2A, and/or soft exudates, venous beading, or intraretinal microvascular abnormalities present but less than severe nonproliferative retinopathy.

Moderate visual loss: The loss of 15 or more letters on the ETDRS visual acuity chart, or doubling of the visual angle (e.g., 20/20 to 20/40, or 20/50 to 20/100).

nci-CSME: Non-center-involving CSME.

New vessels at the optic disc (NVD): New vessels at the optic disc; neovascularization on or within one disc diameter of the optic disc.

New vessels elsewhere in the retina (NVE): New vessels elsewhere in the retina; neovascularization elsewhere in the retina and greater than one disc diameter from the optic disc margin.

New vessels on the iris (NVI): New vessels on the iris; neovascularization of the iris.

Nonproliferative diabetic retinopathy (NPDR): The phases of diabetic retinopathy with no evidence of retinal neovascularization.

NPDR: See Nonproliferative diabetic retinopathy.

NVD: See New vessels at the optic disc.

NVE: See New vessels elsewhere in the retina.

NVI: See New vessels on the iris.

OCT: See Optical coherence tomography.

Optical coherence tomography (OCT): A diagnostic test using low energy lasers that takes a cross-section image of the retina. Used mostly to determine if there are membranes on the surface of the macula or fluid within or beneath it.

Panretinal photocoagulation: A type of laser surgery used for patients with proliferative diabetic retinopathy. The surgery is delivered in a scatter pattern throughout the peripheral fundus and is intended to lead to a regression of neovascularization.

PDR: See Proliferative diabetic retinopathy.

Proliferative diabetic retinopathy (PDR): Advanced disease characterized by NVD and/or NVE.

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Quality adjusted life year (QALY): A measure of health outcome that assigns to each year of a patient's life a weight (ranging from 0 to 1) corresponding to the health-related quality of life during that year, such that a value of 1 indicates a year of optimal health and a value of 0 indicates a year in a health state judged equivalent to death.

QALY: See Quality adjusted life year.

Ranibizumab for Edema of the mAcula in Diabetes (READ-2) study: A prospective multicenter randomized controlled trial that compared 0.5 mg ranibizumab and laser photocoagulation for the treatment of diabetic macular edema.

READ-2: See Ranibizumab for Edema of the mAcula in Diabetes study.

Retinal hard exudate: Protein and lipid accumulation within the retina.

RIDE: A study of ranibizumab injection in subjects with clinically significant macular edema with center-involvement secondary to diabetes mellitus.

RISE: A study of ranibizumab injection in subjects with clinically significant macular edema with center-involvement secondary to diabetes mellitus.

Scatter photocoagulation: See Panretinal photocoagulation.

Severe nonproliferative diabetic retinopathy (NPDR): Using the 4-2-1 rule, the presence of at least one of the following features: (1) severe intraretinal hemorrhages and microaneurysms, equaling or exceeding standard photograph 2A, present in four quadrants; (2) venous beading in two or more quadrants (standard photograph 6A); or (3) moderate intraretinal microvascular abnormalities equaling or exceeding standard photograph 8A in one or more quadrants.



Standard photograph 2A, the standard for hemorrhages/microaneurysms. Eyes with severe NPDR have this degree of severity of hemorrhages and microaneurysms in all four midperipheral quadrants.



Standard photograph 6A, less severe of two standards for venous beading. Two main branches of the superior temporal vein show beading that is definite but not severe.



Standard photograph 8A, the standard for moderate IRMA. Patients with severe NPDR have moderate IRMA of at least this severity in at least one quadrant.

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Severe visual loss: Occurrence of visual acuity worse than 5/200 at any two consecutive visits scheduled at 4-month intervals.

UKPDS: See United Kingdom Prospective Diabetes Study.

United Kingdom Prospective Diabetes Study (UKPDS): A randomized controlled clinical trial of blood glucose control in patients with newly diagnosed Type 2 diabetes. (See Appendix 5.)

VTDR: Vision-threatening diabetic retinopathy.

WESDR: See Wisconsin Epidemiologic Study of Diabetic Retinopathy

Wisconsin Epidemiologic Study of Diabetic Retinopathy: A large epidemiologic study of complications associated with diabetes and of risk factors associated with those complications.



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