

# Diabetic Retinopathy Screening Update

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**D**iabetic retinopathy is the leading cause of blindness among adults aged 20–74 years in the United States, which notably includes the working-age population. With early detection, diabetic retinopathy can be treated with modalities that have been proven to decrease the risk of severe vision loss by > 90%.

Given the proven benefits of early detection, guidelines for screening for diabetic retinopathy have been established by national professional organizations such as the American Diabetes Association (ADA) and the American Academy of Ophthalmology (AAO). Unfortunately, on average, < 50% of diabetic patients in the United States meet these recommendations.<sup>1–3</sup> In fact, 60% of patients who require vision-preserving laser surgery do not receive treatment.<sup>4</sup> The barriers to recommended eye examinations are numerous and include insufficient referrals, socioeconomic factors, and poor geographical access to care.

Recent advances in digital imaging have opened new avenues for assessing retinopathy, which may provide better access to diagnosis and management for this treatable, but often blinding, condition. This article will provide an overview of the epidemiology of diabetic retinopathy, its pathophysiology and classification, and the multicenter prospective clinical trials that have provided rigorous evidence for

its screening and treatment. The technological advances relevant to screening will be discussed, and finally, the important role of primary care providers in retinal screening for patients with diabetes will be examined.

## Epidemiology

Approximately 8% of the U.S. population has diabetes, which equates to > 23.6 million children and adults.<sup>5</sup> The prevalence of diabetes varies among ethnicities: 5.2% for European Americans, 9% for Native Americans, 11% for African Americans, and 10.4% for Mexican Americans.<sup>6</sup> The World Health Organization estimates that > 180 million people worldwide have diabetes. This number is likely to more than double by the year 2030. At least 10% will likely develop visual impairment secondary to diabetic retinopathy.<sup>7</sup>

The prevalence of diabetic retinopathy is high; 20 years after diagnosis, > 90% of patients with type 1 diabetes and > 60% of those

with type 2 diabetes will have some degree of retinopathy.<sup>8,9</sup> The major risk factors for developing diabetic retinopathy are duration of diabetes<sup>8,9</sup> and severity of hyperglycemia.<sup>10–14</sup> Other important factors include hypertension<sup>15,16</sup> and elevated serum lipid levels.<sup>17,18</sup>

## Pathophysiology and Classification

The natural history of diabetic retinopathy typically follows an orderly and predictable pattern. Long-term hyperglycemia causes vascular endothelial dysfunction resulting in loss of endothelial cells and pericytes. The retina then develops microaneurysms, intraretinal hemorrhages, and focal areas of retinal ischemia (cotton-wool spots). At this point, the retinopathy is classified as nonproliferative diabetic retinopathy (NPDR).

As the retinopathy progresses, the vessels become further damaged, resulting in retinal nonperfusion and more widespread ischemia. Clinically, the retina can have signs of vascular damage including venous beading, intraretinal microvascular abnormalities, and more severe hemorrhages (Figure 1). At this point, the retinopathy is classified as severe NPDR. Even at this stage, most patients are asymptomatic.

With further ischemic injury, compensatory chemical mediators, most notably vascular endothelial growth factor, induce the growth of fragile new blood vessels at the inner surface of the retina.<sup>19</sup> This stage, called proliferative diabetic retin-

## IN BRIEF

Diabetic retinopathy is one of the most prevalent but preventable blinding diseases in the United States. This article reviews the pathophysiology of diabetic retinopathy, the evidence for its primary and secondary prevention, and both traditional and emerging strategies for its assessment.



Figure 1. Fundus photo of the right eye demonstrating the severe nonproliferative stage of diabetic retinopathy including A) cotton-wool spot; B) venous beading; C) intraretinal microvascular abnormalities; and D) intraretinal hemorrhages.

opathy (PDR), is characterized by neovascularization of the optic disc and neovascularization elsewhere. When these fragile vessels bleed, the vitreous hemorrhage causes symptoms of “floaters” or, if severe, loss of vision. Over time, the new vessels fibrose and can contract, resulting in tractional retinal detachments, which can cause significant vision loss.

Macular edema, the leading cause of vision loss among patients with diabetes, can occur at any stage of diabetic retinopathy. Damaged retinal vessels result in increased vascular permeability, causing an accumulation of intraretinal fluid and/or lipid, which is clinically apparent with direct ophthalmoscopy. The retina appears thickened and may contain yellow hard exudates (lipid). Macular edema may cause symptoms of blurry vision, or it may cause no symptoms at all.

#### Landmark Studies

Several multicenter randomized controlled clinical trials have demonstrated that diabetic retinopathy can be prevented or that its natural

course can be altered. The landmark Diabetes Control and Complications Trial (DCCT) involved 1,441 subjects with type 1 diabetes, ages 13–39 years, at 29 medical centers in the United States and Canada. Study participants had either no disease or early diabetic retinopathy and were randomized to either intensive blood glucose control (mean A1C 7.2%) or conventional blood glucose control (mean A1C 9.1%). The study demonstrated that intensive blood glucose control reduced the risk of progression of diabetic retinopathy by 54%, reduced the development of severe NPDR or PDR by 47%, reduced the need for laser surgery by 56%, and reduced the risk of diabetic macular edema by 23%.<sup>10,11</sup>

The U.K. Prospective Diabetes Study (UKPDS) confirmed the protective effect of intensive blood glucose control in patients with type 2 diabetes and also evaluated the effect of hypertension. A total of 1,148 patients with type 2 diabetes and hypertension were enrolled and treated with either an angio-

tensin-converting enzyme inhibitor (captopril) or a  $\beta$ -blocker (atenolol). This study demonstrated that patients with tight blood pressure control (< 150/85 mmHg) compared to patients with blood pressure less tightly controlled (< 180/95 mmHg) were found to have a 37% risk reduction in microvascular changes, 34% risk reduction in the need for laser treatment, and 47% risk reduction in decreased vision.<sup>12,13,15</sup>

Several randomized trials have also demonstrated the value of surgical treatments to minimize the complications of diabetic retinopathy. In the Diabetes Retinopathy Study (DRS) of more than 1,700 patients at 15 medical centers, pan-retinal photocoagulation (PRP; laser treatment to the peripheral retina) reduced the risk of severe (defined as 5/200 or worse) vision loss from PDR from 15.9% in untreated eyes to 6.4% in treated eyes.<sup>20</sup> Once a patient reached the PDR stage (fragile new blood vessels), it was observed that argon laser treatment of the retina resulted in regression of the neovascularization.

The Early Treatment of Diabetic Retinopathy Study (ETDRS) enrolled 3,711 patients and provided valuable information regarding management of diabetic retinopathy. First, it demonstrated that PRP can reduce the risk of severe vision loss to < 2% if administered at the appropriate stage (severe NPDR or PDR). Second, focal laser treatment (treatment to the macular area with an argon laser) was found to reduce moderate visual loss (doubling of the visual angle) by 50%. Finally, it was found that aspirin did not alter rates of progression of diabetic retinopathy and did not increase the risk of vitreous hemorrhage.<sup>21–23</sup>

The Diabetic Retinopathy Vitrectomy Study (DRVS) showed that there was a benefit to early vitrectomy (surgical removal of vit-

**Table 1. Recommended Eye Examination Schedule for Patients with Diabetes<sup>27</sup>**

Type of Diabetes	First Retinal Examination	Follow-Up*
Type 1 diabetes	3–5 years after diagnosis	At least yearly
Type 2 diabetes	At time of diagnosis	At least yearly
Before pregnancy	Before conception and early in the first trimester of pregnancy	Less than severe NPDR every 3–12 months; otherwise, every 1–3 months

\*Abnormal findings may necessitate more frequent retinal examinations.

reous) in very severe PDR in patients with type 1 diabetes. Two years after surgery, 36% of the early vitrectomy group and 12% of the late vitrectomy group had visual acuity of 20/40 or better.<sup>24,25</sup>

**Current Screening Guidelines**

These landmark studies have demonstrated that the blinding complications from diabetes can be largely prevented medically, by glycemic and blood pressure control, as well as by early detection and timely treatment of diabetic retinopathy with photocoagulation/surgical techniques. Therefore, screening guidelines have been developed by national professional organizations such as the ADA<sup>26</sup> and AAO.<sup>27</sup>

Adults and children ≥ 10 years of age with type 1 diabetes should have an initial dilated examination by an ophthalmologist within 5 years of the onset of diabetes. Because people may already have type 2 diabetes before they are aware of symptoms and up to 20% of patients with type 2 diabetes have retinopathy at the time of diagnosis, they should have an initial dilated examination by an ophthalmologist at the time of their diabetes diagnosis.<sup>9</sup> Subsequent examinations should be yearly or more frequently if retinopathy is progressing. Pregnant women with preexisting diabetes should have a dilated eye examination early in the first trimester of pregnancy because pregnancy can potentiate rapid progression of retinopathy.

Close follow-up should continue throughout pregnancy and 1 year postpartum. Current recommended screening guidelines are summarized in Table 1.

The retinopathy screening paradigm is based on clinical trials that have demonstrated the benefits of screening. However, current care falls far below these recommendations. Insufficient screening may be partially related to lack of access to eye care specialists. The advent of retinal imaging and digital technology may provide an avenue for greater compliance with screening recommendations.

In 2004, the American Telemedicine Association established consensus recommendations that provided guidelines for clinical, technical, and operational performance standards for diabetic retinopathy screening. The development of retinal imaging and, more recently, digital retinal photography may help address the barriers to access for retinopathy screening. Telehealth (telecommunication to promote health) or telemedicine (telecommunication for diagnostic and therapeutic intervention) programs based on retinal imaging with or without remote interpretation may facilitate early diagnosis of diabetic retinopathy and timely treatment, hence preserving vision.<sup>28</sup>

Methods of screening for diabetic retinopathy include direct and indirect ophthalmoscopy, stereoscopic

color film fundus photography, mydriatic or nonmydriatic digital color (Figure 2), and monochromatic photography. Traditionally, ophthalmologists have screened for diabetic retinopathy by dilating the pupil and performing indirect ophthalmoscopy, in which the entire retina is examined. This method of screening is successful where access to eye care is sufficient. However, the increasing rate of patients with diabetes will soon outpace the supply of eye care providers, both in the United States and worldwide. At present, some communities have poor or even no access to ophthalmologic care. In these settings, remote interpretation of film-based or digital photographs of the retina may be employed.

The gold standard for the detection of diabetic retinopathy consists of 30-degree stereoscopic photography of seven standard fields on color film, as developed for the ETDRS—Classification of Diabetic Retinopathy.<sup>29</sup> This has a sensitivity and specificity for the detection of diabetic retinopathy that is superior to direct<sup>30</sup> and indirect<sup>31</sup> ophthalmoscopy by ophthalmologists. The efficacy of trained readers has been demonstrated in a systematic review, in which the interpretation of mydriatic (dilated) retinal photography provided the most sensitive screening and monitoring test for sight-threatening retinopathy, with sensitivities > 80%.<sup>32</sup> However, this technique is labor intensive, has a long turnaround time, and requires expensive equipment and trained retinal photographers and readers. From a patient’s perspective, it can be time-consuming, and the required pupillary dilation may be uncomfortable. Thus, seven-field stereoscopic fundus photography is an ideal gold standard but is not ideal for widespread implementation.

The development of digital retinal photography has facilitated rapid

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Figure 2. Nonmydriatic digital fundus camera (Zeiss Visucam Pro) with output shown.

acquisition and interpretation of fundus images, quantitative analysis of data for documentation and progression of retinopathy, and the rapid deployment of retinal imaging worldwide. Currently, there are no universally accepted criteria for the detection of diabetic retinopathy using digital imaging. However, several systems are being studied and validated. Retinal imaging can be performed using digital retinal photographs with (mydriatic) or without (nonmydriatic) dilating the pupil. The digital photographs may be interpreted by trained readers or forwarded to a reading center for interpretation and grading (“store and forward”).

Several studies have examined the sensitivity and specificity of digital imaging. Two-field mydriatic<sup>33</sup> and two-field nonmydriatic<sup>34</sup> digital photography performed favorably compared to ophthalmoscopy and seven-field stereophotography.

Because of their ease of use and associated patient comfort, nonmydriatic cameras have facilitated retinal imaging for patients with

diabetes in primary care settings, including family practice, internal medicine, and endocrinology offices. The cameras do not require operation by a trained retinal photographer and their use has been validated.<sup>35,36</sup> Furthermore, an AAO meta-analysis determined that there was sufficient evidence from randomized clinical trials (Level 1) that single-field digital fundus photography can serve as a screening tool for diabetic retinopathy to identify patients with retinopathy for referral for ophthalmologic evaluation and management.<sup>37</sup> Another study evaluated single-field 45-degree nonmydriatic monochromatic images and found them to be highly correlated ( $\kappa = 0.97$ ,  $P = 0.0001$ ) to the gold standard of the stereoscopic seven-field mydriatic images.<sup>38</sup>

As an alternative to a single field, some cameras can photograph three 45-degree fields. A recent report evaluated single-field versus three-field nonmydriatic images compared to the seven-field gold standard and concluded that three color 45-degree nonmydriatic images had a sensitiv-

ity and specificity of 82 and 92%, respectively, and may also be an effective tool in a screening setting to determine levels of diabetic retinopathy for specialist referral.<sup>39</sup>

Recognizing the importance of diabetic retinal imaging, several countries have implemented national screening programs such as the National Plan for Screening in the United Kingdom and the OPHDIAT program in France. The OPHDIAT telemedicine system comprises 11 screening centers equipped with nonmydriatic cameras. Fundus photographs are acquired by technicians, with remote interpretation by ophthalmologists who grade the images. In 28 months, 15,307 diabetic retinopathy screening examinations were performed, and diabetic retinopathy was detected in 3,350 patients (23.4%).<sup>40</sup> It was found that the rates of diabetic retinopathy screening improved from 50% before to more than 70% after the implementation of OPHDIAT.<sup>41</sup>

Acquisition of digitized retinal images allow for novel image analysis methods and Web-based connectivity to create models of remote, computer-assisted, or even automated diagnosis and management of diabetic retinopathy. Several systems are in development and are currently being clinically validated.<sup>42,43</sup>

Although retinal imaging programs are important in improving access to care and identifying patients who need further evaluation, they do not replace comprehensive eye exams by ophthalmologists. A full evaluation is required when a screening retinal photograph is unreadable and for follow-up of abnormalities detected by the screening system. In addition, non-diabetes-related ocular conditions such as cataract, hypertensive retinopathy, and glaucoma

are optimally evaluated during a comprehensive eye exam.

### Role of Primary Care Providers

The importance of systemic factors such as glycemic and blood pressure control in preventing and slowing the progression of diabetic retinopathy was conclusively demonstrated in the DCCT and UKPDS clinical trials. Primary care physicians play a significant role in optimizing glycemic control and managing other risk factors such as hypertension and hyperlipidemia, which can potentially affect eye health.

Appropriate referral by primary care providers at recommended intervals for diabetic retinopathy eye examinations is crucial, because timely treatment with panretinal and focal laser photocoagulation surgery has been proven in the ETDRS, DRS, and DRVS trials to decrease vision loss from diabetes. Primary care physicians can educate their patients with diabetes about the importance of retinal examinations, as diabetic retinopathy is often asymptomatic. Encouragement by primary care providers may increase the likelihood that patients will keep their ophthalmology appointments.

In addition, primary care providers can communicate with ophthalmologists to convey the reason for referrals and supply patient information such as A1C results and presence of any other comorbid conditions. (A sample communication form is provided by Sinclair et al.<sup>44</sup>) After patients get eye examinations, primary care providers can expect to receive assessments from the eye care providers and then can reinforce to patients any recommendations for ophthalmological follow-up care.

Finally, as telehealth and telemedicine programs are implemented, the role of primary care providers may become even more encompassing, as screening retinal photographs

may be obtained directly in the primary care office, and, perhaps in the future, primary care providers may even be trained to evaluate retinal photographs.<sup>45</sup>

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