EVIDENCE-BASED CLINICAL PRACTICE GUIDELINE

Eye Care of the Patient with Diabetes Mellitus

Second Edition

AMERICAN OPTOMETRIC ASSOCIATION

About the American Optometric Association

The American Optometric Association, founded in 1898, is a leading authority on quality care and an advocate for our nation's health, representing more than 44,000 doctors of optometry (O.D.), optometric professionals and optometry students. Doctors of optometry take a leading role in patient care with respect to eye and vision care, as well as general health and well-being. As primary health care providers, doctors of optometry have extensive, ongoing training to examine, diagnose, treat and manage ocular disorders, diseases and injuries, and ocular manifestations of systemic diseases. Doctors of optometry provide more than two-thirds of primary eye care in the United States.

Disclosure Statement

This Evidence-Based Clinical Practice Guideline was funded by the American Optometric Association (AOA) without financial support from any commercial sources. The Evidence-Based Optometry Guideline Development Group and other guideline participants provided full written disclosure of conflicts of interest prior to each meeting and prior to voting on the quality of evidence or strength of clinical recommendations contained within this guideline.

Disclaimer

Recommendations made in this guideline do not represent a standard of care. Instead, the recommendations are intended to assist the clinician in the decision-making process. Patient care and treatment should always be based on a clinician's independent professional judgment, given the patient's circumstances, and in compliance with state and federal laws and regulations.

The information in this guideline is current to the extent possible at the time of publication.

EYE CARE OF THE PATIENT WITH DIABETES MELLITUS

SECOND EDITION

Developed by the AOA Evidence-Based Optometry Guideline Development Group

Approved by the AOA Board of Trustees October 4, 2019

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A. WHAT IS THE EVIDENCE-BASED PROCESS?

As a result of the Medicare Improvements for Patients and Providers Act of 2008, Congress commissioned the Secretary of Health and Human Services to create a public-private program to develop and promote a common set of standards for the development of clinical practice guidelines (CPGs). These standards address the structure, process, reporting, and final products of systematic reviews of scientific research and evidence-based clinical practice guidelines.

The Institute of Medicine (IOM), now the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine (NASEM), in response to a request from the Agency for Healthcare Research and Quality (AHRQ), issued two reports in March 2011: *Clinical Practice Guidelines We Can Trust and Finding What Works in Health Care: Standards for Systematic Reviews.*

In *Clinical Practice Guidelines We Can Trust,*[1] the IOM redefined CPGs as follows:

> *"Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of the evidence and an assessment of the benefits and harms of alternative care options."*

The report states that to be trustworthy, guidelines should:

- Be based on a systematic review of existing evidence
- Be developed by a knowledgeable, multidisciplinary panel of experts and key stakeholders
- Consider important patient subgroups and preferences, as appropriate
- Be based on a transparent process that minimizes conflicts of interest and biases
- Provide a clear explanation of the logical relationships between alternative care options and health outcomes
- Provide a grading of both the quality of evidence and the strength of the clinical recommendation
- Be revised as appropriate when new evidence warrants modifications of recommendations.

Based on the IOM/NASEM reports, the American Optometric Association (AOA) Evidence-Based Optometry (EBO) Committee developed a 14-step process to meet the new evidence-based recommendations for trustworthy guidelines.

AOA's 14 Steps to Evidence-Based Clinical Practice Guideline Development	
1.	**Guideline Development Group (GDG):** The Evidence–Based Optometry (EBO) Committee selects a multidisciplinary panel of experts, including patient and public representatives, to act as the Guideline Development Group (GDG).
2.	**Transparency and COI:** The GDG manages all conflict of interest (COI), which is documented by AOA staff and reviewed during face-to-face meetings.
3.	**Clinical Questions*:** The GDG defines the literature search criteria and identifies all clinical questions through a Question Formulation Meeting.
4.	**Search for Evidence:** The AOA Staff sends the search criteria and clinical questions for a systematic review of the literature (outside researchers) and provides all obtained papers to the Guideline Development Reading Group (GDRG). Systematic reviews, when available, are included in the guideline. There is no inclusion of Systematic Review writers in the GDG or GDRG. **Inclusion Criteria (must meet all):** Scientific studies written in English that address the clinical question and that meet the patient population or age range being addressed. **Exclusion Criteria (meets any of the following):** Scientific studies that are not in English, animal studies, studies outside the patient population or age range (if relevant), studies not addressing any topic of the clinical questions searched.
5.	**Grade Evidence/Quality:** Two members from the GDRG are randomly selected to read and grade each paper. They separately grade the paper for quality of evidence based on predetermined grading criteria and state the clinical recommendation(s).
6.	**Articulate Clinical Recommendations/Strength*:** The GDRG and GDG clinical experts review all clinical recommendations and articulate each for inclusion in the guideline during an "Articulation of Recommendations" meeting(s). There are single and/or aggregate recommendations made and a strength level is assigned. Potential benefits and harms, costs, and patient preferences are identified, as well as any gaps in research, and each is documented.
7.	**Write the Draft:** The AOA staff sends the Articulation results to the writer to develop draft 1.
8.	**Draft Review and Edits*:** The GDG reads draft 1, discusses, and edits.
9.	**Rewrite/Final Drafts:** The AOA staff sends the draft results to the writer for writing/revisions for draft 2 (Peer Review Draft) and sends to medical editor for copy editing. Additional reviews are completed as necessary.
10.	**Approval and Posting for Peer Review:** The AOA staff and/or EBO Committee chair sends the Peer Review Draft to AOA Board of Trustees for approval to post for peer and public review. The draft is posted on the AOA website, along with a comment form, and the review period is announced. Comments are solicited/collected to a separate email and comment authors are not made public.
11.	**Final Document Produced:** The GDRG and GDG clinical experts review all peer comments and revise the final document. They may choose to include the peer review comment, not include the comment, and/or identify further gaps to review when preparing the next edition. All comments are documented regarding actions taken/not taken and the Final Draft is produced.
12.	**Final Draft Approval and Legal Review:** The Final Draft is reviewed by the AOA Board of Trustees and AOA Legal Counsel for approval and verification that the GDG followed the evidence-based process as outlined by the National Academies of Sciences, Engineering, and Medicine (NASEM) - Health and Medicine Division, previously the Institute of Medicine.
13.	**Post Guidelines:** The AOA staff posts the evidence-based guideline to AOA website for public use.
14.	**Schedule Reviews:** The GDG schedules a review to meet the NASEM guideline development standards and reviews all previously identified gaps in medical research and any new evidence and revises the evidence-based guideline every 2 to 5 years.

**Denotes face-to-face meeting*

B. HOW TO USE THIS GUIDELINE

The following table provides the grading system used in this guideline for rating evidence-based clinical statements. Grades are provided for both quality of the evidence and strength of clinical recommendations.

Key to Quality of Evidence and Strength of Clinical Recommendation Grading

Quality of Evidence Levels	
Grade	**Study Type**

A	• **Meta-Analysis**
	• **Systematic Review**
	• **Randomized Clinical Trial**
	• **Diagnostic Studies** (Grade A)
	  ○ Do not have a narrow population
	  ○ Do not use a poor reference standard
	  ○ No case control studies of diseases or conditions

B	• **Randomized Clinical Trial** (weaker design)
	• **Cohort Studies**
	  ○ Retrospective
	  ○ Prospective
	• **Diagnostic Studies** (Grade B - only *one* of the following)
	  ○ Narrow population
	  ○ Sample used does not reflect the population to whom the test would apply
	  ○ Uses a poor reference standard
	  ○ Comparison between the test and reference standard is not blinded
	  ○ Case control studies of diseases or conditions

C	• **Case Control Studies**
	  ○ Study of sensitivity and specificity of a diagnostic test, population-based descriptive study of diseases or conditions
	  ○ Retrospective or prospective
	• **Diagnostic Studies** (Grade C - at least two or more of the following)
	  ○ Narrow population
	  ○ Sample used does not reflect the population to whom the test would apply
	  ○ Uses a poor reference standard
	  ○ Comparison between the test and reference standard is not blinded
	• **Studies of Strong Design**
	  ○ With substantial uncertainty about conclusions or serious doubts about generalizations, bias, research design, or sample size
	• **Nonrandomized Trials**

D	• **Cross Sectional Studies** • **Case Reports/Series** • **Reviews** • **Position Papers** • **Expert Opinion** • **Reasoning from Principle**

Strength of Clinical Recommendation Levels
Strong Recommendation: The benefits of the recommendation clearly exceed the harms (or the harms clearly exceed the benefits in the case of a negative recommendation) and the quality of evidence is excellent (Grade A or B). In some clearly identified circumstances, a strong recommendation may be made on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms. *This recommendation should be followed unless clear and compelling rationale for an alternative approach is present.*
Recommendation: The benefits of the recommendation exceed the harms (or the harms exceed the benefits in the case of a negative recommendation) but the quality of evidence is not as strong (Grade B or C). In some clearly identified circumstances, a recommendation may be made on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms. *This recommendation should generally be followed, but remain alert for new information.*
Discretional: The current evidence is insufficient to assess the balance of benefits and harms of the recommendation. Evidence may be lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined. *There should be an awareness of this recommendation, but a flexibility in clinical decision-making, as well as remaining alert for new information.*

Clinical Notes and Statements

Quality of evidence grades (A, B, C, or D) are shown throughout the guideline for clinical notes and statements. For example, a clinical note or statement with a quality of evidence grade of "B" is shown as "(Evidence Grade: B)".

Evidence-Based Action Statements will be highlighted in an "Action" box, with the quality of evidence, level of confidence, and clinical recommendation grading information listed. For example:

EVIDENCE-BASED ACTION STATEMENT: Individuals with diabetes should be educated about the long-term benefits of glucose control in reducing the risk of onset and progression of diabetic retinopathy.[11,118-121]

Evidence Quality: Grade A. Randomized Clinical Trials, Cohort-prospective Study

Level of Confidence: High

Clinical Recommendation Strength: Strong Recommendation. This recommendation should be followed unless clear and compelling rationale for an alternative approach is present.

Evidence Statements: A slowing of diabetic retinopathy by intensive treatment of glycemia was observed in persons with type 2 diabetes and cardiovascular disease or cardiovascular risk factors and hyperlipidemia in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study.[120] (Evidence Grade: A)

Intensive glycemic control in individuals with type 1 diabetes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study is associated with a substantial reduction in long-term risk of ocular surgery.[118] (Evidence Grade: A)

Although intensive glucose control did not significantly reduce the incidence and progression of retinopathy in the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) Retinal Measurements Study of persons with type 2 diabetes, consistent trends towards a benefit were observed, with significant reductions in some lesions observed.[121] (Evidence Grade: A)

A follow-up study of individuals with type 2 diabetes in the United Kingdom Prospective Diabetes Study (UKPDS) who received intensive glucose therapy had a lower risk of microvascular complications than did those receiving conventional dietary therapy.[11] (Evidence Grade: B)

Intensive glycemic control (<6.5 A1C) with multiple insulin injection therapy was found to effectively delay the onset and progression of diabetic retinopathy in a clinical trial of Japanese patients with type 2 diabetes.[119] (Evidence Grade: B)

Potential Benefits: Reduced risk of onset or progression of diabetic retinopathy	**Potential Risks/Harms:** Hypoglycemia, weight gain, potential transient worsening of retinopathy

Benefit and Harm Assessment: Benefits significantly outweigh harms

Potential Costs: Time for counseling, cost of medication

Value Judgments: None

Role of Patient Preferences: Large

Intentional Vagueness: None

Gaps in Evidence: None identified

The Action Statement profile provides additional information related to the development and implementation of the clinical recommendation. The following is an explanation of the categories listed in the profile:

Evidence Quality – The quality of evidence grade (A, B, C, or D) or the aggregate quality of evidence grade (if multiple studies were available for review) and the type of research study or studies reviewed.

Level of Confidence – The consistency of the evidence and the extent to which it can be trusted specified as high, medium, or low.

Clinical Recommendation Level – The level (Strong Recommendation, Recommendation, or Discretional) assigned to the implementation of the clinical recommendation made in the Action Statement.

Evidence Statements – The clinical statements derived from research studies reviewed that support the Action Statement.

Potential Benefits – Favorable changes which would likely occur if the Action Statement was followed.

Potential Risks/Harms – Adverse effects or unfavorable outcomes that may occur if the Action Statement was followed.

Benefit and Harm Assessment – A comparison of the relationship of benefits to harms specified as "benefits significantly outweigh harms" (or vice versa) or a "balance of benefits and harms."

Potential Costs – Direct and indirect costs may include the costs of the procedure, test, or medication; time spent by the eye doctor counseling the patient; administrative time; patient/parent/caregiver time off from work, etc.

Value Judgments – Determinations made by the Guideline Development Group in the development of the Action Statement relating to guiding principles, ethical considerations, or other priorities.

Role of Patient Preference – The role the patient has in shared decision-making regarding implementation of the Action Statement specified as large, moderate, small, or none.

Intentional Vagueness – Specific aspects of the Action Statement that are left vague due to factors such as the role of clinical judgment, patient variability, concerns over setting legal precedent, etc.

Gaps in Evidence – Areas identified during searches and evaluations of the research that show gaps in available evidence.

Consensus-Based Action Statements, based on consensus by the Guideline Development Reading Group, are also highlighted in an "Action" box, but without any quality of evidence or strength of clinical recommendation grading information listed. For example:

CONSENSUS-BASED ACTION STATEMENT: The ocular examination of an individual suspected of having undiagnosed diabetes should include all aspects of a comprehensive eye and vision examination, with ancillary testing, as needed.
Evidence Quality: There is a lack of published research to support or refute the use of this recommendation.
Benefit and Harm Assessment: Implementation of this recommendation is likely to result in the increased identification of persons with diabetes-related ocular complications. The benefits of this recommendation were established by expert consensus opinion.

C. SUMMARY LISTING OF ACTION STATEMENTS

The following is a listing of the Evidence-Based and Consensus-Based recommendations for care contained in this guideline:

Individuals should be made aware of the effectiveness of diet and physical activity programs in delaying the onset or preventing type 2 diabetes.[110,112] (Evidence Grade: A, Strong Recommendation)

Individuals with diabetes should be educated about the long-term benefits of glucose control in reducing the risk of onset and progression of diabetic retinopathy.[11,118-121] (Evidence Grade: A, Strong Recommendation)

Persons with diabetes should be educated about the potential benefits of blood pressure control in reducing the risk for development or progression of diabetic retinopathy.[57,130,139-141] (Evidence Grade: B, Strong Recommendation)

Individuals with diabetes should be educated about the long-term benefits of optimizing lipid control in reducing the risk for progression of diabetic retinopathy.[54,125,146,147,149] (Evidence Grade: B, Strong Recommendation)

Patients should be counseled about the benefits of physical exercise in delaying or reducing the ocular effects of diabetes.[157,159-161] (Evidence Grade: C, Discretional)

The ocular examination of an individual suspected of having undiagnosed diabetes should include all aspects of a comprehensive eye and vision examination, with ancillary testing, as needed. (Consensus Statement)

Persons without a diagnosis of diabetes who present with signs or symptoms suggestive of diabetes during an eye examination should have appropriate follow-up. This may include a fingerstick A1C test, random plasma glucose or fasting blood glucose analysis, or referral to their primary care physician for evaluation. (Consensus Statement)

Retinal examinations for diabetic retinopathy should be performed through a dilated pupil. (Consensus Statement)

The initial ocular examination of a person with diabetes should include all aspects of a comprehensive eye and vision examination, with ancillary testing, as indicated to diagnose and thoroughly evaluate ocular complications of diabetes. (Consensus Statement)

Fundus photography or retinal imaging should be considered to identify diabetic retinopathy lesions and document retinal status.[244,245] (Evidence Grade: B, Recommendation)

Optical coherence tomography (OCT) should be considered in the assessment of patients with diabetic macular edema (DME).[247,252,256] (Evidence Grade: B, Recommendation)

If ophthalmoscopy and/or optical coherence tomography (OCT) is used, fluorescein angiography (FA) is not needed to confirm a diagnosis of proliferative diabetic retinopathy (PDR) or to assess diabetic macular edema (DME).[263,264] (Evidence Grade: B, Recommendation)

The patient's primary care physician should be informed of eye examination results following each examination, even when retinopathy is minimal or not present.[274] (Evidence Grade: B, Strong Recommendation)

A baseline comprehensive eye and vision examination should be performed on children and adults with type 1 diabetes mellitus, with follow-up examination as directed by their eye doctor.[179,180,282] (Evidence Grade: B, Strong Recommendation)

As diabetes may go undetected for many years, any individual with type 2 diabetes mellitus should have a comprehensive eye and vision examination soon after the diagnosis of the condition, with follow-up examination as directed by their eye doctor.[17] (Evidence Grade: B, Strong Recommendation)

Women with diabetes should have a comprehensive eye and vision examination prior to a planned pregnancy. Women with diabetes who become pregnant should have a comprehensive eye and vision examination during every trimester of pregnancy, with follow-up at 6 to 12 months postpartum.[283,284] (Evidence Grade: B, Strong Recommendation)

Examination of persons with nonretinal ocular complications of diabetes should be consistent with current recommendations of care for each condition. (Consensus Statement)

Individuals with diabetes should receive at least annual dilated eye examinations. More frequent examination may be needed depending on the presence of comorbidities, changes in vision, and/or the severity, progression, or treatment of diabetic retinopathy. (Consensus Statement)

Electronic Health Records (EHRs) can be used to support clinical decision-making and improve preventive care and intervention in persons with diabetes.[290-292] (Evidence Grade: B, Recommendation)

Treatment protocols for persons with nonretinal ocular and visual complications of diabetes should follow current recommendations for care and include education on the condition(s) and recommendations for follow-up visits. (Consensus Statement)

Patients with severe or very severe nonproliferative diabetic retinopathy, early proliferative diabetic retinopathy with risk of progression, or high-risk proliferative diabetic retinopathy should be referred to an ophthalmologist experienced in the management of diabetic retinal disease for possible panretinal photocoagulation (PRP)[44] or intravitreous anti-VEGF treatment.[73,76] (Evidence Grade: A, Strong Recommendation)

Anti-vascular endothelial growth factor (anti-VEGF) agents should be considered as a treatment alternative or adjunct to panretinal photocoagulation (PRP) in the management of proliferative diabetic retinopathy (PDR), with or without diabetic macular edema (DME).[73,76,78,79,308-310] (Evidence Grade: A, Strong Recommendation)

Patients with central-involved diabetic macular edema (DME) should be referred to an ophthalmologist experienced in the management of diabetic retinal disease for treatment with anti-VEGF agents and/or subsequent or deferred focal/grid macular laser therapy.[65,69,71,72,74,75,77,82,298,300,311,313-317,319-324,327,329] (Evidence Grade: A, Strong Recommendation)

Persons who experience persistent diabetic macular edema (DME) following laser and/or anti-vascular endothelial growth factor therapy for DME should be referred to an ophthalmologist experienced in the management of diabetic retinal disease for possible treatment with intraocular steroids.[62,65,302,345,346,348] (Evidence Grade: A, Strong Recommendation)

Persons with vitreous hemorrhage, traction retinal detachment, macular traction, or an epiretinal membrane should be referred to an ophthalmologist experienced in the management of diabetic retinal disease for possible vitrectomy.[66,304,305] (Evidence Grade: B, Recommendation)

Ocular telehealth programs for diabetic retinopathy can be used to increase access to evaluation, educate patients, and promote appropriate follow-up and treatment, but they are not a replacement for a comprehensive eye examination.[364,365,370,372,374] (Evidence Grade: B, Strong Recommendation)

Persons with diabetes should be educated about the ocular signs and symptoms of diabetic retinopathy and other nonretinal ocular complications of diabetes, and encouraged to comply with recommendations for follow-up eye examinations and care. (Consensus Statement)

Patients with diabetes should be encouraged to participate in lifestyle education and diabetes self-management programs.[353,376-381] (Evidence Grade: B, Recommendation)

Individuals should be advised by their health care providers of the risks of smoking and encouraged to quit smoking and/or seek smoking cessation assistance.[389-392] (Evidence Grade: A, Strong Recommendation)

Persons who experience vision loss from diabetes should be counseled on the availability and scope of vision rehabilitation care and provided, or referred for, a comprehensive examination of their visual impairment by a practitioner trained or experienced in vision rehabilitation. (Consensus Statement)

Referral for counseling is indicated for any individual experiencing difficulty dealing with vision and/or health issues associated with diabetes or diabetic retinopathy. Educational literature and a list of support agencies and other resources should be made available to these individuals. (Consensus Statement)

I. INTRODUCTION AND GUIDELINE OBJECTIVES

Diabetes mellitus is a metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.[2] The major categories of diabetes are type 1 and type 2. Type 2 diabetes is the most prevalent form of the disease and often goes undiagnosed for many years because high blood glucose levels develop gradually and initially are often not severe enough for a person to notice any of the symptoms of diabetes. During this time, individuals are at risk of developing microvascular and macrovascular complications of diabetes, including visual impairment and blindness, hypertension, renal failure, heart disease, and stroke.

Diabetic retinopathy, the most common microvascular complication of diabetes, is a leading cause of new cases of vision impairment among people 20 to 74 years of age in the United States and many developed countries.[3-6] Intensive treatment to maintain blood glucose concentrations close to the normal range has been shown to reduce the risk of development of diabetic retinopathy and decrease the risk of its progression in persons with type 1 or type 2 diabetes.[7-9] In addition, early intensive glycemic control appears to have a lasting protective effect on diabetic retinopathy progression and severity due to "metabolic memory."[10,11]

Unfortunately, an estimated 10 to 25 percent of people with diabetes don't know they have the disease.[12-14] For some, signs of diabetes found during an eye examination may be the initial indication of the presence of the disease.[15] About 20 to 40 percent of individuals with type 2 diabetes already have retinopathy at the time of first diagnosis of diabetes.[16,17]

Doctors of optometry may be the first health care practitioners to examine persons with undiagnosed diabetes mellitus or ocular manifestations of diabetes. This Evidence-Based Clinical Practice Guideline on Eye Care of the Patient with Diabetes Mellitus provides doctors of optometry with examination and management recommendations designed to preserve vision and reduce the risk of vision loss in persons with diabetes through timely diagnosis, appropriate management, and referral.

The objectives of this Guideline are to assist doctors of optometry in achieving the following:

- Identification of individuals at risk for diabetes
- Identification of individuals with undiagnosed diabetes
- Identification of individuals at risk of vision loss from diabetes
- Identification of individuals in need of lifestyle management to reduce complications of diabetes
- Preservation of vision by reducing the risk of vision loss in persons with diabetes through timely diagnosis, intervention, determination of need for future evaluation, and appropriate referral
- Improvement in the quality of care rendered to persons with diabetes
- Education of individuals and health care practitioners regarding the ocular complications of diabetes
- Dissemination of information and education of individuals on the benefits of vision rehabilitation
- Provision or referral for vision rehabilitation services for persons with vision loss from diabetes.

II. OVERVIEW OF DIABETES MELLITUS

A. DISEASE DESCRIPTION

Diabetes mellitus is a chronic disease marked by high levels of blood glucose that affects both children and adults. It is a significant, costly, and potentially preventable public health problem and the seventh leading cause of death in the United States.[13] The economic burden of diabetes (all ages) reached nearly $404 billion in 2017, consisting of $327.2 billion for diagnosed diabetes, $31.7 billion for undiagnosed diabetes, $43.4 billion for prediabetes, and nearly $1.8 billion for gestational diabetes.[18] In addition, diabetes imposes high intangible costs on society in terms of reduced quality of life, and pain and suffering for individuals with diabetes and their families.

Depending on the criteria used, an estimated 12 to 14 percent of adults in the United States have diabetes.[14,19] In 2015, about 1.5 million new cases of diabetes (6.7 per 1,000 persons) were diagnosed in Americans aged 18 years or older.[13] If the current trend continues, one in three adults in the United States may have diabetes by 2050.[20,21]

Because it can lead to blindness, diabetic retinopathy is the most significant vision-threatening complication of diabetes. While advances in the management of diabetes and diabetic retinopathy have reduced the risk of vision loss and blindness,[22] more than 1/3 of persons with diabetes do not receive an annual eye examination. The annual rate of dilated eye examinations for adults in the United States varies by state from 49.8 percent in Indiana to 76.7 percent in Massachusetts. Overall, 61.6 percent of American adults with diabetes received a dilated eye examination from 2014-2015.[23-25] Rates of eye examinations for elderly persons with diabetes also remain below recommended levels as reported in a nationally representative sample of persons with health insurance coverage.[26] In addition, a significant number of individuals with diabetes are not adequately evaluated for signs and symptoms of diabetic eye disease by their primary care physician.[27]

These findings are of particular concern as many studies, including the Diabetic Retinopathy Study (DRS),[28-37] Early Treatment Diabetic Retinopathy Study (ETDRS),[38-55] United Kingdom Prospective Diabetes Study (UKPDS),[8,56-58] Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) studies,[7,59-61] and the Diabetic Retinopathy Clinical Research Network (DRCR.net) studies[62-83] provide evidence-based care interventions that rely on early referral for eye care with prompt and appropriate intervention to lessen the risk for, and the severity of, vision loss related to diabetes. Timely diagnosis, intensive diabetes treatment, and consistent, long-term follow-up evaluations for persons with diabetes are essential for effective care, which can preserve vision and substantially lower the risk of vision loss.

B. CLASSIFICATION OF DIABETES MELLITUS

The following definitions and categories of diabetes are based on the classifications reported by the American Diabetes Association (ADA).[84]

1. Type 1 Diabetes Mellitus

Type 1 diabetes (formerly called insulin-dependent or juvenile diabetes) occurs when the body's immune system attacks and destroys insulin-producing beta-cells in the pancreas. It accounts for approximately 6 percent of individuals with diabetes in the United States.[85] The primary characteristic of type 1 diabetes is absolute dependence on exogenous insulin to prevent profound hyperglycemia and ketoacidosis.

Although more frequently diagnosed in children and young adults, type 1 diabetes can occur at any age. It may be caused by genetic, environmental, or other factors, and currently there is no known way to prevent it. Persons with type 1 diabetes may develop other autoimmune disorders such as Hashimoto's disease, Graves' disease, Addison's disease, myasthenia gravis, and pernicious anemia.

There are two forms of type 1 diabetes, both of which are characterized by destruction and/or loss of secretory function by insulin producing pancreatic beta-cells. One form is an immune-mediated disease with autoimmune markers such as islet cell antibodies (ICAs), insulin autoantibodies (IAAs), autoantibodies to glutamic acid decarboxylase (GAD65), and autoantibodies to the tyrosine phosphatases IA-2 and IA-2β, and ZnT8. About 85 to 90 percent of individuals with fasting hyperglycemia are positive for one or more of these markers. Strong human leukocyte antigen (HLA) associations also exist.

The other form of type 1 diabetes, called idiopathic diabetes, has no known causes. Idiopathic diabetes is strongly inherited, but it lacks autoimmune markers and has no HLA association. An absolute dependence on insulin replacement in affected persons may come and go. Only a minority of persons with diabetes falls into this group, and they are predominantly of African or Asian descent.

2. Type 2 Diabetes Mellitus

Type 2 diabetes (formerly termed non-insulin dependent or adult-onset diabetes) occurs when the body does not produce enough insulin (relative insulin deficiency) or cannot use the insulin it makes effectively (insulin resistance). Defects in insulin secretion are primarily related to inflammation, metabolic stress, and genetic factors. In contrast to type 1 diabetes, with this form of the condition, autoimmune destruction of beta-cells does not occur.

Type 2 diabetes is the most common form of diabetes worldwide and its prevalence is increasing. The risk of developing type 2 diabetes increases with age, obesity, and lack of physical exercise. It currently accounts for about 91 percent of diabetes cases in the United States.[85]

This form of diabetes develops more frequently in adults than in children; however, the prevalence of type 2 diabetes in children is increasing, especially in high-risk ethnic groups, such as American Indians, Hispanic Americans, African Americans, Alaska Natives, Asian Americans, Native Hawaiians and other Pacific Islanders. Most of these children are between 10 and 19 years old, have infrequent or mild diabetic ketoacidosis, are obese, and have a strong family history of diabetes.[86] Children with metabolic risk factors, such as high body mass index (BMI) and impaired glucose tolerance (IGT), are at an increased risk of developing type 2 diabetes.[87]

3. Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) refers to any degree of glucose intolerance with onset or first diagnosis during the second or third trimester of pregnancy that is not clearly overt diabetes prior to gestation. It is now recommended that high-risk women found to have diabetes during their initial prenatal visit in the first trimester receive a diagnosis of overt, not gestational, diabetes.[84]

GDM is caused by the hormones secreted during pregnancy or by a shortage of insulin. It occurs predominantly in African American, Hispanic, and American Indian women, as well as women who are obese or have a family history of type 2 diabetes.[20]

Glucose tolerance typically returns to normal within 6 weeks after pregnancy ends, but women who have had GDM have a 35 to 60 percent chance of developing type 2 diabetes in the subsequent 10 to 20 years.[88] In addition, babies born to mothers with GDM also have a higher risk of developing type 2 diabetes in their teens or early adulthood.[89]

4. Other Specific Types of Diabetes

Some forms of diabetes are associated with monogenetic defects resulting in beta-cell dysfunction and are often characterized by the onset of hyperglycemia at an early age (<25 years old). One type, called maturity-onset diabetes of the young (MODY), involves impaired insulin secretion function with minimal or no defects in insulin action. Another form, neonatal diabetes, which is diagnosed in the first six months of life, can be transient or permanent.

Diabetes can also occur secondary to other genetic defects in insulin action, pancreatic diseases, endocrinopathies, drugs or toxic chemicals that impair insulin secretion, infections causing beta-cell destruction, or uncommon forms of immune-mediated diabetes. These forms of the condition account for fewer than 5 percent of all diagnosed cases of diabetes.

5. Prediabetes

Individuals whose blood glucose levels do not meet the criteria for diabetes, but are higher than those considered normal, are classified as having prediabetes. They have an increased risk of developing type 2 diabetes, heart disease, and stroke.[88] Age, race and co-morbid hypertension, obesity, and dyslipidemia are significant risk factors associated with progression from prediabetes to diabetes.[90]

Prediabetes reflects failing islet beta-cell compensation or an underlying state of insulin resistance, often caused by excess body weight or obesity. Persons with prediabetes have impaired glucose tolerance (IGT), impaired fasting glucose (IFG), or abnormal A1C levels, as described below:[84]

- Impaired Glucose Tolerance

  A diagnosis of IGT can only be made with the Oral Glucose Tolerance Test (OGTT), which measures the body's ability to metabolize glucose. Serial testing shows that individuals with IGT may improve, remain stable, or worsen. In persons with IGT, the 2-hour plasma glucose value in the 75-g OGTT is 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L).

- Impaired Fasting Glucose

  IFG signifies the zone between the upper limit of normal fasting plasma glucose (FPG) and the lower limit of diabetic FPG. IFG includes those persons whose fasting glucose is 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L).

- A1C

  Persons at risk for diabetes may also be tested using the glycosylated hemoglobin (A1C) test. It can help identify those individuals at higher risk of developing diabetes in the future. An A1C test level between 5.7 percent and 6.4 percent is considered prediabetes.

C. BACKGROUND

1. Natural History of Diabetes Mellitus

The development of diabetes involves several pathogenic processes. These range from autoimmune destruction of beta-cells of the pancreas causing insulin deficiency to abnormalities that result in resistance to insulin action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same individual; therefore, it is often unclear which abnormality is the primary cause of the hyperglycemia.

a. Type 1 Diabetes Mellitus

The rate of beta-cell destruction in type 1 diabetes varies. Some individuals develop ketoacidosis as the first manifestation of the disease. Others have modest fasting hyperglycemia that can change rapidly to severe hyperglycemia and/or ketoacidosis because of infection or other stress.

Some people retain sufficient residual beta-cell function to prevent ketoacidosis for many years; however, they eventually become dependent on insulin for survival. In the later stage of the disease, there is little or no insulin secretion. In type 1 diabetes, persons tend to be acutely symptomatic at onset, often complaining of polydipsia, polyphagia, polyuria, unexplained weight loss, dry mouth, or blurred vision.

b. Type 2 Diabetes Mellitus

The metabolic processes leading to type 2 diabetes occur years or even decades before the development of hyperglycemia. They progress from an asymptomatic stage, with insulin resistance, to mild postprandial (after a meal) hyperglycemia, and finally to diabetes.

Initially, pancreatic beta-cells can compensate by increasing insulin levels (hyperinsulinemia), keeping glucose levels normalized for a period (up to several years), but eventually IGT develops with mild hyperglycemia. As compensatory insulin resistance worsens, more difficulty with insulin secretion occurs resulting in increased hyperglycemia. Together, these defects lead to further increases in fasting blood glucose. Over time, the beta-cells are unable to compensate for insulin resistance, resulting in type 2 diabetes.[91]

2. Diagnostic Criteria

Due to a lack of a more specific biological marker to define diabetes, plasma glucose criteria remain the basis for diagnosis. The cutoff glycemic levels used to diagnose diabetes are based on the observed association between certain glucose levels and a dramatic increase in the prevalence of microvascular complications (retinopathy and nephropathy).[92]

For decades, the diagnosis of diabetes has been based on glucose criteria, using either the FPG or the 75-g OGTT. A1C testing is also an accepted method for diagnosing diabetes. A1C indicates a person's average blood glucose level for the previous two or three months by measuring the percentage of blood glucose attached to hemoglobin. It may be a better biochemical marker for the disease than FPG or 2-hour plasma glucose testing.[93]

The current ADA diagnostic criteria for diabetes are:[84]

- **A1C ≥6.5 percent***

  The test should be performed using a method that is certified by the National Glycohemoglobin Standardization Program and standardized to the Diabetes Control and Complications Trial assay (point-of-care A1C assays are not sufficiently accurate to use for diagnostic purposes)

- **Fasting plasma glucose level ≥126 mg/dL (7.0 mmol/L)***

  Fasting is defined as no caloric intake for at least eight hours

- **Two-hour plasma glucose level ≥200 mg/dL (11.1 mmol/L) during an OGTT***

  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

- **Random plasma glucose level ≥200 mg/dL (11.1 mmol/L) in a person with classic symptoms of hyperglycemia (polyuria, polydipsia, weight loss) or hyperglycemic crisis**

  Random is defined as any time of the day without regard to time since the last meal.

  ** In the absence of unequivocal hyperglycemia, these results should be confirmed by repeat testing.*

Gestational diabetes mellitus screening can be accomplished with either of two approaches:

- **The one-step 2-hour 75-g OGTT taken at 24-28 weeks of pregnancy**

  This test is recommended by the International Association of Diabetes and Pregnancy Study Group and the ADA for diagnosis of gestational diabetes.[94]

- **A two-step process for the screening and diagnosis of GDM**

  All pregnant women should be screened by patient history, clinical risk factors, or a 50-g 1-hour glucose challenge test (non-fasting) at 24 to 28 weeks of gestation. For those who screen positive, the diagnosis of GDM can be made on the basis of a 100-g, 3-hour OGTT.

Because some cases of GDM may represent preexisting undiagnosed type 2 diabetes, the ADA recommends that women with a history of GDM should be tested for diabetes four to twelve weeks postpartum. In addition, they should have lifelong screening for the development of diabetes or prediabetes at least every three years, if a postpartum test for diabetes is normal.[84]

D. EPIDEMIOLOGY OF DIABETES MELLITUS

1. Prevalence and Incidence

Diabetes mellitus is a large and growing health care problem in the United States and around the world. The prevalence of diagnosed and undiagnosed diabetes in the United States (2015)[13] is shown in Table 1

Table 1
Prevalence of Diagnosed and Undiagnosed Diabetes
Among People Ages 18 Years or Older, United States, 2015

Group	Number or percentage who have diabetes
Ages 18 years or older	30.2 million, or 12.2 percent of all people in this age group, of which 7.2 million were not aware or did not report having diabetes
Ages 18 to 44 years	4.6 million, or 4.0 percent of all people in this age group
Ages 45 to 64 years	14.3 million, or 17.0 percent of all people in this age group
Ages 65 years or older	12.0 million, or 25.2 percent of all people in this age group
Men	15.3 million, or 12.7 percent of all men ages 18 years or older
Women	14.9 million, or 11.7 percent of all women ages 18 years or older

An estimated 415 million or 8.8 percent of adults worldwide have diabetes. This number is expected to grow to 642 million by 2040 owing to the rising frequency of obesity, increasing life span, and improved detection of the disease.[95]

In developing countries, the largest number of people with diabetes is in the age group 45 to 64 years, while in developed countries the largest is found in those aged 65 and over. Worldwide rates of diabetes are similar in men and women, although they are slightly higher in men less than 60 years of age and in women over age 65.[96]

Diabetes is also becoming an increasing concern among children and adolescents, especially those who are overweight or obese.[97] In the United States, about 208,000 people younger than 20 years of age have diagnosed diabetes.[98] The incidence and prevalence of both type 1 and type 2 diabetes is increasing in this age group, particularly among youth of minority racial and ethnic groups.[13,98,99] In children younger than 10 years of age, most have type 1 diabetes. The highest rates of type 2 diabetes in children occur among 15 to 19-year-old minority groups.[100]

a. Type 1 Diabetes Mellitus

Type 1 diabetes accounts for the majority of childhood and adolescent diabetes. The number of children (0-14 years of age) with type 1 diabetes worldwide is estimated to be 542,000, with 86,000 newly diagnosed cases occurring each year.[95] Because of the early age of onset and longer duration of diabetes, children are at risk for developing

diabetes-related complications at a younger age. Persistent poor blood glucose control in childhood is significantly related to the development of diabetic retinopathy in children with type 1 diabetes.[101]

b. Type 2 Diabetes Mellitus

Type 2 diabetes is more common in older people, especially those who are overweight. Diabetes rates vary by race and ethnicity. American Indian, Alaska Native, African American, Hispanic/Latino, Asian American, Native Hawaiians and other Pacific Islander adults are nearly twice as likely as non-Hispanic white adults to have type 2 diabetes.[20] People of Caribbean and Middle Eastern descent also have an increased risk of developing type 2 diabetes.

c. Gestational Diabetes Mellitus

The rates of GDM have been increasing significantly, with the highest rates of increase occurring among Hispanic women.[102] The prevalence of GDM in pregnant women in 2010 varied from 4.6 percent to 8.7 percent depending on the reporting source.[103,104] The ADA estimates that approximately 7 percent of all pregnancies are complicated by GDM.[2]

d. Prediabetes

An estimated 33.9 percent of adults (18 years of age or older) in the United States had prediabetes in 2015 based on their fasting glucose or A1C level. Nearly half (48.3 percent) of adults ages 65 years or older had prediabetes;[13] therefore, about 86 million Americans had prediabetes and are at high risk for developing type 2 diabetes.

E. RISK FACTORS FOR DIABETES MELLITUS

1. Type 1 Diabetes Mellitus

Specific risk factors for type 1 diabetes are unclear. Possible factors include:

- **Family history of diabetes** - Having a parent or sibling with type 1 diabetes
- **Viral exposure** - Exposure to Epstein-Barr virus, coxsackie virus, mumps virus, or cytomegalovirus may trigger the autoimmune destruction of islet cells, or the virus may directly infect the islet cells
- **Autoimmune conditions** - Hashimoto's disease, Graves' disease, Addison's disease, celiac disease, Crohn's disease, rheumatoid arthritis.

2. Type 2 Diabetes Mellitus

The risk factors for type 2 diabetes include:[13,105,106]

- **Family history of diabetes** - First-degree relatives of individuals with type 2 diabetes are three times more likely to develop the disease
- **Being overweight or obese** - Having a body mass index (BMI) ≥25 kg/m^2 (at-risk BMI may be lower in some ethnic groups)
- **Age** - Being 45 years old or older
- **Ethnic background** - Being African American, Hispanic/Latino, American Indian, Alaska Native, Asian American, or Pacific Islander
- **Gestational diabetes** - Having diabetes while pregnant
- **Prediabetes** - Persons with IGT or IFG

- **Hypertension** - Blood pressure ≥140/90 mmHg (The American College of Cardiology and the American Heart Association have defined two stages of high blood pressure: Stage 1 = 130-139 /80-89 mmHg and Stage 2 = ≥140/90 mmHg)[107]
- **Abnormal lipid levels** – High density lipoprotein (HDL) level ≤35 mg/dL and/or a triglyceride level ≥250 mg/dL
- **Physical inactivity** - Less than 10 minutes a week of activity in each of the physical activity areas of work, leisure time, and transportation.

F. SCREENING FOR DIABETES MELLITUS

Because of the acute onset of symptoms, most cases of type 1 diabetes are detected soon after the onset of hyperglycemia; therefore, widespread clinical testing of asymptomatic individuals for the presence of autoantibodies related to type 1 diabetes is not recommended as a means to identify persons at risk.[108]

There is no direct evidence supporting the effectiveness of screening for type 2 diabetes or prediabetes in individuals without risk factors;[109] however, due to the high prevalence of type 2 diabetes and the increased morbidity and mortality associated with the disease, the ADA recommends that all adults aged 45 years and older be screened.[108] In high-risk individuals (as discussed above), screening at younger ages should be considered and performed more frequently. In addition, all pregnant women not known to have diabetes should be screened for GDM.

Screening for type 2 diabetes mellitus is recommended using the FPG test following an 8-hour overnight fast, a 2-hour OGTT (75-g glucose load), or the A1C test. Individuals whose results are normal by a single test, but who have retinal findings consistent with diabetic retinopathy, should receive additional laboratory testing to exclude diabetes. Persons whose results are normal should be re-screened in three years or more frequently if there are risk factors or initial results were borderline.[108] Individuals with positive results need to be retested using the same or a different blood sample. Screening of urine glucose levels is not recommended.

G. PREVENTION OF DIABETES MELLITUS

There is no way to prevent type 1 diabetes mellitus. Preventing or delaying the development of type 2 diabetes, or intervening early in the care of persons with type 1 or type 2 diabetes, provides the potential for reduction in the development of long-term complications, which can lead to major morbidity and mortality, reduce the quality of life, and increase the total costs of diabetes care. Lifestyle modifications serve as the basis for prevention of type 2 diabetes. Combined diet and physical activity programs and the use of insulin-sensitizing medications have been shown to achieve the largest diabetes risk reductions.[110] (Evidence Grade: A)

The Diabetes Prevention Program (DPP), a randomized trial comparing an intensive lifestyle intervention (including self-management strategies for weight loss and supervised physical activity sessions) with metformin, a biguanide derivative which blocks hepatic glucose production, showed that weight loss through moderate diet changes and physical activity can delay and prevent type 2 diabetes.[111] Diabetes incidence rates after an average follow-up of 15 years were reduced by 27 percent in the lifestyle intervention group and by 18 percent in the metformin group compared with the placebo group. The long-term reduction in diabetes development with preventative lifestyle intervention can be substantial.[112] (Evidence Grade: A)

EVIDENCE-BASED ACTION STATEMENT: Individuals should be made aware of the effectiveness of diet and physical activity programs in delaying the onset or preventing type 2 diabetes.[110,112]	
Evidence Quality: Grade A. Systematic Review, Randomized Clinical Trial **Level of Confidence:** High **Clinical Recommendation Strength:** Strong Recommendation. This recommendation should be followed unless clear and compelling rationale for an alternative approach is present.	
Evidence Statements: Combined diet and physical activity programs and the use of insulin-sensitizing medications have been shown to achieve the largest diabetes risk reductions.[110] (Evidence Grade: A) The long-term reduction in diabetes development with preventative lifestyle intervention can be substantial.[112] (Evidence Grade: A)	
Potential Benefits: Decreased risk of diabetes and diabetes complications, better diabetes control	**Potential Risks/Harms:** None
Benefit and Harm Assessment: Benefits significantly outweigh harms	
Potential Costs: Time for counseling	
Value Judgments: None	
Role of Patient Preferences: Large	
Intentional Vagueness: None	
Gaps in Evidence: None identified	

H. MANAGEMENT OF DIABETES MELLITUS, SYSTEMIC COMPLICATIONS, AND CO-MORBIDITIES

The management of persons with diabetes mellitus involves the use of individualized glucose targets, lifestyle modifications, including weight management and physical exercise, and lowering blood pressure and cholesterol levels as needed. Some individuals with type 2 diabetes can achieve adequate glycemic control with weight reduction, exercise, and/or oral glucose-lowering agents and do not require insulin. Others, who have only limited residual insulin secretion, often require insulin for adequate glycemic control. Individuals with type 1 diabetes, who have extensive beta-cell destruction and therefore no residual insulin secretion, require insulin for survival.[2]

Type 1 diabetes mellitus is associated with various genetic and autoimmune diseases. Conditions, including genetic (e.g., Down, Turner, Noonan, and Klinefelter syndromes), autoimmune (thyroid and adrenal disorders, myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis), and central nervous system diseases occur in persons with type 1 diabetes.[113] (Evidence Grade: B) Common type 2 diabetes co-morbidities include hypertension, dyslipidemia, obesity, cardiovascular disorders, nonalcoholic fatty liver disease, and chronic kidney disease. Routine evaluations by the patient's primary care physician are required for early diagnosis and treatment of these diabetes-related conditions.

1. Glycemic Control

The glycemic goal for persons with diabetes should take into consideration their risk of hypoglycemia, anticipated life expectancy, duration of disease, and co-morbid conditions. An A1C level of <7.0 percent is a reasonable goal for most non-pregnant adults; however, a more stringent goal of ≤6.5 percent may be considered for some individuals, if it can be achieved safely, but glycemic targets may change over time.[106,114] For individuals with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, or extensive co-morbid conditions, a less stringent A1C goal, such as <8 percent, may be appropriate.[106] The American College of Physicians has recommended a glycemic target between 7 percent and 8 percent for most non-pregnant adults with type 2 diabetes.[115] A consensus statement for managing diabetes during pregnancy recommends that pregnant women with pre-existing type 1 or type 2 diabetes maintain an A1C goal of <6 percent throughout pregnancy, if it can be achieved without excessive hypoglycemia.[116]

Intensive treatment to achieve glucose levels as close to the nondiabetic range as safely as possible has been shown to delay the onset and slow the progression of diabetic retinopathy in several studies.[117] The EDIC Study[9], an observational follow-up study of the Diabetes Control and Complications Trial (DCCT),[7,60] found that intensive treatment with the goal of achieving blood glucose levels as close to the nondiabetic range as safely possible reduced the risk of onset and progression of diabetic retinopathy in persons with type 1 diabetes compared with conventional therapy. In addition, intensive glycemic control in individuals with type 1 diabetes in the EDIC Study was associated with a substantial reduction in long-term risk of ocular surgery.[118] (Evidence Grade: A)

Follow-up monitoring over ten years of patients in the United Kingdom Prospective Diabetes Study (UKPDS) found that individuals with type 2 diabetes who received intensive glucose therapy had a lower risk of microvascular complications than did those receiving conventional dietary therapy.[11] (Evidence Grade: B) Intensive glycemic control (<6.5 A1C) with multiple insulin injection therapy was found to effectively delay the onset and progression of diabetic retinopathy, nephropathy, and neuropathy in a clinical trial of Japanese patients with type 2 diabetes.[119] (Evidence Grade: B) A slowing of diabetic retinopathy by intensive treatment of glycemia was also observed in participants with type 2 diabetes and cardiovascular disease or cardiovascular risk factors and hyperlipidemia in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study.[120] (Evidence Grade: A)

The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) Retinal Measurements Study of persons with type 2 diabetes mellitus found that intensive glucose control did not significantly reduce the incidence and progression of retinopathy, although consistent trends towards a benefit were observed, with significant reductions in some lesions observed with both interventions.[121] (Evidence Grade: A)

After a median five-year follow-up, another clinical trial of intensive blood glucose control in patients with type 2 diabetes using gliclazide (modified release) and other drugs used to lower the glycated hemoglobin value to 6.5 percent yielded a 10 percent relative reduction in the combined outcome of major macrovascular and microvascular events, with no significant effect on retinopathy.[122] (Evidence Grade: A)

A study of intensive glucose control in United States veterans with poorly controlled type 2 diabetes found no significant effect on the rates of major cardiovascular events, death, or microvascular complication; however, factors such as levels of HDL cholesterol, weight gain, systolic blood pressure, and pharmacologic agents could have played a role in the observed lack of benefit of intensive glucose control.[123] (Evidence Grade: B)

Intensive treatment of glycemia may have potential complications for some individuals. The ACCORD Study of persons with type 2 diabetes, which compared standard therapy to the use of intensive therapy for 3.5 years, found intensive therapy increased mortality, weight gain, and risk for severe hypoglycemia, and did not significantly reduce major cardiovascular events.[124] (Evidence Grade: A) These findings identified a previously unrecognized harm of intensive glucose lowering in high-risk patients with type 2 diabetes;[125] (Evidence Grade: A) however, the DCCT showed that persons undergoing intensive diabetes treatment, with the goal of achieving glycemic control as close to

normal levels as possible, do not face deterioration in the quality of their lives, despite the increasing demands of their diabetes care and the increased frequency of hypoglycemia.[126] (Evidence Grade: A)

The beneficial effects of intensive glycemic control achieved by early intervention can persist for several years, a phenomenon described as "metabolic memory." Likewise, the stressors of diabetic vasculature (oxidative stress, advanced glycogen end products, and epigenetic changes) persist beyond the point when glycemic control has been achieved.

Daily self-monitoring of blood glucose, using fingerstick blood samples or glucose monitoring devices, is a well-accepted practice. Such monitoring, which is absolutely necessary for intensive management programs, should be encouraged for all persons with diabetes.[106] It allows a person to assess whether glycemic targets are being met.

EVIDENCE-BASED ACTION STATEMENT: Individuals with diabetes should be educated about the long-term benefits of glucose control in reducing the risk of onset and progression of diabetic retinopathy.[11,118-121]	
Evidence Quality: Grade A. Randomized Clinical Trials, Cohort-prospective Study **Level of Confidence:** High **Clinical Recommendation Strength:** Strong Recommendation. This recommendation should be followed unless clear and compelling rationale for an alternative approach is present.	
Evidence Statements: A slowing of diabetic retinopathy by intensive treatment of glycemia was observed in persons with type 2 diabetes and cardiovascular disease or cardiovascular risk factors and hyperlipidemia in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study.[120] (Evidence Grade: A) Intensive glycemic control in individuals with type 1 diabetes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study was associated with a substantial reduction in long-term risk of ocular surgery.[118] (Evidence Grade: A) Although intensive glucose control did not significantly reduce the incidence and progression of retinopathy in the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) Retinal Measurements Study of persons with type 2 diabetes, consistent trends towards a benefit were observed, with significant reductions in some lesions observed.[121] (Evidence Grade: A) A follow-up study of individuals with type 2 diabetes in the United Kingdom Prospective Diabetes Study (UKPDS) who received intensive glucose therapy had a lower risk of microvascular complications than did those receiving conventional dietary therapy.[11] (Evidence Grade: B) Intensive glycemic control (<6.5 A1C) with multiple insulin injection therapy was found to effectively delay the onset and progression of diabetic retinopathy in a clinical trial of Japanese patients with type 2 diabetes.[119] (Evidence Grade: B)	
Potential Benefits: Reduced risk of onset or progression of diabetic retinopathy	**Potential Risks/Harms:** Hypoglycemia, weight gain, potential transient worsening of retinopathy
Benefit and Harm Assessment: Benefits outweigh harms	
Potential Costs: Time for counseling, cost of medication	
Value Judgments: None	
Role of Patient Preferences: Large	
Intentional Vagueness: None	
Gaps in Evidence: None identified	

Medications for Diabetes Mellitus

Oral and injectable (non-insulin) diabetes medications are used to control glucose levels in persons with type 2 diabetes. These glucose-lowering agents may be used in combination with each other or with insulin to achieve the best blood glucose control. A variety of classes of oral and injectable medications are available to treat type 2 diabetes.

For persons with recent-onset type 2 diabetes or mild hyperglycemia (A1C <7.5 percent), lifestyle therapy plus antihyperglycemic monotherapy (e.g., metformin) is recommended.[114] Metformin, which allows the body to use insulin more effectively, is the first-line pharmaceutical therapy of choice in these patients.[56] (Evidence Grade: A)[11] (Evidence Grade: B) It may be continued as background therapy and used in combination with other agents, including insulin, in individuals who do not reach their glycemic targets on monotherapy. Other hyperglycemic medications used to lower glucose levels include sodium-glucose cotransporter-2 (SGLT-2) inhibitors, dipeptidyl peptidase 4 (DPP-4) inhibitors, thiazolidinediones (TZDs), glucagon-like peptide-1 (GLP-1) and sulfonylurea compounds.

In persons who need the greater glucose-lowering effect of an injectable medication, glucagon-like peptide-1 (GLP-1) receptor agonists are the preferred choice to insulin.[127] They can affect glucose control by increasing insulin secretion, slowing gastric emptying, and reducing postprandial glucagon from the liver. Currently available GLP-1 receptor agonists include exenatide, liraglutide, lixisenatide, and dulaglutide.[128] They may be effective for persons with type 2 diabetes who are either uncontrolled or intolerant of metformin therapy.

Insulin therapy is the mainstay of treatment for persons with type 1 diabetes and for those with type 2 diabetes if other therapies are no longer sufficient. A major advantage of insulin over other glucose lowering medications is that insulin lowers glucose in a dose-dependent manner over a wide range to almost any glycemic target.[127] The many forms of insulin are classified by how fast they start to work and how long their effects last. Rapid-acting insulins, such as lispro, aspart or glulisine, start working in 15 minutes and last about three to five hours. A rapid-acting insulin allows the patient to control postprandial hyperglycemia more effectively. Most patients require some type of multiple or split dosage regimen to maintain adequate blood glucose control.

The longacting basal insulin analogs (e.g., glargine, detemir) and the longer-acting basal analogs (e.g., U-300 glargine, degludec, human NPH insulin) mimic continuous endogenous background insulin secreted by the pancreas and have a slow release, long-acting effect to help control glucose levels throughout the day and night. All insulins may be administered as subcutaneous injection. Only short- or rapid-acting insulins are delivered by continuous subcutaneous insulin pump infusion.

The use of combination oral therapies and injectable therapies along with insulin is increasing. A combination approach enables the patient to obtain the benefit of synergistic actions of the different medications while reducing adverse effects.

2. Blood Pressure Control

Hypertension is a common co-morbidity of diabetes mellitus and a major risk factor for cardiovascular disease (CVD) and microvascular complications. Treatment for hypertension may include lifestyle modifications (e.g., weight loss, diet changes, exercise), along with pharmacological agents, when needed.[106]

There is substantial evidence that antihypertensive treatment reduces the risk of mortality and cardiovascular morbidity in individuals with and without diabetes mellitus.[129] (Evidence Grade: A) Among persons with type 2 diabetes, blood pressure lowering is associated with improved mortality and other clinical outcomes, including a lower risk of retinopathy.[130] (Evidence Grade: B) Blood pressure <140/90 mmHg is a recommended goal by the ADA for most patients with diabetes.[131] (Evidence Grade: D)

There are differing conclusions from clinical studies regarding whether lowering systolic blood pressure to <130 mmHg in persons with diabetes is beneficial. In the ACCORD Study of persons with type 2 diabetes who were at high risk for stroke or death from cardiovascular causes, lowering systolic blood pressure to <120 mmHg did not reduce the rate of cardiovascular events.[132] (Evidence Grade: A) Several systematic reviews of randomized clinical trials also concluded that lowering systolic blood pressure below 130 mmHg does not add any further benefit.[129] (Evidence Grade: A)[133] (Evidence Grade: B)[134] (Evidence Grade: C)

A more aggressive blood pressure goal (<130 mmHg) may be beneficial for those at higher risk for stroke;[135] (Evidence Grade: A) however, it may also result in an increased risk of serious adverse events including cardiovascular death.[136] (Evidence Grade: A) In one systematic review, strong support was found for lowering systolic blood pressures to <130 mmHg in individuals with a history of cardiovascular disease, coronary heart disease, stroke, diabetes, heart failure, or chronic kidney disease. It recommended that treatment shift from focusing on rigid blood pressure targets to use of risk-based targets.[137] (Evidence Grade: A)

Several studies have looked at the relationship between lowering blood pressure and the development of diabetic retinopathy:

- Tight blood pressure control (<150/85 mmHg) in patients with hypertension and type 2 diabetes was shown in the UKPDS to provide a clinically important reduction in complications related to diabetes, including progression of diabetic retinopathy and deterioration in visual acuity. After nine years of follow up, the group assigned to tight blood pressure control had a 34 percent reduction in risk in the proportion of patients with deterioration of retinopathy by two steps and a 47 percent reduced risk of deterioration in visual acuity by three lines of the ETDRS chart.[57] (Evidence Grade: A) Although early improvement in blood pressure control in patients with both type 2 diabetes and hypertension in the UKPDS was associated with a reduced risk of complications, it appears that good blood pressure control must be continued if the benefits are to be maintained.[138] (Evidence Grade: B)
- The Wisconsin Epidemiologic Study of Diabetic Retinopathy showed that elevated blood pressure is directly related to the progression of diabetic retinopathy[139] (Evidence Grade: B) and the development of diabetic macular edema (DME) in persons with type 1 diabetes mellitus.[140] (Evidence Grade: B).
- There is some evidence from a systematic review of 15 clinical trials to support lowering blood pressure to prevent diabetic retinopathy for up to four or five years in persons with type 1 or type 2 diabetes mellitus, but not to slow its progression.[141] (Evidence Grade: B)
- The ACCORD Study did not find a significant difference in the progression of diabetic retinopathy between patients receiving standard antihypertensive therapy and those receiving intensive antihypertensive therapy according to their treatment protocols.[125] (Evidence Grade: A)

Overactivity of the renin-angiotensin system (RAS), which regulates blood pressure and fluid balance in the body, is associated with the development of hypertension, cardiovascular events, and chronic kidney disease. In adults with type 1 diabetes, a renin-angiotensin blockade has been shown to reduce the progression of diabetic retinopathy in normotensive, normoalbuminuric patients.[142] (Evidence Grade: A)[143] (Evidence Grade: A) In patients with diabetes, RAS inhibitors reduce the risk of diabetic retinopathy and increase the possibility of diabetic retinopathy regression; however, angiotensin-converting enzyme inhibitors might be better than angiotensin-receptor blockers for treating diabetic retinopathy, and might exert the most beneficial effect on diabetic retinopathy of all widely used antihypertensive drug classes.[144] (Evidence Grade: A)

EVIDENCE-BASED ACTION STATEMENT: Persons with diabetes should be educated about the potential benefits of blood pressure control in reducing the risk for development or progression of diabetic retinopathy.[57,130,139-141]

Evidence Quality: Grade B. Systematic Review, Randomized Clinical Trial, Cohort-prospective Studies.

Level of Confidence: Medium

Clinical Recommendation Strength: Strong Recommendation. This recommendation should be followed unless clear and compelling rationale for an alternative approach is present.

Evidence Statements: In the United Kingdom Prospective Diabetes Study (UKPDS) of patients with hypertension and type 2 diabetes, tight blood pressure control (<150/85 mm/Hg) had a 34 percent reduction in risk in the proportion of patients with deterioration of retinopathy by two steps and a 47 percent reduced risk of deterioration in visual acuity by three lines of the Early Treatment of Diabetic Retinopathy Study chart.[57] (Evidence Grade: A)

The Wisconsin Epidemiologic Study of Diabetic Retinopathy showed that elevated blood pressure is directly related to the progression of diabetic retinopathy[139] (Evidence Grade: B) and the development of diabetic macular edema in persons with type 1 diabetes mellitus.[140] (Evidence Grade: B)

Among persons with type 2 diabetes, blood pressure lowering is associated with improved mortality and other clinical outcomes, including a reduced risk of retinopathy.[130] (Evidence Grade: B)

Evidence from a systematic review of 15 clinical trials supports lowering blood pressure to prevent diabetic retinopathy for up to four or five years in persons with type 1 or type 2 diabetes mellitus, but not to slow its progression.[141] (Evidence Grade: B)

Potential Benefits: Reduced risk for development or progression of diabetic retinopathy and DME	**Potential Risks/Harms:** Hypotension

Benefit and Harm Assessment: Benefits significantly outweigh harms

Potential Costs: Time for counseling

Value Judgments: None

Role of Patient Preferences: Large

Intentional Vagueness: None

Gaps in Evidence: None identified

3. Lipid-Lowering Treatment

Individuals with type 2 diabetes mellitus have an increased prevalence of lipid abnormalities, which contribute to a higher risk for CVD. Lowering LDL cholesterol to <100 mg/dL is a recommended goal for individuals without overt CVD; however, in individuals with overt CVD, LDL <70 mg/dL is recommended. This level may be achieved through lifestyle modifications (e.g., reduction in saturated fats and cholesterol, weight loss, increased physical activity), along with statin therapy.[106]

Statins are the first drug choice for reducing high cholesterol. The ADA recommends that statin therapy should be initiated for all persons with diabetes and atherosclerotic cardiovascular disease (ASCVD). In addition, statin therapy should be initiated for persons with diabetes without ASCVD risk factors who are ≥40 years old. Those individuals with diabetes <40 years of age who have one or more ASCVD risk factors (family history of CVD, hypertension, smoking, or albuminuria) should also be considered for statin therapy;[106] however, the use of statins may be related to an increase in A1C levels. In patients with type 2 diabetes mellitus, some statins (e.g., moderate-intensity pitavastatin) have been found to improve glycemic control, whereas others (e.g., high-intensity atorvastatin) worsened it.[145] (Evidence Grade: A)

Clinical studies on the potential impact of lipid-lowering therapy on the development of diabetic retinopathy have reported the following:

- Elevated serum lipid levels may be associated with an increased risk for the development of retinal hard exudates. Observational data from the ETDRS suggest that lipid lowering may decrease the risk of hard exudate formation and associated vision loss in patients with diabetic retinopathy.[54] (Evidence Grade: B)
- In a study of Taiwanese patients with type 2 diabetes and dyslipidemia, those taking statins had a lower rate of diabetic retinopathy and the need for treatment of vision-threatening diabetic retinopathy than those not taking statins. The benefits were reported to increase as the statin intensity and patient adherence increased.[146] (Evidence Grade: B)
- Lipid-lowering therapy with statins was reported to protect against the development of diabetic macular edema and progression of diabetic retinopathy in a records review of 110 patients with type 2 diabetes.[147] (Evidence Grade: D)
- Intensive treatment of dyslipidemia using a combination of simvastatin and fenofibrate, along with intensive glucose control, has been shown to slow the rate of progression of diabetic retinopathy in type 2 diabetes mellitus;[125] (Evidence Grade: A) however, the combination of fenofibrate and simvastatin has not been found to reduce the rate of cardiovascular events.[148] (Evidence Grade: A)

Fenofibrate may also have a role in reducing the risk of diabetic retinopathy and its progression independent of its lipid modifying action. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study reported that patients treated with fenofibrate had statistically significant reduction in the need for laser treatment for maculopathy and proliferative retinopathy.[149] (Evidence Grade: A) The ACCORD Eye Sub-study reported a statistically significant reduction in diabetic retinopathy progression in patients treated with fenofibrate and statin combination therapy compared to statin therapy alone.[150]

Clinical note: *The use of fenofibrate and statin therapy has not been widely adopted and additional study is needed to confirm the efficacy of their use in treating diabetic retinopathy.*

EVIDENCE-BASED ACTION STATEMENT: Individuals with diabetes should be educated about the long-term benefits of optimizing lipid control in reducing the risk for progression of diabetic retinopathy.[54,125,146,147,149]
Evidence Quality: Grade B. Randomized Clinical Trials, Cohort-prospective Study, Cohort-retrospective Study **Level of Confidence:** High **Clinical Recommendation Strength:** Strong Recommendation. This recommendation should be followed unless clear and compelling rationale for an alternative approach is present.
Evidence Statements: Intensive treatment of dyslipidemia using a combination of simvastatin and fenofibrate, along with intensive glucose control, has been shown to slow the rate of progression of diabetic retinopathy in type 2 diabetes mellitus.[125] (Evidence Grade: A) The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study reported that patients treated with fenofibrate had statistically significant reduction in the need for laser treatment for maculopathy and proliferative retinopathy.[149] (Evidence Grade: A) In a study of Taiwanese patients with type 2 diabetes and dyslipidemia, those taking statins had a lower rate of diabetic retinopathy and the need for treatment of vision-threatening diabetic retinopathy than those not taking statins. The benefits were reported to increase as the statin intensity and patient adherence increased.[146] (Evidence Grade: B) Observational data from the Early Treatment Diabetic Retinopathy Study (ETDRS) suggest that lipid lowering may decrease the risk of hard exudate formation and associated vision loss in patients with diabetic retinopathy.[54] (Evidence Grade: B) Lipid-lowering therapy with statins protected against the development of diabetic macular edema and progression of diabetic retinopathy in patients with type 2 diabetes.[147] (Evidence Grade: D)
Potential Benefits: Reduced risk of progression of diabetic retinopathy / **Potential Risks/Harms:** Side effects of medications
Benefit and Harm Assessment: Benefits significantly outweigh harms
Potential Costs: Time for counseling
Value Judgments: None
Role of Patient Preferences: Large
Intentional Vagueness: None
Gaps in Evidence: None identified

4. Cardiovascular Risk Reduction

A major cause of death and complications in individuals with type 2 diabetes mellitus is cardiovascular disease. Persons with type 2 diabetes have a substantially increased risk of CVD. Intensive glucose lowering has been shown to increase mortality among persons with advanced type 2 diabetes and a high risk of CVD. The ACCORD Study compared standard therapy with the use of intensive therapy to target a glycated hemoglobin level below 6 percent and reported a reduction in five-year nonfatal myocardial infarctions, but increased five-year mortality; therefore, such a strategy cannot be recommended for high-risk patients with advanced type 2 diabetes.[151] (Evidence Grade: A)

Hypertension and hyperlipidemia are also synergistic risk factors for CVD. Both show a degree of cross-correlation through sharing mechanisms of pathogenesis including insulin resistance and endothelial dysfunction.[152] Optimal control of blood pressure and LDL cholesterol can help prevent adverse cardiovascular outcomes.

Successful prevention and treatment of CVD risk factors have reduced the burden of coronary heart disease among adults with diabetes in the United States.[153] Significant progress can be achieved when multiple risk factors such as blood pressure control, lipid management, antiplatelet agents, and smoking cessation are addressed globally.[154]

5. Physical Exercise

Exercise is a vital component for the prevention and management of type 2 diabetes.[155] Regular exercise can prevent or delay the onset of type 2 diabetes in high-risk populations.[156] (Evidence Grade: D) The benefits are greatest when used early in the course of the disease.

Regular exercise has also been shown to improve blood glucose control, reduce cardiovascular risk factors, contribute to weight loss and improve well-being. In addition, increased physical activity is associated with less severe levels of diabetic retinopathy, independent of the effects of A1C or BMI.[157] (Evidence Grade: D)

Both aerobic and resistance training improve insulin action and can assist with the management of blood glucose levels, lipids, blood pressure, cardiovascular risk factors, and quality of life. In Denmark, a clinical trial tested whether an intensive lifestyle intervention (dietary planning and five to six weeks of aerobic training, along with resistance training) results in equivalent glycemic control compared with standard medical care in persons with type 2 diabetes. The results showed that among adults diagnosed for fewer than ten years, the intensive lifestyle intervention led to modest reduction in A1C that was not equivalent to standard medical care, but was in a direction consistent with a benefit. Overall, 56.3 percent of the participants in the lifestyle intervention group eliminated the use of glucose lowering medication in comparison to 14.7 percent in the standard care group from baseline to twelve month follow-up.[158] (Evidence Grade: B)

A meta-analysis of clinical trials on the association between walking and glycemic control found that walking decreases A1C among patients with type 2 diabetes. When walking is recommended for individuals with diabetes, supervision or the use of motivational strategies should be suggested to ensure optimal glycemic control.[159] (Evidence Grade: A)

Higher levels of physical activity have been associated with reduced signs of retinal microvascular disease.[160] (Evidence Grade: D) One study which looked at the association between physical activity and nonproliferative diabetic retinopathy found that women who engage in more physical activity have reduced odds of developing advanced diabetic retinopathy, while men demonstrate a non-significant association in the same direction.[161] (Evidence Grade: C)

Strenuous anaerobic exercise and exercises that involve straining, jarring, near maximal isometric contractions or valsalva-type maneuvers in patients with advanced stages of retinopathy may aggravate or increase the risk for vitreous hemorrhage. Individuals with active proliferative diabetic retinopathy, retinal fibrovascular tissue, and retinal traction should have a retinal evaluation prior to initiating activity programs that involve strenuous lifting and high-

impact components and/or activities that place the head in an inverted position, since these activities may precipitate or aggravate vitreous hemorrhage or traction retinal detachment.[162]

Most persons with type 2 diabetes can perform exercise safely as long as certain precautions are taken.[163] (Evidence Grade: D) Individuals initiating an intensive exercise program should check with their primary care physician and should be monitored for any ocular changes. Some individuals may need a cardiovascular evaluation before beginning an exercise program. The ADA recommends that all persons with diabetes should participate in at least 150 minutes per week of moderate-to-vigorous intensity aerobic exercise, spread over at least three days per week, and unless contraindicated, perform resistance training at least twice per week. Children and adolescents with type 1 or type 2 diabetes or prediabetes should engage in 60 minutes per day of moderate or vigorous intensity activity.[106]

<table>
<tr><td colspan="2">EVIDENCE-BASED ACTION STATEMENT: Patients should be counseled about the benefits of physical exercise in delaying or reducing the ocular effects of diabetes.[157,159-161]</td></tr>
<tr><td colspan="2">Evidence Quality: Grade C. Systematic Review, Cross-sectional Studies
Level of Confidence: Low
Clinical Recommendation Strength: Discretional. There should be an awareness of this recommendation, but a flexibility in clinical decision-making, as well as remaining alert for new information.</td></tr>
<tr><td colspan="2">Evidence Statements: A meta-analysis of clinical trials on the association between walking and glycemic control found that walking decreases A1C among patients with type 2 diabetes.[159] (Evidence Grade: A)

Women who engage in more physical activity have reduced odds of developing advanced diabetic retinopathy, while men demonstrate a non-significant association in the same direction.[161] (Evidence Grade: C)

Increased physical activity is associated with less severe levels of diabetic retinopathy, independent of the effects of A1C or body mass index (BMI).[157] (Evidence Grade: D)

Higher levels of physical activity have been associated with reduced signs of retinal microvascular disease.[160] (Evidence Grade: D)</td></tr>
<tr><td>Potential Benefits: Reduced risk of development or progression of diabetic retinopathy</td><td>Potential Risks/Harms: None</td></tr>
<tr><td colspan="2">Benefit and Harm Assessment: Benefits significantly outweigh harms</td></tr>
<tr><td colspan="2">Potential Costs: Time for counseling</td></tr>
<tr><td colspan="2">Value Judgments: None</td></tr>
<tr><td colspan="2">Role of Patient Preferences: Large</td></tr>
<tr><td colspan="2">Intentional Vagueness: None</td></tr>
<tr><td colspan="2">Gaps in Evidence: Further study is needed to correlate lack of physical activity with diabetic retinopathy risk factors.</td></tr>
</table>

6. Weight Management

Being overweight or obese is associated with increased risk of developing type 2 diabetes. It is important for individuals to understand this association, as well as how to prevent or remedy excess body weight through dietary modification and increased physical activity.

Adults with obesity, who are at high risk for developing diabetes, can reduce their cardiometabolic risk with primary weight management. Modest weight loss (5 percent to 9.9 percent) during a one-year period is an appropriate short-term goal for people who are severely obese.[164] Behavioral modification such as medical nutrition therapy and physical activity are essential elements of weight loss programs and are especially critical in the weight maintenance phase.[106] Individuals with diabetes should receive nutrition and dietary recommendations preferably provided by a registered dietician who is knowledgeable about diabetes management. If used early in the disease, nutritional therapy and weight loss may be sufficient for controlling type 2 diabetes in many individuals.

Metabolic (bariatric) surgery provides the potential for health benefits for moderately and severely obese persons with type 2 diabetes, including a reduction in microvascular and macrovascular events.[165] (Evidence Grade: B) Metabolic surgery is considered effective for glycemic control and reduction of CVD risk factors and may be recommended to treat type 2 diabetes in appropriate surgical candidates with BMI ≥40 kg/m^2 (BMI ≥37.5 kg/m^2 in Asian Americans) regardless of the level of glycemic control, and in adults with BMI of 35.0-39.9 kg/m^2 (32.5-37.4 kg/m^2 in Asian Americans) when hyperglycemia is inadequately controlled with nonsurgical methods.[106]

> For additional information on the systemic management of diabetes and related co-morbidities see the American Diabetes Association *Standards of Medical Care in Diabetes - 2019*
> http://care.diabetesjournals.org/content/42/Supplement_1

III. OCULAR COMPLICATIONS OF DIABETES MELLITUS

A. DIABETIC RETINAL DISEASE

Diabetic retinal disease, primarily manifesting as diabetic retinopathy and/or diabetic macular edema (DME), is the most common microvascular complication of diabetes.[166] Despite the availability of highly effective treatments, diabetic retinopathy remains a leading cause of moderate and severe visual loss among working-aged adults in the United States and other industrialized countries.

Diabetic retinopathy is often asymptomatic early in the disease and visual loss is primarily due to the development of DME, vitreous hemorrhage, or traction retinal detachment.[34] Diabetes duration and sustained hyperglycemia are among the primary risk factors for the development of diabetic retinopathy.[167]

The progression of diabetic retinopathy occurs in well-defined stages. It may progress from mild nonproliferative diabetic retinopathy (NPDR), characterized by increased vascular permeability, to moderate and severe NPDR, with vascular closure, to proliferative diabetic retinopathy (PDR), with the growth of new vessels on the retina and posterior surface of the vitreous.

The level of retinopathy does not always correlate with visual function and severe diabetic retinopathy can be present initially without significant visual loss. Identifying the severity level of diabetic retinopathy is important for determining the risk of progression and the appropriate care for preservation of vision. Each level of NPDR is associated with a corresponding risk for progression to PDR and subsequent risk of severe visual loss.

Diabetic macular edema may be present at any severity level of nonproliferative or proliferative diabetic retinopathy. DME is caused by the breakdown of the blood-retinal barrier that leads to intraretinal fluid accumulation in the macula, causing photoreceptor disruption, and, if untreated, increased risk of loss of vision.[38]

Multiple biological pathways have been implicated in the development of diabetic retinopathy. Current studies have pointed to specific biochemical pathways, molecular mechanisms, and hemodynamic alterations in early diabetes mellitus that include the sorbitol pathway,[168] advanced glycation end-products,[169] protein kinase C activation,[170] oxidative stress,[171] inflammatory markers,[172] alteration in retinal blood flow,[173] and growth factors, such as vascular endothelial growth factor (VEGF).[174] These studies demonstrate that changes in retinal biochemistry and physiology occur long before clinically evident disease is observed.

Early neuronal degeneration may also develop in the inner retina in persons with diabetes before the onset of clinical diabetic retinopathy. Changes in retinal thickness and visual function can be observed with optical coherence tomography (OCT), contrast sensitivity, and pattern electroretinogram testing. It has not been determined if these changes are caused directly by damage from chronic hyperglycemia or from the effects of vascular diabetic retinopathy.[175] (Evidence Grade: D)

1. Epidemiology of Diabetic Retinal Disease and Vision Loss

In the United States, an estimated 40.3 percent of adults ≥40 years of age with diabetes have diabetic retinopathy and 8.2 percent have vision-threatening retinopathy (proliferative or severe nonproliferative retinopathy and/or macular edema).[176] The worldwide prevalence of diabetic retinopathy in persons with diabetes is estimated to be 34.6 percent, with 10.2 percent having vision-threatening diabetic retinopathy.[167] In addition, approximately 3.8 percent of individuals in the United States ≥40 years of age with diabetes have DME.[177] Globally, 6.8 percent of persons 20 to 79 years of age are estimated to have DME.[167]

In 2010, 800,000 people worldwide were blind and 3.7 million were visually impaired due to diabetic retinopathy, an increase of 27 percent and 64 percent, respectively, from 1990 to 2010.[178] The number of Americans aged 40 years or older with diabetic retinopathy and vision-threatening diabetic retinopathy is projected to triple by 2050, from 5.5

million (in 2005) to 16 million for diabetic retinopathy, and from 1.2 million to 3.4 million for vision-threatening diabetic retinopathy.[5]

The prevalence of diabetic retinopathy and vision loss among persons with diabetes is highly associated with the duration of the disease rather than the person's age.[179,180] Diabetic retinopathy occurs more frequently in individuals with longstanding disease (over ten years); however, the actual duration of diabetes for individuals with type 2 diabetes can be difficult to determine because the initial diagnosis is typically made after a five to ten year period of asymptomatic or clinically undetected diabetes.

2. Classification and Signs of Diabetic Retinopathy

Diabetic retinopathy is broadly classified as nonproliferative diabetic retinopathy and proliferative diabetic retinopathy. In addition, diabetic macular edema can occur at any stage of retinopathy.

Characteristics of diabetic retinopathy:

- Retinal blood flow alteration is one of the early changes resulting from diabetes;[181,182] however, changes in retinal blood flow are not readily observed in routine clinical settings.
- Saccular outpouchings of retinal capillaries, termed microaneurysms, are frequently the earliest clinical sign of diabetic retinopathy. These microaneurysms result from the loss of intramural pericytes of the retinal capillaries, which weakens the capillary walls.
- Retinal hemorrhages are usually caused by ruptured or leaking microaneurysms or retinal capillaries. Hemorrhages due to diabetes typically lie deep in the retina (within the inner nuclear and outer plexiform layers), wherein the arrangement of cells is more compact and perpendicular to the surface of the retina, causing the hemorrhages to assume a pinpoint or dot shape.
- Intraretinal microvascular abnormalities (IRMA) represent either new vessel growth within the retina or, more likely, pre-existing vessels with endothelial cell proliferation that serve as "shunts" through areas of nonperfusion. The development of severe IRMA commonly indicates severe ischemia and frank neovascularization is likely to occur on the surface of the retina or optic disc within a short time.
- Venous caliber abnormalities are indicators of severe retinal hypoxia. These abnormalities can take the form of venous dilation, venous beading (VB), or loop formation. Large areas of nonperfusion can appear adjacent to these abnormalities and are indicative of a substantial risk for progression to proliferative diabetic retinopathy.
- New vessels, either at or near the optic disc (NVD) or elsewhere in the retina (NVE), signify the presence of proliferative diabetic retinopathy, with an increased risk for visual loss due to the development of vitreous hemorrhage or traction retinal detachment.

One of the important contributions that arose from the Diabetic Retinopathy Study (DRS) and Early Treatment Diabetic Retinopathy Study (ETDRS) was a standardized classification of the varying levels of diabetic retinopathy. The following classification of diabetic retinopathy and diabetic macular edema is based on the ETDRS grading scale for diabetic retinopathy and DME[45,47] (See Appendix 1: Selected Airlie House Classification of Diabetic Retinopathy Standard Photographs).

a. Nonproliferative Diabetic Retinopathy

Eyes with NPDR have not developed neovascularization. They are characterized by the presence of hemorrhages and/or microaneurysms (H/Ma), intraretinal microvascular abnormalities (IRMA), venous looping, venous beading (VB), hard exudates (HE), and/or soft exudates (cotton wool spots). Neovascularization is absent. In the absence of macular edema or ischemia, NPDR typically does not present a threat to vision; however, the presence of severe

H/Ma, VB, and IRMA confers a substantial risk for progression to PDR, with a corresponding increased risk for severe vision loss.[47]

Mild NPDR

Mild NPDR is marked by at least one retinal microaneurysm. Only H/Ma are present and the severity of H/Ma is less than that depicted in ETDRS standard photograph 2A.[32,45,47]

No other more severe retinal lesions or abnormalities associated with diabetes are present.

Moderate NPDR

Moderate NPDR is characterized by H/Ma greater than that depicted in ETDRS standard photograph 2A in one to three retinal quadrants or soft exudates, VB, and IRMAs may be present to a mild degree.[45,47]

Severe NPDR

Severe NPDR is based on the extent and severity of H/Ma, VB and IRMA, and is characterized by any one of the following lesions:

- H/Ma ≥ETDRS standard photograph 2A in **four** retinal quadrants
- Definite VB in **two** or more retinal quadrants
- Prominent IRMA (≥ETDRS standard photograph 8A) in at least **one** quadrant.[45,47]

Clinical note: *This **"4-2-1"** rule is an important clinical tool for determining the risk of progressing to PDR, as eyes with severe NPDR have a greater than 50 percent risk of developing PDR in one year.*

Very Severe NPDR

In very severe NPDR, two or more criteria for severe NPDR are met, in the absence of frank neovascularization. Eyes with very severe NPDR have an over 75 percent risk of developing PDR in one year.

b. Proliferative Diabetic Retinopathy

The most severe sight-threatening form of diabetic retinopathy is proliferative diabetic retinopathy. In PDR, neovascularization is accompanied by an influx of inflammatory cells and myofibroblasts into the retina leading to extraretinal fibrovascular proliferation that may cause vitreous hemorrhages and retinal detachment.[183] Most individuals with PDR are at substantial risk for severe vision loss.

Characteristics of PDR include new vessels on or within one disc diameter of the disc (NVD), new vessels elsewhere on the retina (i.e., not on or within one disc diameter of the optic disc) (NVE), fibrous proliferation on or within one disc diameter of the optic disc (FPD) or fibrous proliferation elsewhere (FPE) on the retina, preretinal hemorrhage (PRH), and/or vitreous hemorrhage (VH).[45,47]

PDR

PDR is characterized by NVD or NVE.

High-Risk PDR

High-risk PDR is characterized by the presence at least 3 of the 4 risk factors for severe visual loss from diabetic retinopathy:

- Presence of pre-retinal or vitreous hemorrhage
- Presence of new vessels
- Presence of new vessels on or near the disc (NVD)
- Presence of moderate or severe new vessels (NV ≥standard photograph 10A or NVE ≥1/2 disc area [DA])

c. Diabetic Macular Edema

Diabetic macular edema is a retinal complication that is assessed in addition to the level of diabetic retinopathy. DME is the collection of intraretinal fluid in the macular area of the retina, with or without lipid exudates or cystoid changes. Visual acuity is generally compromised when DME affects the fovea.

Macular edema is retinal thickening within two disc diameters (DD) of the center of the macula, which can either be focal or diffuse. Focal macular edema may be associated with circinate rings of hard exudates resulting in leakage from microaneurysms that lead to edema. Diffuse macular edema represents a more extensive breakdown of the blood-retinal barrier with leakage from both microaneurysms and retinal capillaries.[184]

The term clinically significant macular edema (CSME) was introduced in the ETDRS to signify an increased risk for moderate visual loss, defined as doubling of the visual angle (e.g., from 20/40 to 20/80).[38] To be classified as CSME, one or more of the following criteria must be present:

- Thickening of the retina ≤500 microns (1/3 DD) from the center of the macula
- Hard exudates ≤500 microns (1/3 DD) from the center of the macula with thickening of the adjacent retina
- A zone or zones of retinal thickening ≥1 disc area (DA) in size, any portion of which is ≤1 DD from the center of the macula.[41]

Diabetic macular edema can be further classified as:

- Non-central-involved – retinal thickening in the macula that does not involve the center subfield zone that is 1mm in diameter
- Central-involved – retinal thickening in the macula that does involve the central subfield zone.

Clinical note: *The use of the terms non-central and central-involved have largely replaced CSME in the grading of DME.*

An increased risk for visual loss was observed in eyes with DME that have retinal thickening involving the center of the macula (central-involved DME), which is an important factor in determining short- and long-term visual acuity outcomes. Data from the ETDRS regarding eyes with CSME have shown that by one year of follow-up, eyes with central-involved DME had nearly a ten-fold greater risk for developing moderate visual loss compared to eyes without center involvement, stressing the importance of determining central involvement in eyes with macular edema.[38,52]

To simplify the classification of diabetic retinopathy and diabetic macular edema and standardize communication between health care providers, a consensus panel developed an International Classification of Diabetic Retinopathy and Diabetic Macular Edema Severity Scale[185] (See Appendix 5). This simplified classification scale provides a practical and valid method of grading the severity of diabetic retinopathy that is appropriate in most eye care settings and provides a useful scale for clinicians to use in assessing risk for vision loss.

B. NONRETINAL OCULAR COMPLICATIONS

1. Classification and Signs of Nonretinal Ocular Complications

Diabetic eye disease is an end-organ response to a systemic medical condition. All structures of the eye and many aspects of visual function are susceptible to the deleterious effects of diabetes. These effects are summarized as follows:

a. Visual Function

Loss of visual acuity

Reductions in visual acuity can occur due to refractive shifts, cataracts, ischemic optic neuropathy, papillopathy, macular edema, ocular surface disease, or other diabetes-related ocular changes.

Refractive error changes

Persons with diabetes may experience transient changes in their refractive status. The fluctuations may be myopic or hyperopic in association with hyperglycemia or hypoglycemia.[186,187] These changes are thought to involve fluid absorption by the crystalline lens.

Refractive shifts often occur as a symptom or sign of undiagnosed diabetes. The refractive shift may be several diopters or more. Regardless of the magnitude or direction of the changes, the refractive status tends to normalize within weeks of initiation of treatment for diabetes.[188] Transient hyperopic changes may occur after glycemic control in patients with severe hyperglycemia. The degree of transient hyperopia is highly dependent on A1C levels before treatment and the rate of reduction of the blood glucose level.[189] (Evidence Grade: C)

In persons of similar age, those with type 1 diabetes are more likely to be slightly myopic than those with type 2 diabetes; however, overall mean refractive errors are similar to those reported in populations without diabetes.[190] (Evidence Grade: D)

Changes in color vision

Color vision changes may appear in persons with diabetes and can precede the development of diabetic retinopathy. Acquired color vision changes can occur in both blue-yellow and red-green discrimination and, when diabetic retinopathy is present, have been shown to correlate with the duration of diabetes.[191] The presence of macular edema is also a strong predictor of poor color discrimination in persons with diabetes, with the degree of impairment increasing with the severity of the macular edema.[192]

Accommodative dysfunction

Accommodative ability may be altered in persons with diabetes. A decrease of accommodation is usually transient and improves with control of glucose levels.[193] A reduction in accommodation has also been observed in persons who undergo panretinal (scatter) laser photocoagulation.[194,195]

Visual field changes

Visual field loss can occur in individuals with diabetes secondary to preretinal and vitreous hemorrhages, new vessel growth and fibrous proliferation on the retina, neovascular or primary open angle glaucoma, posterior vitreous detachment, papillopathy, ischemic optic neuropathy[196] or peripheral retinal ischemia.[197] In addition, persons undergoing panretinal (scatter) laser photocoagulation may experience a reduction in their visual fields.[198]

Contrast sensitivity loss

Changes in contrast sensitivity may be an early sign of retinal changes not demonstrated by visual acuity testing.

b. Ocular Motility

Ocular motility disorders may occur in individuals with diabetes secondary to diabetic neuropathy involving the third, fourth, or sixth cranial nerves.[193] Mononeuropathies may present a significant diagnostic challenge, since a substantial number that occur in persons with diabetes are not due to the diabetes itself; therefore, other potential causes need to be ruled out.

Pupillary involvement in diabetes-associated oculomotor nerve palsy occurs in about one fourth of all cases. Certain characteristics of the pupil can help to differentiate an ischemic insult from an aneurysmal injury to the third nerve. The resolution can be variable in duration depending on the amount of pupillary involvement.[199] (Evidence Grade: B) These patients can generally be treated conservatively and monitored on a regular basis.

Palsies of the third nerve are generally more common.[193] They usually are accompanied by a ptosis of the eyelid, with exotropia and hypotropia of the affected eye. Acute pain may be associated with the onset of the palsy. Pupil sparing is an important diagnostic feature in helping to distinguish diabetes-related third nerve palsy from intracranial aneurysms or tumors.

Persons with sixth nerve palsy usually present with horizontal diplopia. The affected eye is esotropic and is generally unable to be moved past the mid-line. Patients may turn their heads in the direction of their paretic field of action in order to eliminate diplopia.

Persons with fourth nerve palsy usually complain of vertical diplopia, which is typically sudden in onset and initially worsens. The vertical deviation increases with downward gaze or lateral gaze away from the affected muscle when the head is tilted toward the side of the affected muscle. Full ocular motility recovery generally occurs within two to six months;[188,193] however, recurrences are common.[200]

c. Pupillary Reflexes

Diabetes may affect sympathetic innervation of the iris. Persons with diabetes may exhibit sluggish pupillary reflexes.[188] Pupils may also be more miotic and have a weaker reaction to topical mydriatics. In addition, panretinal photocoagulation can affect pupillary response, potentially due to short and long ciliary nerve damage, resulting in a significant increase in pupil size.[201]

d. Conjunctiva

Microaneurysms in the bulbar conjunctiva are more common in persons with diabetes. In addition, individuals with diabetes are at increased risk of developing conjunctival bacterial infections.[188]

e. Tear Film

Tear film abnormalities occur frequently in persons with diabetes, leading to an increased incidence of dry eye.[188, 202] Tear break-up time may be diminished, affecting tear film stability. The presence of an abnormal tear film may contribute to discomfort and to the increased risk of ocular surface epithelial defects. An evaluation of the ocular surface is important for patients with diabetes, as they may be asymptomatic but have severe dry eye disease.[203] (Evidence Grade: D)

Meibomian gland dysfunction is an important cause of dry eye in persons with diabetes and the more severe form tends to occur more frequently in these individuals.[204] In addition, persons with diabetes may experience reduced corneal sensitivity due to neuropathy of the ophthalmic division of the trigeminal nerve, which may reduce reflex

tear secretion,[188,205] decrease subjective symptomatology, and increase risk of neurotrophic keratitis. Longstanding diabetes may also damage the microvascular supply to the lacrimal gland, impairing lacrimation.

f. Cornea

Corneal wound healing

The cornea of a person with diabetes is more susceptible to injury and slower to heal after injury than the cornea of a person without diabetes;[193] therefore, persons with diabetes are at higher risk of corneal complications, including superficial punctate keratitis, recurrent corneal erosions, persistent epithelial defects, and corneal endothelial damage. These complications have been linked to tear secretion abnormalities, decreased corneal sensitivity, and poor adhesion between epithelial cells and the basement membrane.

Reduced corneal sensitivity

Persons with diabetes often have reduced corneal sensitivity,[188,193] which may result in increased susceptibility to corneal ulceration or abrasion in individuals with dry eye syndrome or in those who wear contact lenses.

Corneal abrasions and erosions

Corneal abrasions and erosions in persons with diabetes are more likely to be recurrent and to involve detachment of the basement membrane. In addition, persons with diabetes experience delayed reepithelization of the cornea due to abnormal adhesion of the epithelium to the underlying basement membrane. They are also at increased risk for the development of infectious keratitis and it tends to be more severe than in persons without diabetes.[188]

Contact lens wear

Diabetes increases the risk of contact lens related microbial keratitis, especially in those who use extended wear contact lenses.[188] In addition, persons with diabetes may not recover as readily from contact lens induced corneal edema; however, the response of the eyes in persons with diabetes does not differ appreciably from eyes of individuals without diabetes. Studies[206,207] have concluded that daily wear contact lenses are a safe option for vision correction for persons with diabetes;[208] (Evidence Grade: C) however, individuals with diabetes need to be evaluated initially and on a continuing basis by their eye care provider.

Refractive surgery

Persons with diabetes may experience corneal changes including compromised corneal stability and denervation, which may affect safety and outcomes when undergoing refractive laser surgery. In addition, they are at increased risk for infection and poor wound healing. The United States Food and Drug Administration (FDA) advises against people who have a disease that may affect wound healing, such as diabetes, from undergoing refractive surgery; however, some people may be considered suitable candidates if a thorough preoperative assessment shows evidence of excellent glucose control for at least one year prior to surgery and finds no other systemic complications.[209,210]

g. Iris

Depigmentation

Glycogen deposits in the pigment epithelial cells of the iris can cause thickening of ocular tissue and depigmentation of the epithelial layer of the iris. Depigmentation of the iris may result in pigment deposits on the corneal endothelium.[188]

Neovascularization of the iris (Rubeosis iridis)

Neovascularization of the iris (NVI) is a serious complication marked by a growth of new blood vessels. These vessels usually are first observed at the pupillary margin, but may be present in the filtration angle without any visible vessels on the pupil border. NVI can involve the entire iris surface and angle. If NVI progresses, a fibrovascular network of vessels may grow over the iris tissue and into the filtration angle of the eye. The new vessels and accompanying fibrosis may contract and pull the underlying pigment layer of the iris through the pupillary opening, resulting in ectropion uveae.[211]

Neovascular glaucoma

Neovascular glaucoma (NVG) occurs due to a proliferation of new blood vessels on the iris which extends into the filtration angle of the anterior chamber blocking aqueous outflow.[212] Studies have shown a consistent association between diabetes and NVG.[202] NVG is a complication of PDR or ischemic retinal vascular disease that is thought to develop because of VEGF-induced neovascularization of the iris and angle. The presence of NVG in one eye is strongly correlated with its development in the other. Even with treatment, vision loss may occur.

h. Lens

Cataracts

Cataracts are a major cause of vision impairment in people with diabetes and tend to develop earlier and progress more rapidly, compared to persons without diabetes.[193,202] One study found cataracts to occur four times more frequently in persons with type 2 diabetes than in those without diabetes.[213] The risk of cataract development increases with the duration of diabetes and the severity of hyperglycemia.[200] Children and adolescents may develop cataracts, especially if they have had periods of severe, prolonged hyperglycemia.[214] Persons with DME are also at an increased risk for cataract development.[215]

Studies[216-218] have reported an increased prevalence and incidence of posterior subcapsular and cortical cataracts in persons with diabetes. Deposition of advanced glycation end-products in the lens has been postulated as one possible mechanism for diabetic cataract.

Type 2 diabetes is strongly associated with the development of nuclear sclerosis and cortical cataract. Compared with nondiabetic persons, individuals with type 2 diabetes have a substantially higher use of statins, which may be associated with the development of age-related cataracts (nuclear sclerosis and posterior subcapsular cataract). In addition, cataracts have been reported to occur earlier in persons with type 2 diabetes using statins compared with persons without diabetes who don't use statins.[219] A meta-analysis of seventeen studies on statin use, however, concluded that there is no clear evidence that it increases the risk of cataracts.[220]

Metabolic Syndrome (MetS), which includes abdominal obesity, dyslipidemia, hypertension, and hyperglycemia, has also been found to contribute to an increased incidence of cortical cataracts and posterior subcapsular cataract. Among MetS components, low HDL cholesterol has been linked to an increase in the ten-year incidence of cortical cataract and elevated glucose was positively associated with the incidence of posterior subcapsular cataract over ten years.[221]

Reversible opacities and snowflake cataracts

Although rare, reversible lenticular opacities have been reported and are frequently related to poor metabolic control of diabetes. These cataracts are usually bilateral and are characterized by dense bands of white, subcapsular spots that are snowflake in appearance.[200]

i. Vitreous

Persons with diabetes may exhibit vitreous degeneration and posterior vitreous detachment (PVD), which may play a role in PDR. New vessel growth on the surface of the retina may project into the posterior vitreous causing biochemical changes in it. The vitreous may exert traction on these vessels resulting in vitreous hemorrhage.

Proliferative diabetic retinopathy is associated with an increased incidence of PVD. Partial vitreous detachment may result in vitreous hemorrhage, an increase in retinal neovascularization, and tractional retinal detachment.[193]

j. Optic Disc

Papillopathy

Diabetic papillopathy is a distinct clinical entity that must be distinguished from papilledema or other etiologies of optic disc swelling.[222] It is characterized by unilateral or bilateral hyperemic disc swelling, which may present with or without an afferent pupillary defect or visual field defect.[223]

Diffuse microangiopathy may be associated with the etiology of diabetic papillopathy, although there appears to be no correlation between diabetic papillopathy and either the degree of diabetic retinopathy or the level of clinical control of the individual's diabetes;[222-224] however, diabetic papillopathy is a risk factor for the progression of diabetic retinopathy.[200]

Visual acuity is usually moderately reduced and the prognosis for improvement upon resolution is good. In most individuals, diabetic papillopathy resolves without treatment within a year and visual acuity improves to a level of ≥20/30.[200]

Optic disc pallor

Optic disc pallor can occur following panretinal laser photocoagulation. This disc pallor does not result in a change in the cup/disc ratio.[225]

Ischemic optic neuropathy

Diabetes represents an independent risk factor for the development of nonarteritic anterior ischemic optic neuropathy (NAION) and has been shown to increase the risk of NAION among individuals older than 67 years of age.[226]

Diabetes-related anterior ischemic optic neuropathy usually presents with optic disc pallor, swelling and hemorrhages, sudden decreased vision, an afferent pupillary defect, and an altitudinal visual field defect. The condition often results in optic atrophy and reduced visual acuity. The clinical appearance of early anterior ischemic optic neuropathy is difficult to distinguish from diabetic papillopathy,[223] although younger age is more consistent with the latter. Persons with diabetes are also susceptible to retrobulbar ischemic optic neuropathy. As many as 25 percent of persons with anterior ischemic optic neuropathy have a history of diabetes.[200]

Open angle glaucoma

Diabetes has been found to be associated with elevated intraocular pressure (IOP); however, evidence suggesting that diabetes is a risk factor for glaucoma is conflicting.[188,227] In one study, diabetes or higher long-term hyperglycemia was found to be associated with higher IOP. Central cornea thickness contributed a small proportion of mediating effect to the total effect of diabetes on IOP; however, the high IOP observed in persons with diabetes was reported to be mainly due to the direct association of diabetes and IOP. This finding may have pathophysiologic significance with respect to the risk of glaucoma among persons with diabetes.[228]

Diabetes can influence ocular vasculature in individuals with open angle glaucoma and may contribute to the disease process. Persons with diabetes who have open angle glaucoma (OAG) may have lower retrobulbar flow in the central retinal artery, as well as possible higher retinal microcirculation flow, specifically in the inferior retinal sector. These ocular diabetic vascular abnormalities could contribute to glaucomatous optic neuropathy.[229]

In addition, persons with diabetes often have concomitant hypertension that may potentially affect vascular perfusion of the optic nerve head. Formation of advanced glycation end-products within the trabecular meshwork and the lamina cribrosa of the optic nerve may further increase the risk of both ocular hypertension and damage to the optic nerve axons.[230]

IV. DIAGNOSIS OF OCULAR COMPLICATIONS OF DIABETES MELLITUS

The components of patient care described in this guideline are not intended to be all-inclusive. Professional judgment and individual patient symptoms and findings may have a substantial impact on the nature, extent, and course of the services provided and/or recommended.

A. INDIVIDUALS WITH UNDIAGNOSED OR SUSPECTED DIABETES MELLITUS

A comprehensive eye and vision examination* may be the basis for the initial diagnosis of an individual who is unaware of having diabetes mellitus. The examination provides the means to evaluate the structure, function and health of the eyes and visual system in persons with undiagnosed diabetes. During the examination, information is obtained to explain symptoms reported by the patient and diagnose the cause of signs noted by the eye doctor. It also provides the means to identify the presence of other ocular or systemic conditions that may exist without symptoms. The examination is a dynamic and interactive process. It involves collecting subjective data directly from the patient and obtaining objective data by observation, examination, and testing.

*Refer to the *Evidence-Based Optometric Clinical Practice Guideline for a Comprehensive Adult Eye and Vision Examination*

1. Patient History

The patient history is used to investigate any ocular and systemic complaints and symptoms that may be related to diabetes:

- Common ocular symptoms of undiagnosed diabetes may include the recent onset of visual changes. Individuals may report blurred or fluctuating vision, improved near vision if they have a myopic shift and are presbyopic, or new-onset diplopia. Symptoms of ocular surface disease and staphylococcal eyelid disease may also be more common, as a result of hyperglycemia.
- Systemic symptoms may include polyuria, polydipsia, polyphagia, unexplained weight changes, dry mouth, pruritus, leg cramps or pains, erectile dysfunction in men and reduced sexual response in women, delayed healing of bruises or wounds, and recurrent infections of the skin, genitalia, or urinary tract.

2. Diabetes Risk Assessment

Noninvasive risk assessment tools, such as the ADA Diabetes Risk Test (www.diabetes.org/are-you-at-risk/diabetes-risk-test/), are available to help identify people at risk for the development of type 2 diabetes. Other examples of validated risk assessment tools include the Diabetes Risk Calculator[231] (https://www.aafp.org/afp/2009/0715/p175.html) and the Weill-Cornell Medical College Patient Self-Assessment Score for Diabetes[232] (http://annals.org/aim/fullarticle/745369/new-diabetes-screening-score).

These tools provide a risk rating based on answers to a number of questions regarding variables such as age, gender, race, weight, body mass index, blood pressure, physical activity, and family history of diabetes. Diabetes risk scores can be used to identify individuals with undiagnosed type 2 diabetes who might benefit from more comprehensive assessment, such as determination of blood glucose levels.[233]

Clinical note: *Diabetes risk assessment tools are not diagnostic and further testing is needed for a definitive diagnosis.*

3. Ocular Examination

CONSENSUS-BASED ACTION STATEMENT: The ocular examination of an individual suspected of having undiagnosed diabetes should include all aspects of a comprehensive eye and vision examination, with ancillary testing, as needed.
Evidence Quality: There is a lack of published research to support or refute the use of this recommendation.
Benefit and Harm Assessment: Implementation of this recommendation is likely to result in the increased identification of persons with diabetes-related ocular complications. The benefits of this recommendation were established by expert consensus opinion.

If, on the basis of the results of the eye examination or risk assessment tools, diabetes is suspected, a fingerstick (FS) capillary glucose measurement using a glucose meter may be performed, an A1C test may be ordered, or a random plasma glucose or fasting plasma glucose analysis may be obtained.

- Persons with any glucose measurement ≥200 mg/dL and symptoms of hyperglycemia should receive an urgent referral to their primary care physician.
- Persons who are asymptomatic with random plasma glucose or FS ≥200 mg/dL should be referred to their primary care physician as soon as possible. Those with random plasma glucose or FS of 141-199 mg/dL should also see their primary care physician for further evaluation.
- Normal fasting plasma glucose measurements are ≥70 - <100 mg/dL. Persons with FPG measurements ≥100 mg/dL should be referred to their primary care physician for further evaluation.
- A1C values between 4.0 percent and 5.6 percent usually indicate adequate blood glucose levels. Persons with values between 5.7 percent and 6.4 percent (prediabetes) and those with readings ≥6.5 percent should be referred to their primary care physician for further evaluation or treatment.
- All pregnant women should be screened for glucose intolerance. Because a pregnant patient is usually under medical care, her prenatal care provider should coordinate this evaluation.

CONSENSUS-BASED ACTION STATEMENT: Persons without a diagnosis of diabetes who present with signs or symptoms suggestive of diabetes during an eye examination should have appropriate follow-up. This may include a fingerstick A1C test, random plasma glucose or fasting blood glucose analysis, or referral to their primary care physician for evaluation.
Evidence Quality: There is a lack of published research to support or refute the use of this recommendation.
Benefit and Harm Assessment: Implementation of this recommendation can help to identify persons with previously undiagnosed diabetes. The benefits of this recommendation were established by expert consensus opinion.

B. INDIVIDUALS WITH DIAGNOSED DIABETES MELLITUS

A comprehensive eye and vision examination serves as the basis for the diagnosis and evaluation of diabetes-related ocular complications. The methods used for testing may vary and change as new information and technology is developed and made available in the clinical setting. The examination should include, but is not limited to:

1. Patient History

The patient history is a key component of the examination. It includes a review of both the ocular and systemic status of the patient:

- **Quality of vision and other ocular complaints** - including symptoms such as blurred, distorted, or fluctuating vision, diplopia, night vision problems, ocular pain/discomfort, and flashes or floaters.
- **Ocular history** - including previous ocular trauma, disease, or surgery that might contribute to ocular complications associated with diabetes.
- **Medical history** - including obesity, pregnancy, and gestational diabetes. Additional information useful for patient assessment includes a review of other medical problems, all prescribed medications, use of nutritional supplements, and history of allergy to medications. (See Appendix 4: Effect of Systemic Medications on the Onset and Progression of Diabetic Retinopathy)
- **Duration of diabetes** - the risks for ocular complications are closely related to the duration of diabetes.[179,180] Age at the time of onset of diabetes is not as significant as the duration of the disease in the prediction of complications.[234-236]
- **Recent values for the ABCs of diabetes** - A1C, blood pressure and cholesterol levels. In addition, individuals should be questioned about their use of tobacco. Smoking may be considered the final letter(s) in the ABCs of diabetes. Awareness of these values may provide information on the patient's understanding and management of their diabetic condition.

Clinical note: *An individual's A1C level, at initial examination, has been shown to be a strong predictor of the incidence and progression of any retinopathy or progression to proliferative retinopathy.*[237,238]

- **The patient's prescribed management of diabetes, including:**
  1. Medical nutrition therapy
  2. Exercise and physical activity
  3. Oral or injectable medications
  4. Insulin type, dosage, and timing of administration
  5. Method, frequency, and results of self-monitoring of blood glucose
  6. Names of and contact information for the patient's other health care providers should be noted in their record to facilitate communication and coordination of care, when appropriate.

  This information provides insight into the patient's adherence to therapeutic regimens and control of diabetes, which may affect the development of ocular complications.[59,60,237]

2. Measurement of Visual Acuity

3. Preliminary Examination

- General observation of the patient, evaluation of pupillary responses, eye movements and alignment, stereopsis, and color vision, as appropriate

4. Determination of Refractive Status

5. Assessment of Ocular Motility, Binocular Status, and Accommodation, as appropriate

6. Ocular and Systemic Health Assessment

- Evaluation of the anterior and posterior segments
- Measurement of intraocular pressure
- Visual field testing
- Blood pressure measurement

Clinical note: *The presence of retinopathy, regardless of the person's diabetes status, may also indicate other underlying subclinical vascular disease.*[239] *The clinician should consider other etiologies, especially cardiovascular disease, hypertension, and smoking status.*[240]

CONSENSUS-BASED ACTION STATEMENT: Retinal examinations for diabetic retinopathy should be performed through a dilated pupil.
Evidence Quality: There is a lack of published research to support or refute the use of this recommendation.
Benefit and Harm Assessment: Implementation of this recommendation is likely to provide more thorough examination for diabetes-related retinal disease. The benefits of this recommendation were established by expert consensus opinion.

Proper documentation of retinal status, including retinal imaging and/or the use of drawings is valuable for determining any progression or stability of the retinopathy at future examinations. Use of the standard protocol for color coding retinal drawings is recommended. A protocol for color coding retinal drawings can be accessed at: *http://www.eophtha.com/Must%20Know/drawing.html*

CONSENSUS-BASED ACTION STATEMENT: The initial ocular examination of a person with diabetes should include all aspects of a comprehensive eye and vision examination, with ancillary testing, as indicated to diagnose and thoroughly evaluate ocular complications of diabetes.
Evidence Quality: There is a lack of published research to support or refute the use of this recommendation.
Benefit and Harm Assessment: Implementation of this recommendation is likely to result in more effective diagnosis of diabetes-related ocular complications. The benefits of this recommendation were established by expert consensus opinion.

7. Ancillary Testing

Additional procedures in diagnosing and evaluating diabetic retinopathy may be indicated. Such procedures include, but are not limited to:

a. Fundus Photography or Retinal Imaging

Stereoscopic photography is useful for identifying lesions of diabetic retinopathy and for documenting diabetic retinopathy severity. Mydriatic ETDRS 7-field stereo 35 mm fundus photography has been considered the standard for evaluating the presence and severity of diabetic retinopathy and DME; however, the results of digital and film evaluations of diabetic retinopathy have been shown to be comparable for ETDRS severity levels and DCCT/EDIC

Study design outcomes.[241-243] Similarly, the use of standardized retinal video recording evaluated using a defined protocol has been found to be comparable to standard retinal photography in imaging and evaluating for diabetic retinopathy.[244] (Evidence Grade: B)

Nonmydriatic ultrawide field imaging using a scanning laser ophthalmoscope, which extends the field of view allowing visualization of the peripheral retina (see Figure 1), also has been shown to compare favorably to standard ETDRS 7-field photographs and dilated retinal examination in determining the clinical severity of diabetic retinopathy and DME.[245] (Evidence Grade: B) Nonmydriatic image capture with a scanning laser ophthalmoscope provides the additional benefits of easier operation, no pupil dilation, and more rapid image acquisition.

(Source: Beetham Eye Institute, Joslin Diabetes Center, Boston, MA)

Figure 1: *Ultrawide field image of an eye with high risk proliferative diabetic retinopathy marked by preretinal hemorrhage, new vessels elsewhere, and fibrous proliferation elsewhere. There are also extensive hemorrhages, microaneurysms, and intraretinal microvascular abnormalities. There is central-involved diabetic macular edema.*

EVIDENCE-BASED ACTION STATEMENT: Fundus photography or retinal imaging should be considered to identify diabetic retinopathy lesions and document retinal status.[244,245]
Evidence Quality: Grade B. Diagnostic Studies **Level of Confidence:** Medium **Clinical Recommendation Strength:** Recommendation. This recommendation should generally be followed, but remain alert for new information.
Evidence Statements: Mydriatic Early Treatment Diabetic Retinopathy Study (ETDRS) 7-field stereo 35 mm fundus photography has been considered the standard for evaluating the presence and severity of diabetic retinopathy and diabetic macular edema (DME); however, standardized digital and video recording has been found to be comparable to standard retinal photography in imaging and evaluating for diabetic retinopathy.[244] (Evidence Grade: B) Nonmydriatic ultrawide field imaging using a scanning laser ophthalmoscope has been shown to compare favorably to ETDRS 7-field photographs and dilated retinal examination in determining the clinical severity of diabetic retinopathy and diabetic macular edema.[245] (Evidence Grade: B)
Potential Benefits: Enhanced ability to identify and document diabetic retinopathy / **Potential Risks/Harms:** None
Benefit and Harm Assessment: Benefits significantly outweigh harms
Potential Costs: Direct cost of testing
Value Judgments: None
Role of Patient Preferences: None
Intentional Vagueness: None
Gaps in Evidence: None identified

b. Optical Coherence Tomography

Optical coherence tomography (OCT) uses low-coherence interferometry to noninvasively provide high resolution images of cross sections of the retina and choroid. OCT is particularly useful in quantifying the degree of retinal thickening and for identifying retinal thickening that may not have been evident on clinical examination.[246] Also, OCT is used in clinical practice to evaluate macular edema, vitreoretinal interface abnormalities,[247-250] and optic nervehead abnormalities. Data suggest macular OCT imaging is not indicated when retinal thickening is absent on clinical examination in persons with no retinopathy or mild to moderate diabetic retinopathy.[251]

Central retinal thickness measured with OCT is widely recognized as the reference standard for the assessment of DME; however, central retinal thickness measured with OCT is not sensitive enough or specific enough to detect the central type of CSME defined using fundus examination or photography according to the conventional ETDRS definition.[252] (Evidence Grade: A) Central macular thickness only shows moderate correlation with visual acuity in eyes with DME.[251,253] This finding indicates that functional and structural determinants of visual function other than retinal thickness are present in quantifying visual loss from DME.

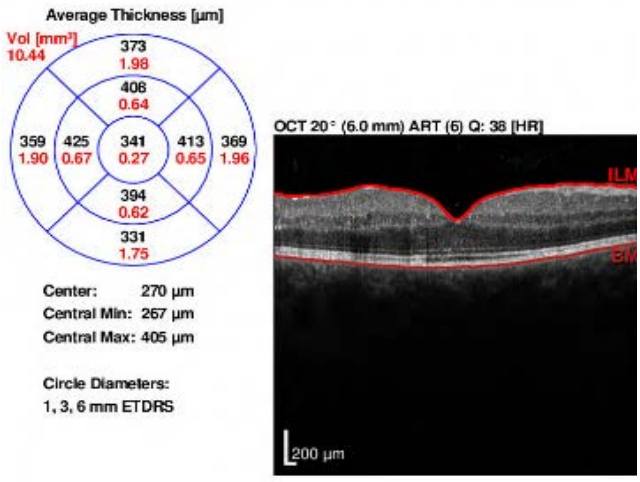
The two common measures of central retinal thickness are the center point thickness (foveal center point thickness) and central subfield thickness (foveal thickness). In two DRCR.net studies, the correlation between these two measures was 0.98, and 0.99[254,255] suggesting that the conclusions derived from analyses based on center point and central subfield are equivalent. The central subfield measures an area with a circular diameter of 1 mm central around the center point with 128 thickness measurements. Central subfield mean thickness has become the preferred OCT measurement for the central macula because of its higher reproducibility and high correlation with other measurements of the central macula.[247] (see Figure 2)

The use of OCT enables accurate assessment of intraretinal abnormalities commonly observed in DME. In patients with DME, spectral-domain OCT provides easier observation of normal and abnormal retinal and vitreoretinal findings than does time-domain OCT and images for assessing thickened structures are more adequately defined.[256] (Evidence Grade: C)

Central subfield mean thickness is the preferred OCT measurement for the central macula because of its higher reproducibility and correlation with other measurements of the central macula. Total macular volume may be preferred when the central macula is less important. Absolute change in retinal thickness is the preferred analysis method in eyes with mild macular thickening, but relative change in thickening may be preferable when retinal thickening is more severe.[247] (Evidence Grade: B)

OCT biomarkers, such as the presence of intraretinal cystoid fluid and subretinal fluid, can be used clinically to inform retreatment decisions in DME. A fully automated artificial intelligence method using applied deep learning model software has been designed and validated to detect and perform classification of intraretinal and subretinal fluid from OCT images. Automated analysis of OCT data represents a promising prospect for clinical practice.[257] (Evidence Grade: B)

Optical coherence tomography angiography (OCTA) provides a noninvasive, dye-free approach to visualize blood vessels in the retina down to the capillary level. It is a functional extension of OCT, which provides a three-dimensional retinal image. Since it does not require intravenous dye injection, it can be used more frequently than traditional fluorescein angiography.[258]



(Source: Beetham Eye Institute, Joslin Diabetes Center, Boston, MA)

Figure 2: *Optical coherence tomography showing central involved diabetic macular edema*

Clinical note: *Use of OCT is an important tool in assessing DME, especially for monitoring the efficacy of treatment;[259] however, substantial discrepancies often occur between OCT results and the clinical examination of DME, because OCT can detect early, subclinical retinal thickening in persons with CSME and more advanced retinopathy.[252] (Evidence Grade: A)*

EVIDENCE-BASED ACTION STATEMENT: Optical coherence tomography (OCT) should be considered in the assessment of patients with diabetic macular edema (DME).[247,252,256]
Evidence Quality: Grade B. Systematic Review, Cohort-retrospective Studies **Level of Confidence:** Medium **Clinical Recommendation Strength:** Recommendation. This recommendation should generally be followed, but remain alert for new information.
Evidence Statements: Central retinal thickness measured with OCT is the reference standard for the assessment of DME.[252] (Evidence Grade: A) Central subfield mean thickness is the preferred OCT measurement for the central macula because of its higher reproducibility and correlation with other measurements of the central macula. Total macular volume may be preferred when the central macula is less important. Absolute change in retinal thickness is the preferred analysis method in eyes with mild macular thickening, but relative change in thickening may be preferable when retinal thickening is more severe.[247] (Evidence Grade: B) The use of OCT enables accurate assessment of intraretinal abnormalities commonly observed in DME. Spectral-domain OCT provides easier observation of normal and abnormal retinal and vitreoretinal findings than does time-domain OCT and images for assessing thickened structures are more adequately defined.[256] (Evidence Grade: C)
Potential Benefits: Enhanced ability to diagnose and manage diabetic macular edema — **Potential Risks/Harms:** None
Benefit and Harm Assessment: Benefits significantly outweigh harms
Potential Costs: Direct cost of testing
Value Judgments: None
Role of Patient Preferences: None
Intentional Vagueness: None
Gaps in Evidence: None identified

c. Fluorescein Angiography

Fluorescein angiography (FA) may be used to identify vascular leakage and treatable lesions in eyes with diabetic retinopathy. Fluorescein leakage (particularly diffuse), capillary loss and dilation, and various arteriolar abnormalities are associated with retinopathy severity and with the likelihood of progression to proliferative retinopathy.[48] (Evidence Grade: A)

Traditional FA examines 30 to 50 degrees of the retina at once. The use of wide-field (>30 degrees to <200 degrees) and ultra-wide-field (≥200 degrees) FA enables visualization of the peripheral retina in a single frame providing enhanced assessment of peripheral capillary nonperfusion, vascular leakage, microvascular anomalies, and neovascularization.[260,261] Microvascular abnormalities such as capillary telangiectasia, microaneurysms, and vascular leakage are more frequently observed in the peripheral retina with loop patterns than with branching patterns. This finding shows that the retinal peripheral vascular morphology may be used as an indicator of retinal peripheral oxygenation status.[262] (Evidence Grade: C) Fluorescein angiography can also be used for determining the presence of foveal ischemia in cases where vision is reduced beyond that expected based on ophthalmoscopic appearance of the macula.

Clinical note: *Fluorescein angiography (FA) may be used for identifying treatable lesions in retinal ischemia and guiding treatment for DME.*

Fluorescein angiography is not indicated to confirm a suspected clinical diagnosis of PDR, as ophthalmoscopy has been proven to be comparable to FA.[263] (Evidence Grade: B) In addition, the use of FA for assessing DME is not recommended, since it offers little additional information beyond that provided by OCT imaging.[264] (Evidence Grade: B)

Clinical note: *The use of fluorescein angiography (FA) in pregnant women may pose a potential threat to the fetus. Insufficient studies have been performed to assess FA's safety in pregnant women and its use should be confined to where it is clearly indicated.*[265]

EVIDENCE-BASED ACTION STATEMENT: If ophthalmoscopy and/or optical coherence tomography (OCT) is used, fluorescein angiography (FA) is not needed to confirm a diagnosis of proliferative diabetic retinopathy (PDR) or to assess diabetic macular edema (DME).[263,264]	
Evidence Quality: Grade B. Randomized Clinical Trial, Cohort-prospective Study **Level of Confidence:** Medium **Clinical Recommendation Strength:** Recommendation. This recommendation should generally be followed, but remain alert for new information.	
Evidence Statements: Fluorescein angiography is not indicated to confirm a suspected clinical diagnosis of PDR, as ophthalmoscopy has been proven to be comparable to FA.[263] (Evidence Grade: B) The use of FA for assessing DME is not recommended, since it offers little additional information beyond that provided by OCT imaging.[264] (Evidence Grade: B)	
Potential Benefits: Avoidance of unnecessary testing and reduced risk of injection complications	**Potential Risks/Harms:** None
Benefit and Harm Assessment: Benefits significantly outweigh harms	
Potential Costs: Direct cost of testing	
Value Judgments: None	
Role of Patient Preferences: None	
Intentional Vagueness: None	
Gaps in Evidence: None identified	

d. Fundus Autofluorescence

Fundus autofluorescence (FAF) is a noninvasive "in vivo" imaging method for metabolic mapping of fluorophores of the fundus. FAF is increasingly used to detect and objectively quantify disease severity in patients with nonexudative age-related macular degeneration[266] and has the potential for use in detecting and monitoring changes in the retina.[267] Evidence suggests that FAF may provide information beyond that obtained by fundus photography, fluorescein angiography, and OCT in eyes with DME.[268]

e. Ocular Ultrasound

Ocular ultrasound (ultrasonography) can be helpful in detecting retinal detachment and traction when viewing of the retina is obscured by cataract, vitreous hemorrhage, or other media opacity.

f. Contrast Sensitivity Testing

Contrast sensitivity testing can be used as an early indicator of visual changes not shown by visual acuity measurements.[269] Deficits in contrast sensitivity may occur before the onset of clinically detectable retinopathy.[270]

g. Blood Pressure Measurement

As hypertension is more prevalent in persons with diabetes and is a potential risk factor for the development of diabetic retinopathy,[141] blood pressure may be measured at the time of the eye examination, particularly in individuals who may not be under regular medical care. Blood pressure <140/90 mmHg has been recommended for most patients with diabetes.

h. Color Vision Testing

Changes in color perception may occur in persons with diabetes. Color vision testing may be appropriate, but it should not be used for the diagnosis of diabetic retinopathy.[271]

i. Amsler Grid

The Amsler Grid can be used to detect the presence of metamorphopsia in persons with DME.[272,273]

At the conclusion of testing, the clinician should discuss with the patient the results of the examination and their implications for current and future care. In addition, the individual's primary care physician should be provided with the results along with information on proposed management or treatment of any eye or vision problems diagnosed. Written communication between the eye care provider and a patient's primary care physician has been found to be associated with improved adherence to recommendations for follow-up diabetic eye examinations.[274] (Evidence Grade: B)

EVIDENCE-BASED ACTION STATEMENT: The patient's primary care physician should be informed of eye examination results following each examination, even when retinopathy is minimal or not present.[274]	
Evidence Quality: Grade B. Cohort-retrospective Study **Level of Confidence:** High **Clinical Recommendation Strength:** Strong Recommendation. This recommendation should be followed unless clear and compelling rationale for an alternative approach is present.	
Evidence Statements: Written communication between the eye care provider and a patient's primary care physician has been found to be associated with improved adherence to recommendations for follow-up diabetic eye examinations.[274] (Evidence Grade: B)	
Potential Benefits: Coordination of care	**Potential Risks/Harms:** None
Benefit and Harm Assessment: Benefits significantly outweigh harms	
Potential Costs: None	
Value Judgments: None	
Role of Patient Preferences: None	
Intentional Vagueness: None	
Gaps in Evidence: None identified	

C. OCULAR EXAMINATION SCHEDULE

In the United States, many people with diabetes mellitus do not receive annual eye examinations, including those with diabetic retinopathy who would benefit from treatment.[25,275,276] The likelihood of receiving an annual comprehensive eye examination varies with patient age, income level, education level, health insurance status, time constraints, symptoms, insulin dependence, and participation in diabetic education classes.[276,277] Barriers to receiving eye care for persons with diabetes include perceived lack of need, cost, cultural and language capabilities, lack of access to an eye doctor or transportation, and social support.[275,278,279]

Many youths with diabetes are not receiving evaluations for diabetic retinopathy as frequently as recommended. A study assessing the rate of obtaining eye examinations and factors associated with receipt of eye examinations for youths with diabetes reported that only 64.9 percent of those with type 1 diabetes and 42.2 percent of those with type 2 diabetes had undergone an eye examination by six years after initial diabetes diagnosis. In addition, 54.7 percent of white and 57.3 percent of Asian youths had undergone an eye examination, compared with 44.6 percent of African American and 41.6 percent of Latino youths.[280] (Evidence Grade: B)

Another study of children 15 to 20 years of age in a pediatric clinic found that only 35 percent were referred for an eye examination despite having diabetes mellitus.[281] (Evidence Grade: B) Physicians who care for children may need additional education about the need for referring for eye examinations to prevent vision loss.

1. Persons with Diabetes Mellitus

Everyone with diabetes is potentially at risk for the development of eye and vision problems, either retinal or nonretinal; therefore, the initial and follow-up eye examination for persons with diabetes mellitus should follow the guidelines for care recommended for at-risk children and adults.*

Evidence-Based Clinical Practice Guideline on Adult Eye and Vision Examination, and *Evidence-Based Clinical Practice Guideline on Pediatric Eye and Vision Examination*.

Type 1 Diabetes Mellitus

Current recommendations by several national medical associations for initial testing for diabetic retinopathy in adolescents with type 1 diabetes mellitus indicate examinations should begin at puberty or three to five years after the diagnosis of type 1 diabetes; however, in a study of newly diagnosed youth in a large managed care network, waiting three to five years after the initial diagnosis of type 1 diabetes to examine for diabetic retinopathy would have delayed the diagnosis of ocular disease in 18 percent of patients by three years and 25 percent by five years. In addition, youths with type 1 diabetes appear to develop diabetic retinopathy faster than those with type 2 diabetes and need to receive regular examinations to ensure timely diagnosis and treatment.[282] (Evidence Grade: B)

The Wisconsin Epidemiological Study of Diabetic Retinopathy is a population-based study of the incidence and progression of diabetic retinopathy in persons with diabetes mellitus diagnosed before age 30 and those diagnosed after age 30. The study reported a worsening of retinopathy occurring after four years in 59 percent of those diagnosed before age 30 who were taking insulin and had no retinopathy at their first examination. In addition, 11 percent of those without proliferative diabetic retinopathy developed it. Overall, worsening of retinopathy occurred in 41 percent of the study population.[179] (Evidence Grade: B) For persons >30 years of age at diagnosis who were insulin users, 47 percent of those who did not have any retinopathy at the first visit developed it in the four-year interval, and an additional 7 percent of the persons without proliferative retinopathy developed it. Worsening of retinopathy occurred in a total of 34 percent of the patients.[180] (Evidence Grade: B)

These data underscore the need for initial comprehensive eye and vision examination and follow-up of individuals with type 1 diabetes mellitus; therefore, it is important not to delay the initial eye examination in order to prevent or reduce the impact of the development of vision-threatening conditions.

EVIDENCE-BASED ACTION STATEMENT: A baseline comprehensive eye and vision examination should be performed on children and adults with type 1 diabetes mellitus, with follow-up examination as directed by their eye doctor.[179,180,282]

Evidence Quality: Grade B. Systematic Review, Cohort-prospective Studies

Level of Confidence: Medium

Clinical Recommendation Strength: Strong Recommendation. This recommendation should be followed unless clear and compelling rationale for an alternative approach is present.

Evidence Statements: Waiting three to five years after the initial diagnosis of type 1 diabetes to examine for diabetic retinopathy would have delayed the diagnosis of ocular disease in 18 percent of patients by three years and 25 percent by five years. In addition, youths with type 1 diabetes appear to develop diabetic retinopathy faster than those with type 2 diabetes and need to receive regular examinations to ensure timely diagnosis and treatment.[282] (Evidence Grade: B)

The Wisconsin Epidemiological Study of Diabetic Retinopathy reported a worsening of retinopathy occurring after four years in 59 percent of those diagnosed before age 30 who were taking insulin and had no retinopathy at their first examination. In addition, 11 percent of those without proliferative diabetic retinopathy developed it. Overall, worsening of retinopathy occurred in 41 percent of the study population.[179] (Evidence Grade: B)

For persons >30 years of age at diagnosis who were insulin users, 47 percent of those who did not have any retinopathy at the first visit developed it in the four-year interval, and an additional 7 percent of the persons without proliferative retinopathy developed it. Worsening of retinopathy occurred in a total of 34 percent of the patients.[180] (Evidence Grade: B)

Potential Benefits: Earlier identification of persons with diabetes-related ocular complications	**Potential Risks/Harms:** None

Benefit and Harm Assessment: Benefits significantly outweigh harms

Potential Costs: Cost of testing

Value Judgments: None

Role of Patient Preferences: Large

Intentional Vagueness: None

Gaps in Evidence: None identified

Type 2 Diabetes Mellitus

The clinical signs of diabetic retinopathy can appear early in the natural history of the disease. Unfortunately, individuals may not experience symptoms until relatively late, at which time treatment may be less effective. The success of appropriate intervention and management strategies depends upon accurate and timely detection of diabetic eye disease.

Diabetic retinopathy is common in patients with newly diagnosed type 2 diabetes. The United Kingdom Prospective Diabetes Study (UKPDS) found a high prevalence of diabetic retinopathy in patients with newly diagnosed type 2 diabetes mellitus. Retinopathy, defined as microaneurysms or worse lesions in at least one eye, was present in 39 percent of men and 35 percent of women. Marked retinopathy with cotton wool spots or intraretinal microvascular abnormalities was present in 8 percent of men and 4 percent of women;[17] (Evidence Grade: B) therefore, individuals diagnosed with type 2 diabetes should receive a comprehensive eye and vision examination soon after diagnosis.

EVIDENCE-BASED ACTION STATEMENT: As diabetes may go undetected for many years, any individual with type 2 diabetes mellitus should have a comprehensive eye and vision examination soon after the diagnosis of the condition, with follow-up examination as directed by their eye doctor.[17]	
Evidence Quality: Grade B. Randomized Clinical Trial **Level of Confidence:** High **Clinical Recommendation Strength:** Strong Recommendation. This recommendation should be followed unless clear and compelling rationale for an alternative approach is present.	
Evidence Statements: The United Kingdom Prospective Diabetes Study (UKPDS) found a high prevalence of diabetic retinopathy in patients with newly diagnosed type 2 diabetes mellitus. Retinopathy, defined as microaneurysms or worse lesions in at least one eye, was present in 39 percent of men and 35 percent of women. Marked retinopathy with cotton wool spots or intraretinal microvascular abnormalities was present in 8 percent of men and 4 percent of women.[17] (Evidence Grade: B)	
Potential Benefits: Earlier identification of persons with diabetes-related ocular complications	**Potential Risks/Harms:** None
Benefit and Harm Assessment: Benefits significantly outweigh harms	
Potential Costs: Cost of testing	
Value Judgments: None	
Role of Patient Preferences: Large	
Intentional Vagueness: None	
Gaps in Evidence: None identified	

Diabetes During Pregnancy

Pregnancy in women with pre-existing diabetes may aggravate retinopathy and threaten vision.[265, 283] In women with type 1 diabetes, pregnancy induces a transient increase in the risk of retinopathy. As a result, increased frequency of eye examinations is needed during pregnancy and the first year postpartum; however, the long-term risk of progression of early retinopathy does not appear to be increased.[283] (Evidence Grade: A) Women with moderate or more severe diabetic retinopathy at conception are at a greater risk for progression during pregnancy. In women with less than adequate control of their diabetes (i.e., glycosylated hemoglobin levels >6 standard deviations above the control mean), rates of progression of retinopathy may double, especially if retinopathy was present at conception. Patients with no retinopathy or only microaneurysms at conception have a low risk for progression.[284] (Evidence Grade: B)

Prior to becoming pregnant, women with type 1 or type 2 diabetes should be counseled regarding the effect of pregnancy on their retinopathy. Following pregnancy, an increased risk of diabetic retinopathy progression persists for six to twelve months and women should continue to be monitored during this time.[265]

Due to the relatively short and temporary duration of GDM, it does not lead to the development of diabetic retinopathy; therefore, retinal evaluation for diabetic retinopathy in these individuals is not indicated.

EVIDENCE-BASED ACTION STATEMENT: Women with diabetes should have a comprehensive eye and vision examination prior to a planned pregnancy. Women with diabetes who become pregnant should have a comprehensive eye and vision examination during every trimester of pregnancy, with follow-up at 6 to 12 months postpartum.[283,284]	
Evidence Quality: Grade: B. Randomized Clinical Trial, Cohort-prospective Study **Level of Confidence:** Medium **Clinical Recommendation Strength:** Strong Recommendation. This recommendation should be followed unless clear and compelling rationale for an alternative approach is present.	
Evidence Statements: A transient increase in the risk of retinopathy occurs in pregnant women with type 1 diabetes mellitus. As a result, increased frequency of eye examinations is needed during pregnancy and the first year postpartum.[283] (Evidence Grade: A) Women with moderate or more severe diabetic retinopathy at conception are at a greater risk for progression during pregnancy. In women with less than adequate control of their diabetes, rates of progression of retinopathy may double, especially if retinopathy was present at conception.[284] (Evidence Grade: B)	
Potential Benefits: Earlier identification of persons with diabetes-related ocular complications	**Potential Risks/Harms:** None
Benefit and Harm Assessment: Benefits significantly outweigh harms	
Potential Costs: Cost of testing	
Value Judgments: None	
Role of Patient Preferences: Large	
Intentional Vagueness: None	
Gaps in Evidence: None identified	

2. Persons with Nonretinal Ocular Complications of Diabetes Mellitus

Individuals with nonretinal ocular complications of diabetes should receive periodic eye and vision examinations to detect and treat any eye disease in its early stages to prevent or minimize vision loss. The recommended frequency of a comprehensive eye and vision examination varies with an individual's ocular and medical history and other related risk factors.

CONSENSUS-BASED ACTION STATEMENT: Examination of persons with nonretinal ocular complications of diabetes should be consistent with current recommendations of care for each condition.
Evidence Quality: Published research to support or refute the use of this recommendation has not been provided in this guideline, but strong evidence for periodic examination for most conditions does exist.
Benefit and Harm Assessment: Implementation of this recommendation is likely to improve the eye health and quality of life for patients with diabetes. The benefits of this recommendation were established by expert consensus opinion.

3. Persons with Retinal Complications of Diabetes Mellitus

Regular, ongoing examinations are needed to monitor for the development of any retinal complications for individuals with either type 1 or type 2 diabetes. Persons with diabetes, who are at higher risk for the development of eye and vision problems, should have an eye examination more frequently than persons with no history of ocular or general health problems.

The recommended frequency of ocular examination is determined on the basis of several factors, including, but not limited to:

- Type of diabetes
- Duration of the disease
- Age of the patient
- Level of patient adherence to and understanding of their treatment plan
- Concurrent medical status
- Both nonretinal and retinal ocular findings and symptoms
- Subjective changes in vision.

Studies on the frequency of ocular examination for people with diabetes have produced varying recommendations. The Diabetes Control and Complications Trial evaluated an individualized examination schedule for diabetic retinopathy and macular edema for patients with type 1 diabetes. When intensive glycemic control is maintained, the probability of progression to PDR or CSME was found to be limited; therefore, the study recommended persons with no retinopathy could be reevaluated every four years, mild NPDR every three years, moderate NPDR every six months, and severe NPDR every three months.[285] (Evidence Grade: B) In another study, three-year retinal examination intervals were suggested for persons with mild type 2 diabetes and no retinopathy.[286] (Evidence Grade: C)

A systematic review of the published literature looked at the relationship between follow-up examination intervals for diabetic retinopathy and the incidence of visual loss. The aggregated evidence from both natural history and cost-effectiveness models favors a reexamination interval greater than one year, but no longer than two years. Such an interval was found to be appropriate, safe, and cost-effective for people with no diabetic retinopathy at diagnosis. In high-risk patients with no diabetic retinopathy at diagnosis, but with poor glycemic or blood pressure control, more frequent examination may be warranted. A reexamination interval of one year or less would be preferable for people with any diabetic retinopathy on a previous examination.[287] (Evidence Grade: B)

Identifying individuals most at risk for diabetic retinopathy progression and intervening early can limit vision loss and reduce costs associated with managing more advanced disease.[288]

No Diabetic Retinopathy/Mild NPDR

An annual dilated eye examination is generally recommended for monitoring the patient with no retinopathy or mild NPDR, as long as there is neither DME nor coincident medical risk factors such as hypertension, renal disease, or pregnancy that may predispose patients to progression.

If DME or medical risk factors are present, reexamination should occur every 4 to 6 months. When CSME is present, follow-up every 1 to 3 months is recommended.

Moderate NPDR

For patients with moderate NPDR, reexamination in 6 to 9 months is appropriate in the absence of DME or complicating medical risk factors.

If DME is present, but does not meet criteria for CSME, follow up every 4 to 6 months. When CSME is present, follow-up every 1 to 3 months is advisable.

Severe or Very Severe NPDR

Follow-up every 3 to 4 months in consultation with an ophthalmologist experienced in the management of diabetic retinal disease is advisable for patients with severe or very severe NPDR. When macular edema, including CSME, is present, follow-up every 1 to 3 months may be considered. Laser treatment or injection of anti-VEGF agents may be strongly considered.

PDR

Consultation with an ophthalmologist experienced in the management of diabetic retinal disease is indicated if PDR or DME is suspected or if there is an unexplained loss of visual acuity. Follow-up every 3 to 4 months is recommended for non-high-risk PDR without DME. Laser treatment or injection of anti-VEGF agents may be strongly considered.

High-Risk PDR

With or without DME, patients with high-risk PDR should receive laser treatment and/or injection of anti-VEGF agents with follow-up every 2 to 3 months, or as determined by the treating ophthalmologist.

A summary of follow-up visits for management of patients with retinal complications of diabetes can be found in Table 2A and 2B. Follow-up can be more frequent for proper management of the retinopathy, if required. Patient education and written communication with the patient's primary care physician are integral to management of diabetic retinopathy.

Table 2A
Frequency and Composition of Evaluation and Management Visits for Retinal Complications of Diabetes Mellitus

Severity of Condition	Natural Course Rate of Progression to		Frequency of follow-up	Components of Follow-up Evaluations		
	PDR (1 year)	High-risk category (5 years)		Fundus Photography	Fluorescein Angiography	OCT
No diabetic retinopathy			12 months	No	No	No
Mild NPDR	5%	15%				
No macular edema			12 months	No	No	No
Macular edema (not CSME)			4-6 months	Yes	Based on clinical judgment	Based on clinical judgment
CSME or central-involved DME			1-4 months*	Yes	Based on clinical judgment	Yes
Moderate NPDR	12-27%	33%				
No macular edema			6-9 months	Yes	No	No
Macular edema (not CSME)			4-6 months	Yes	Based on clinical judgment	Based on clinical judgment
CSME or central-involved DME			1-4 months*	Yes	Based on clinical judgment	Yes
Severe or Very Severe NPDR	52-75%	60-75%				
No macular edema			3-4 months	Yes	Based on clinical judgment	No
Macular edema (not CSME)			2-3 months	Yes	Based on clinical judgment	Based on clinical judgment
CSME or central-involved DME			1-4 months*	Yes	Based on clinical judgment	Yes
Non-high-risk PDR		75%				
No macular edema			3-4 months	Yes	Based on clinical judgment	No
Macular edema (not CSME)			2-3 months	Yes	Based on clinical judgment	Based on clinical judgment
CSME or central-involved DME			1-4 months*	Yes	Based on clinical judgment	Yes

Table Continued on next page

Table 2A *(Continued)*
Frequency and Composition of Evaluation and Management Visits for Retinal Complications of Diabetes Mellitus

Severity of Condition	Natural Course Rate of Progression to		Frequency of follow-up	Components of Follow-up Evaluations		
	PDR (1 year)	High-risk category (5 years)		Fundus Photography	Fluorescein Angiography	OCT
High-risk PDR						
No macular edema			2-3 months	Yes	Based on clinical judgment	No
Macular edema (not CSME)			2-3 months	Yes	Based on clinical judgment	Based on clinical judgment
CSME or central-involved DME			1-4 months*	Yes	Based on clinical judgment	Yes

*Intravitreous anti-VEGF therapy for central-involved DME requires monthly injections until the DME resolves or vision reaches 20/20 or better, until additional treatment is unlikely to be beneficial, or if edema worsens or remains unaffected by treatment. The monthly follow-up time could be doubled if edema does not recur or worsen, and could be doubled again (up to 16 weeks) if edema continues not to recur or worsen.[289]

Table 2B
Frequency and Composition of Evaluation and Management Visits for Retinal Complications of Diabetes Mellitus

Severity of Condition	Management Plan*			
	Referral for Consultation and/or Treatment	Panretinal Laser Treatment	Focal Laser Treatment	Intravitreal Anti-VEGF Injections
No diabetic retinopathy	Communicate with patient's physician	No	No	No
Mild NPDR				
No macular edema	Communicate with patient's physician	No	No	No
Macular edema (not CSME)	Obtain retinal consult in 2-4 weeks	No	No	No
CSME or central-involved DME	Obtain retinal consult in 2-4 weeks	No	Based on clinical judgment	Yes, if vision impaired*
Moderate NPDR				
No macular edema	Communicate with patient's physician	No	No	No
Macular edema (not CSME)	Obtain retinal consult in 2-4 weeks	No	No	No
CSME or central-involved DME	Obtain retinal consult in 2-4 weeks	No	Based on clinical judgment	Yes, if vision impaired*

Table Continued on next page

Table 2B *(Continued)*
Frequency and Composition of Evaluation and Management Visits for Retinal Complications of Diabetes Mellitus

Severity of Condition	Management Plan*			
	Referral for Consultation and/or Treatment	Panretinal Laser Treatment	Focal Laser Treatment	Intravitreal Anti-VEGF Injections
Severe or Very Severe NPDR				
No macular edema	Obtain retinal consult in 2-4 weeks	Sometimes**	No	Alternative, Sometimes**
Macular edema (not CSME)	Obtain retinal consult in 2-4 weeks	Sometimes**	No	Alternative, Sometimes**
CSME or central-involved DME	Obtain retinal consult in 2-4 weeks	Sometimes**	Based on clinical judgment	Yes, if vision impaired*
Non-high-risk PDR				
No macular edema	Obtain retinal consult in 2-4 weeks	Sometimes**	No	Alternative, Sometimes**
Macular edema (not CSME)	Obtain retinal consult in 2-4 weeks	Sometimes**	No	Alternative, Sometimes**
CSME or central-involved DME	Obtain retinal consult in 2-4 weeks	Sometimes**	Based on clinical judgment	Yes, if vision impaired*
High-risk PDR				
No macular edema	Obtain retinal consult in 24-48 hours	Yes	No	Alternative
Macular edema (not CSME)	Obtain retinal consult in 24-48 hours	Yes	No	Usually
CSME or central-involved DME	Obtain retinal consult in 24-48 hours	Yes	Based on clinical judgment	Usually

* At the present time, anti-VEGF therapy is the initial treatment choice for center-involving macular edema with vision impairment (20/32 or worse), with possible subsequent or deferred focal laser treatment.

** Consider scatter laser treatment (PRP), especially if very severe NPDR (see levels of diabetic retinopathy), significant medical complication, or type 2 diabetes mellitus. The alternative use of anti-VEGF injections may be considered in eyes with severe NPDR in settings where PRP would be considered.

*** Consider scatter laser treatment (PRP) or anti-VEGF injections, especially if moderate PDR (see levels of diabetic retinopathy), significant medical complication, or type 2 diabetes mellitus.

CONSENSUS-BASED ACTION STATEMENT: Individuals with diabetes should receive at least annual dilated eye examinations. More frequent examination may be needed depending on the presence of co-morbidities, changes in vision and/or the severity, progression, or treatment of diabetic retinopathy.
Evidence Quality: There is a lack of published research to support or refute the use of this recommendation.
Benefit and Harm Assessment: Implementation of this recommendation is likely to result in the earlier diagnosis and treatment of potentially sight-threatening vision problems. The benefits of this recommendation were established by expert consensus opinion.

D. CLINICAL RECORDKEEPING

Electronic Health Records (EHRs) are helpful for identifying at-risk populations for preventive care and intervention.[290] (Evidence Grade: B) The use of EHRs to support clinical decision-making can lead to modest but significant improvements in glucose control and some aspects of blood pressure control in adults with type 2 diabetes.[291] (Evidence Grade: A) It is possible to identify patients at risk of developing diabetes and coronary heart disease by identifying risk factors associated with metabolic syndrome available in EHRs.[290] (Evidence Grade: B) When compared to paper record based practices, the use of EHRs may improve the quality of care and outcomes for patients with diabetes.[292] (Evidence Grade: C)

Use of an EHR phenotype-based prescreening system has been proposed that could be used to identify at-risk patients or those with untreated diabetes who require more formal testing. Risk scores could be computed automatically within EHRs to efficiently identify at-risk patients. Risk scores could also be created by insurance companies using existing claims databases.[293] Diabetes risk forecasting using data from EHRs is an emerging tool for clinical decision-making that may allow for early intervention with life style modifications such as diet and exercise to prevent or delay the development of type 2 diabetes.[294] (Evidence Grade: B)

EVIDENCE-BASED ACTION STATEMENT: Electronic Health Records (EHRs) can be used to support clinical decision-making and improve preventive care and intervention in persons with diabetes.[290-292]
Evidence Quality: Grade B. Randomized Clinical Trial, Cohort-prospective Study, Case Series **Level of Confidence:** Medium **Clinical Recommendation Strength:** Recommendation. This recommendation should generally be followed, but remain alert for new information.
Evidence Statements: The use of EHRs to support clinical decision-making can lead to modest but significant improvements in glucose control and some aspects of blood pressure control in adults with type 2 diabetes.[291] (Evidence Grade: A) Electronic Health Records are helpful for identifying at-risk populations for preventive care and intervention.[290] (Evidence Grade: B) When compared to paper record-based practices, the use of EHRs may improve the quality of care and outcomes for patients with diabetes.[292] (Evidence Grade: C)
Potential Benefits: Improved quality of care | **Potential Risks/Harms:** None
Benefit and Harm Assessment: Benefits significantly outweigh harms
Potential Costs: Cost of implementing EHR system
Value Judgments: None
Role of Patient Preferences: None
Intentional Vagueness: None
Gaps in Evidence: None identified

V. TREATMENT AND MANAGEMENT

A. MANAGEMENT OF OCULAR COMPLICATIONS OF DIABETES MELLITUS

Treatment recommendations depend upon the nature and severity of the patient's ocular condition and desired visual outcome. Treatment decisions should reflect the patient's preferences and values. Appendix 2 presents a flowchart for the optometric management of the patient with undiagnosed or suspected diabetes. Appendix 3 presents a flowchart outlining the optometric management of the patient diagnosed with diabetes.

1. Treatment of Persons with Nonretinal Ocular Complications

Management of nonretinal ocular complications of diabetes should be consistent with current recommendations of care for each condition. Although a comprehensive discussion of these therapy regimens is beyond the scope of this Guideline, Table 3 briefly reviews current clinical practice for management of common nonretinal ocular and visual complications. Communication with the patient's other health care provider(s) regarding ocular and visual findings and patient care are an integral part of management for all conditions.

CONSENSUS-BASED ACTION STATEMENT: Treatment protocols for persons with nonretinal ocular and visual complications of diabetes should follow current recommendations for care and include education on the condition(s) and recommendations for follow-up visits.

Evidence Quality: Published research to support or refute the use of this recommendation has not been provided in this guideline, but strong evidence for treatment of most conditions does exist.

Benefit and Harm Assessment: Implementation of this recommendation is likely to improve the quality of care for patients with diabetes. The benefits of this recommendation were established by expert consensus opinion.

Table 3
Management of Nonretinal Ocular Complications of Diabetes

Category	Ocular/Visual Complications	Management
Functional	Loss of visual acuity	Assess visual acuity as recommended in the Evidence-Based Clinical Practice Guideline on Adult Eye and Vision Examination, and Evidence-Based Clinical Practice Guideline on Pediatric Eye and Vision Examination.
	Refractive error changes	Assess refractive error, distance and near, and pinhole acuity. Change spectacle or contact lenses prescription, as indicated by the patient's visual requirements. Earlier use of spectacle correction for reading may be indicated. Counsel patients about variable refractive status due to fluctuations in blood glucose.
	Changes in color vision	Perform color vision assessment that is sensitive to acquired color vision loss.
	Changes in visual fields	Assess visual field changes and manage. Rule out other causes of visual field changes.
	Contrast sensitivity	Perform assessment of contrast sensitivity.

Table Continued on next page

Table 3 *(Continued)*
Management of Nonretinal Ocular Complications of Diabetes

Category	Ocular/Visual Complications	Management
Eye movement anomalies	Cranial nerve palsies	Assess multiple diagnostic positions of gaze, tests of smooth pursuits (versions and ductions), and saccades. Rule out other cranial nerve palsies or other etiologies.
Pupils	Sluggish pupillary reflexes Afferent pupillary defects	Rule out optic neuropathy and other neurological etiologies.
Conjunctiva	Bulbar microaneurysms	Monitor
Tear film	Dry eye syndrome	Use artificial tears, ocular lubricants, and other dry eye management techniques. Monitor for corneal complications.
Cornea	Reduced corneal sensitivity	Monitor for abrasions, keratitis, or ulcerations. Monitor contact lens wear.
	Basement membrane anomalies Recurrent corneal erosions	Recommend lubricating drops/artificial tears. Prescribe sodium chloride solution/ointment or ocular surface lubricant. Use bandage contact lenses or patching, as necessary.
Iris	Neovascularization on the iris (Rubeosis iridis)	Perform gonioscopy to rule out anterior chamber angle involvement and neovascular glaucoma. Conduct dilated retinal examination to evaluate proliferative diabetic retinopathy. Refer to an ophthalmologist experienced in the management of diabetic retinal disease for possible panretinal photocoagulation and/or anti-VEGF agents.
Eyelids	Ptosis	Determine etiology (neurologic, mechanical, immunological).
Lens	Cataracts	Assess and monitor degree of lens opacification. Perform refraction to obtain best visual acuity. Surgery may be indicated if adequate visualization of the retina is no longer possible.
Vitreous	Hemorrhage Premature syneresis/degeneration Detachment	Use ultrasound if retinal view is obscured. Perform dilated retinal examination. Use ultrasound if retinal view is obscured. Consult with an ophthalmologist experienced in the management of diabetic retinal disease.
Optic Disc	Papillopathy Ischemic Optic Neuropathy Glaucoma	Management of diabetic papillopathy or ischemic optic neuropathy may require consultation with a neuro-ophthalmologist or neurologist to rule out all other potential etiologies. Manage with medication and/or consult with an ophthalmologist experienced in the management of glaucoma.

2. Treatment Options for Retinal Complications

Major clinical trials provide the scientific basis for clinical management of diabetic retinopathy. These studies have guided the treatment and management of diabetic retinal disease.

The current options for the care of persons with diabetic retinopathy and DME include careful retinal examination and follow-up, timely laser photocoagulation, monitored regimens of intravitreous anti-vascular endothelial growth factor (anti-VEGF) injections, and appropriate use of vitrectomy surgery in clearing vitreous hemorrhage, removing fibrous tissue, and relieving traction or repairing retinal detachment. Intraocular corticosteroids also play a role in the treatment of chronic DME, and in persons who are anti-VEGF resistant or are pseudophakic.

a. Laser Photocoagulation

Panretinal (scatter) photocoagulation (PRP), in which laser burns are scattered throughout the retina, sparing the macula, has been the standard of care for the treatment of high-risk PDR for many years. Early treatment with PRP has been found to reduce the risk of severe vision loss by 50 percent or more.[33]

The mechanisms by which PRP results in the regression of retinal neovascularization are thought to involve improved oxygenation of the retina due to retinal layer thinning with subsequent improved oxygenation from the choroid. In addition, destruction of ischemic retinal tissue prevents the further release of angiogenic growth factors, thus improving effective retinal oxygenation. Pigmented cells in the retina absorb the laser light resulting in heat and cellular destruction of the outer retina, including the outer photoreceptors and retinal pigment epithelium. The laser burns thus result in thinning of the retina and thereby increase the ability of the retina to derive oxygenation from the choroid. This resulting increase in retinal oxygenation has been demonstrated with vitreous and retinal microelectrode studies. Not only does thinning of the retina improve relative oxygenation in the remaining retinal tissue, but destruction of ischemic retina also reduces release of angiogenic growth factors such as VEGF. As retinal oxygenation improves and concentrations of angiogenic growth factors decrease, retinal neovascular vessels regress or disappear.

The primary goals of retinal laser photocoagulation are to preserve useful vision and to prevent the adverse consequences of PDR; however, laser therapy may be associated with well documented and expected ocular side effects due to its inherent destructive nature to the retina. Complications and side effects of PRP may include visual field constriction, onset or worsening of DME, night blindness, color vision changes, decreased accommodation, scotoma, anisocoria, and glaucoma.

The ETDRS established the efficacy of focal/grid photocoagulation for the treatment of eyes with CSME and it has been shown to substantially reduce the risk of moderate vision loss.[38] (Evidence Grade: A) Focal laser therapy is used to seal microaneurysms and help prevent leakage. It increases the chance of visual improvement, decreases the frequency of persistent macular edema, and causes only minor visual field losses. Grid laser therapy is used to treat areas of diffuse leakage and capillary nonperfusion. It increases oxygen availability to areas of hypoxia by reducing demands elsewhere, thereby reducing the total area of abnormal leakage.

Focal treatment may be considered for eyes with macular edema that involves or threatens the center of the macula;[44] (Evidence Grade: A) however, findings from DRCR.net studies have established the use of intravitreous anti-VEGF agents as the preferred initial therapy for central-involved DME.[65] (Evidence Grade: A)[69] (Evidence Grade: A)[71] (Evidence Grade: A)[74] (Evidence Grade: A)

To reduce potential complications from PRP, a modified-ETDRS (mETDRS) laser therapy technique was developed using a smaller laser spot size and reduced duration.[295] Other techniques available for laser therapy to reduce side effects include:

- Pattern scan laser (Pascal), a form of target retinal laser photocoagulation, designed to treat areas of retinal capillary non-perfusion and intermediate retinal ischemic zones in PDR and spare better-perfused tissue from laser-induced tissue scarring.[296]
- Subthreshold diode micropulse (SDM) laser using a diode laser with micropulse technology to minimize the negative thermal effects on the retina. SDM therapy delivers short pulses and confines the laser energy to a smaller zone causing less damage on the neural retina and choriocapillaries.[297]

While laser photocoagulation has been shown to be beneficial in reducing the risk of further vision loss in DME, it generally is not effective in reversing already reduced visual acuity. The use of anti-VEGF agents has been shown to not only reduce the risk of vision loss, but also improve vision.

b. Intravitreous Injections

Vascular endothelial growth factor (VEGF) is an essential moderator of blood-retinal barrier breakdown. Hypoxia resulting from microvascular occlusion in diabetic retinopathy stimulates the release of VEGF to compensate for lack of perfusion. The presence of elevated vitreous VEGF levels in patients with diabetic retinopathy and DME has led to the use of VEGF inhibitors as a treatment option.

The use of anti-VEGF agents has substantially changed the treatment of DME. Intraocular injection of anti-VEGF agents is now considered to be the standard of care in patients with central-involved DME, especially if visual acuity is reduced.[298] (Evidence Grade: A) Clinical trials have shown that intraocular administration of anti-VEGF agents can help preserve and improve vision in patients with DME; however, repeated injections of anti-VEGF medications are required. Most patients need near-monthly administration of anti-VEGF agents during the first year of treatment, with fewer injections needed in subsequent years.

The most commonly used anti-VEGF agents for DME are:

- Ranibizumab (Lucentis®) is FDA approved for treatment of wet age-related macular degeneration, retinal vein occlusion, and diabetic retinopathy with or without DME.
- Aflibercept (Eylea®) is FDA approved for the treatment of wet age-related macular degeneration, central retinal vein occlusion, and DME.
- Bevacizumab (Avastin®) is FDA approved for treatment of cancer and its systemic use is known to be associated with an increased risk of stroke. It is unknown if a substantially smaller dose, when used intravitreally, has any significant systemic toxicity.[299] It has been used off-label for the treatment of DME.

Repeated intravitreous administration of anti-VEGF agents has been shown to be more effective than conventional focal/grid laser alone in the treatment of central-involved DME. The full benefit of intravitreous injections with prompt or deferred macular laser treatment may not manifest until the second year of treatment.[300] (Evidence Grade: A)

Clinical note: *Anti-VEGF agents have significantly improved the ability to treat DME; however, the use of focal/grid macular laser therapy still plays an important role and can be used to individualize treatment for persons who do not respond or cannot tolerate injections with anti-VEGF agents.*

The pathogenesis of diabetic retinopathy and DME is multifactorial involving both angiogenic and inflammatory pathways. The anti-inflammatory and anti-angiogenic properties of intraocular corticosteroids may be of benefit in the treatment of PDR and DME.

Currently, three types of intravitreous steroids are available:

- triamcinolone acetonide
- fluocinolone acetonide
- dexamethasone.

The use of intravitreous triamcinolone acetonide (IVTA) injections and intraocular corticosteroid sustained release drug delivery systems, fluocinolone acetonide (Retisert® or Iluvien®) and dexamathasone (Ozurdex®) for the treatment of persistent or refractory DME[299,301] have been shown effective in decreasing macular thickness and improving visual acuity,[302] (Evidence Grade: A) although intravitreous anti-VEGF agents are the primary treatment.

c. Vitrectomy

Vitrectomy is a treatment option for patients with severe complications from diabetic retinopathy. It is used for treating vitreous hemorrhage, and PDR with non-clearing vitreous hemorrhage or fibrosis, areas of traction threatening the macula, and persistent DME with vitreous traction.[303]

The potential benefits and risks of vitrectomy have not been clearly defined by long-term, randomized clinical trials.[304] (Evidence Grade: B) There is little evidence for use of vitrectomy for treating DME in the absence of epiretinal membrane or vitreomacular traction and vitrectomy has not been shown to be superior to laser in terms of functional outcomes.[305] (Evidence Grade: B)

Potential complications of vitrectomy include neovascular glaucoma, retinal detachment, vitreous hemorrhage, retinal tear formation, cataract, and endophthalmitis.[66] (Evidence Grade: B) Glaucoma is more likely to occur in people with associated preoperative retinal detachment.[299]

3. Treatment of Persons with Retinal Complications

Numerous clinical studies have evaluated the efficacy and safety of the treatment and management options for retinal complications of diabetes mellitus. Their use in the care of persons with NPDR, PDR, DME, and vitreous hemorrhage is discussed below.

a. Nonproliferative Diabetic Retinopathy

In the absence of CSME, mild or moderate NPDR usually is not sight-threatening; therefore, if the patient can be followed closely, PRP is not indicated for persons with mild or moderate NPDR.[44] (Evidence Grade: A) When central-involved CSME is present, anti-VEGF agents may provide an effective treatment. PRP or intravitreous anti-VEGF injections may be considered for severe NPDR, since patients with severe NPDR or worse have a high risk of progression to PDR.[306]

b. Proliferative Diabetic Retinopathy

Proliferative diabetic retinopathy is marked by new vessel growth on the optic disc or elsewhere on the retina, vitreous hemorrhage, pre-retinal hemorrhage, or by the proliferation of fibrous tissue on the optic disc or elsewhere on the retina. When high-risk proliferative diabetic retinopathy is present, PRP[44] (Evidence Grade: A) or intravitreous anti-VEGF agents[73] (Evidence Grade: A)[76] (Evidence Grade: B) should be considered and should not be delayed.

Panretinal laser photocoagulation can exacerbate DME in some individuals. Persons receiving PRP for severe NPDR or early PDR have similar risks of developing macular edema, whether the PRP is delivered in a single session or over four sessions; however, single session treatment may reduce travel and lost productivity costs for some patients.[64] (Evidence Grade: B) Since the relative risk of vision loss in patients without high-risk characteristics is low, treatment of CSME or central-involved DME should be considered before PRP is used.[307] (Evidence Grade: A)

EVIDENCE-BASED ACTION STATEMENT: Patients with severe or very severe nonproliferative diabetic retinopathy, early proliferative diabetic retinopathy with risk of progression, or high-risk proliferative diabetic retinopathy should be referred to an ophthalmologist experienced in the management of diabetic retinal disease for possible panretinal photocoagulation (PRP)[44] or intravitreous anti-VEGF treatment.[73,76]	
Evidence Quality: Grade A. Randomized Clinical Trials **Level of Confidence:** High **Clinical Recommendation Strength:** Strong Recommendation. This recommendation should be followed unless clear and compelling rationale for an alternative approach is present.	
Evidence Statements: When high-risk proliferative diabetic retinopathy is present, panretinal (scatter) photocoagulation[44] (Evidence Grade: A) or intravitreous anti-VEGF agents[73,76] should be considered and should not be delayed.	
Potential Benefits: Preservation of vision	**Potential Risks/Harms:** Complications from laser treatment or intravitreous injections
Benefit and Harm Assessment: Benefits significantly outweigh harms	
Potential Costs: Direct cost of treatment	
Value Judgments: None	
Role of Patient Preferences: Small	
Intentional Vagueness: None	
Gaps in Evidence: None identified	

Although PRP remains a standard treatment for PDR, several studies have also investigated the use of anti-VEGF agents for the treatment of NPDR and PDR:

- A DRCR.net clinical trial compared changes in diabetic retinopathy severity during anti-VEGF (aflibercept, bevacizumab, or ranibizumab) treatment for DME. At one and two years, eyes with NPDR receiving anti-VEGF treatment experienced improvement in diabetic retinopathy severity. Less improvement was demonstrated with bevacizumab (BVZ) at one year than with aflibercept or ranibizumab (RBZ). Aflibercept was associated with more improvement at one and two years in the smaller subgroup of participants with PDR at baseline. All three anti-VEGF treatments were associated with low rates of diabetic retinopathy worsening.[79] (Evidence Grade: A)
- In a study designed to evaluate the effect of RBZ or triamcinolone acetonide used to treat DME on the progression of PDR, RBZ and triamcinolone acetonide were both shown to reduce the probability of diabetic retinopathy progression through three years in eyes with or without PDR.[308] (Evidence Grade: A)
- In eyes with PDR, treatment with RBZ 0.5 mg resulted in visual acuity that was noninferior to (not worse than) PRP treatment at two years. The use of RBZ resulted in better visual acuity, less visual field loss, and fewer eyes developing DME or undergoing vitrectomy.[73] (Evidence Grade: A) Although anti-VEGF therapy requires a more frequent visit schedule than PRP, these findings provide evidence supporting the use of RBZ as an alternative to laser therapy for PDR, at least through two years.[78] (Evidence Grade: A) Five-year follow-up results found visual acuity was very good and similar in both groups. The number of RBZ injections needed were reduced from year one, with approximately 75 percent of eyes in the RBZ group receiving at least one injection per year through four years. Severe vision loss or serious PDR complications were uncommon with PRP or RBZ.[309] (Evidence Grade: A)
- When comparing patient-centered outcomes in persons with PDR treated with RBZ versus PRP, results from a randomized clinical trial found little difference in visual function between treatment regimens at two years.[76] (Evidence Grade: B)
- A study of the effects of RBZ, when administered to patients with DME for 12 to 36 months, found that RBZ improved diabetic retinopathy severity and prevented worsening; however, prolonged delays in initiation of RBZ therapy may limit this therapeutic effect. Although uncommon, the development of PDR still occurs in a small percentage of eyes undergoing anti-VEGF therapy, which may be related to the presence of macular nonperfusion.[310] (Evidence Grade: A)

Clinical note: *Anticipated visit compliance, cost, and frequency of visits need to be considered when considering treatment options for patients with PDR.*[309]

EVIDENCE-BASED ACTION STATEMENT: Anti-vascular endothelial growth factor (anti-VEGF) agents should be considered as a treatment alternative or adjunct to panretinal photocoagulation (PRP) in the management of proliferative diabetic retinopathy (PDR), with or without diabetic macular edema (DME).[73,76,78,79,308-310]

Evidence Quality: Grade A. Randomized Clinical Trials

Level of Confidence: High

Clinical Recommendation Strength: Strong Recommendation. This recommendation should be followed unless clear and compelling rationale for an alternative approach is present.

Evidence Statements: Ranibizumab (RBZ), when administered to patients with DME for 12 to 36 months, improved diabetic retinopathy severity and prevented worsening; however, prolonged delays in initiation of RBZ therapy may limit this therapeutic effect.[310] (Evidence Grade: A)

In eyes with PDR, treatment with RBZ resulted in visual acuity that was noninferior to (not worse than) PRP treatment at two years.[73] (Evidence Grade: A) Although anti-VEGF therapy requires a more frequent visit schedule than PRP, these findings provide evidence supporting the use of RBZ as an alternative to laser therapy for PDR, at least through two years.[78] (Evidence Grade: A) Five-year follow-up results found visual acuity was very good and similar in both groups. Severe vision loss or serious PDR complications were uncommon with PRP or RBZ.[309] (Evidence Grade: A)

When comparing outcomes in persons with PDR treated with RBZ versus PRP, results from a randomized clinical trial found little difference in visual function between treatment regimens at two years.[76] (Evidence Grade: B)

When comparing changes in diabetic retinopathy severity during anti-VEGF (aflibercept, bevacizumab, or ranibizumab) treatment for DME, all three anti-VEGF treatments were associated with low rates of diabetic retinopathy worsening.[79] (Evidence Grade: A)

In a study designed to evaluate the effect of RBZ or triamcinolone acetonide used to treat DME on the progression of PDR, RBZ and triamcinolone acetonide were both shown to reduce the probability of diabetic retinopathy progression through three years in eyes with or without PDR.[308] (Evidence Grade: A)

Potential Benefits: Preservation of vision	**Potential Risks/Harms:** Complications from intravitreous injections or laser treatment

Benefit and Harm Assessment: Benefits significantly outweigh harms

Potential Costs: Cost of treatment

Value Judgments: None

Role of Patient Preferences: Small

Intentional Vagueness: None

Gaps in Evidence: None identified

c. Diabetic Macular Edema

The management of patients with DME has evolved substantially in recent years. Studies have demonstrated that intravitreous anti-VEGF agents significantly reduce macular edema and result in improved visual acuity for persons with DME. In several studies, anti-VEGF agents were more effective than focal laser therapy at reducing DME, with laser therapy providing no additional benefit. Patients with DME who have early response (after one injection) to anti-VEGF treatment by reduction in central retinal thickness (CRT) may have significant response to treatment by three months.[311] (Evidence Grade: D) Anti-VEGF therapy for DME provides similar results in patients taking oral anti-diabetic agents compared to patients with type 2 diabetes on chronic insulin therapy.[312] (Evidence Grade: C)

The DRCR.net (Protocol I) studied the role of ranibizumab (RBZ) with either prompt or delayed (≥24 weeks) laser for patients with central-involved DME and vision impairment. It showed the superior effect of RBZ (with or without deferred macular laser) on visual acuity and macular thickening when compared with laser alone.[65] (Evidence Grade: A) Three year study results suggested that the use of focal/grid laser treatment at the time of initiation of intravitreous RBZ is no better, and possibly worse, for vision outcomes than deferring laser treatment for 24 weeks or more in eyes with DME involving the fovea.[69] (Evidence Grade: A) Although more than half of eyes in which laser treatment is deferred may avoid laser therapy for at least five years, such eyes may require more injections to achieve these results. Most eyes treated with RBZ and either prompt or deferred laser maintain vision gains obtained by the first year through five years with little additional treatment after three years.[72] (Evidence Grade: A)

Another DRCR.net randomized trial evaluated the short-term effects of intravitreous RBZ or triamcinolone acetonide on macular edema after focal/grid laser for DME in eyes also receiving panretinal photocoagulation. The addition of one intravitreous triamcinolone injection or two intravitreous RBZ injections is associated with better visual acuity and decreased macular edema by 14 weeks. Whether continued long-term intravitreous treatment is beneficial was not determined from this study.[67] (Evidence Grade: A)

In a study comparing the long-term effects of RBZ with prompt or deferred laser versus laser or triamcinolone plus laser with deferred RBZ, eyes receiving initial RBZ therapy for central-involved DME likely have better long-term vision improvements than eyes managed with laser or triamcinolone plus laser followed by very deferred RBZ for persistent central retinal thickening and vision impairment.[74] (Evidence Grade: A) Visual acuity and retinal thickness improvements obtained with RBZ treatment in conjunction with immediate or deferred laser were sustained over time.

An additional DRCR.net study evaluated the prevalence of persistent DME after months of anti-VEGF therapy and its effect on visual acuity. Forty percent of eyes treated for DME with intravitreous RBZ had persistent central-involved DME through 24 weeks after initiating treatment. Nevertheless, long-term improvement in visual acuity from baseline was typical and substantial (≥2-line) loss of visual acuity is likely uncommon through three years, even when central-involved DME chronically persists.[83] (Evidence Grade: B)

A study of long-term outcomes of RBZ injections given as needed based on functional and anatomical responses for 48 months in an ordinary clinical setting reported a substantial and continuous visual benefit in patients with DME. The best corrected visual acuity (BCVA) improved by 6.6 ETDRS letters. The visual gains achieved after the initial loading dose were sustained during a four-year follow-up.[313] (Evidence Grade: C)

Comparative Effectiveness Studies

A DRCR.net (Protocol T) study evaluated the relative efficacy and safety of aflibercept, BVZ and RBZ for the treatment of central-involved DME. The one- and two-year results concluded that all three agents improved vision in eyes with DME. In eyes with initial visual acuity of 20/40 or better at baseline, there was no significant difference among the three agents. In eyes with 20/50 visual acuity or worse, aflibercept provided greater average gains in visual acuity compared to BVZ and RBZ.[71] (Evidence Grade: A) [75] (Evidence Grade: A) [77] (Evidence Grade: B) [82] (Evidence Grade: A)

A secondary analysis of data from the DRCR.net comparative effectiveness trial evaluated the use of repeated injections of aflibercept, BVZ, and RBZ in the treatment of DME. Aflibercept was associated with more improvement of DME severity at one and two years. All three anti-VEGF treatments were associated with low rates of diabetic retinopathy worsening in eyes with PDR.[79] (Evidence Grade: A)

The comparative efficacy of BVZ and RBZ for diabetic macular edema (DME) was also evaluated using a crossover study design. The 36-week randomized trial of RBZ compared with BVZ for treatment of DME demonstrated a statistically significant but small relative clinical benefit in improved visual acuity and central subfoveal macular thickness.[314] (Evidence Grade: A)

A meta-analysis of randomized clinical trials comparing aflibercept, BVZ and RBZ concluded that all are more effective than focal/grid laser photocoagulation for improving visual acuity three or more lines after one year.[298] (Evidence Grade: A) Approximately one in ten people improve vision with laser, and about three in ten improve with anti-VEGF treatment. There is moderate-certainty evidence that aflibercept conferred some visual and anatomic advantage over BVZ and RBZ in people with DME after one year of treatment.

Another meta-analysis of current treatment options for DME confirmed that intravitreous aflibercept is more favorable for both BCVA improvement and central macular thickness decrease than other current therapies in the management of DME within 12 months. In addition, both intravitreous RBZ and intravitreous BVZ were found to be significantly superior to laser alone.[315] (Evidence Grade: A)

Table 4 provides a summary of additional studies on the efficacy of intravitreous anti-VEGF agents for the treatment of DME.

TABLE 4
Clinical Studies of Anti-VEGF Agents

Study name / study type	Evidence grade	Background	Results
RESOLVE Study[316] RCT	A	Evaluated the use of RBZ versus a placebo over twelve months for the treatment of central-involved DME.	RBZ led to significant and continuous improvement in both BCVA and central retinal thickness compared with sham treatment in patients with visual impairment due to DME.
READ-2 Study[317,318] RCT	A	Compared the use of RBZ alone to laser therapy alone or RBZ plus laser over two years.	Patients treated with intraocular RBZ and PRP, if needed, and/or a combination of both showed a mean improvement in visual acuity of 7.4 ETDRS letters. A follow-up study using more aggressive treatment with RBZ during year three found continued improvement in best corrected visual acuity with RBZ, but many patients required frequent injections to optimally control edema and maximize vision.
RESTORE Study[319] RCT	A	Conducted a twelve-month randomized trial of RBZ plus macular laser photocoagulation.	Demonstrated the superiority of RBZ monotherapy over standard macular laser photocoagulation in patients with visual impairment due to DME and found no additional benefit of RBZ therapy combined with macular laser therapy.
RESTORE Extension Study[320] Cohort-prospective Study	A	Evaluated the long-term (3 year) efficacy and safety of RBZ treatment in persons with DME.	Reported RBZ was effective in improving and maintaining BCVA and central retinal subfield thickness outcomes and was generally well tolerated, with a progressively declining number of injections over three years of individualized dosing.
RISE and RIDE Studies[321-323] RCT, Cohort-prospective Study	A	Conducted two parallel, identical studies on the efficacy and safety of RBZ in patients with DME.	Showed that RBZ monotherapy provided rapid and sustained results in improving macular edema and BCVA in persons with DME, which was maintained over three years. Initial, intensive therapy with RBZ, followed by observation and maintenance therapy when indicated, was shown to maintain visual and anatomic gains for patients with DME. In addition, patients treated with RBZ experienced fewer complications, such as vitreous hemorrhage, and fewer developed PDR or underwent PRP.
REVEAL Study[324] RCT	A	Evaluated whether the use of RBZ alone or combined with laser was superior to laser therapy alone based on mean change in best corrected visual acuity.	Showed RBZ monotherapy or RBZ combined with laser provided superior BCVA improvements over laser treatment alone in Asian patients with visual impairment resulting from DME.
RETAIN Study[325] RCT	A	Conducted to determine the non-inferiority of RBZ treat-and-extend (incremental increase in treatment intervals for a given patient based on disease progression) with/without laser to RBZ pro re nata (PRN) for best corrected visual acuity in patients with DME.	Concluded that treat-and-extend is a feasible treatment option for patients with DME, with a potential to reduce treatment burden.
BOLT Study[300] RCT	A	Compared intravitreous BVZ to laser therapy alone.	Found mean BCVA to be significantly better in the BVZ group versus laser therapy alone. For persistent central-involved CSME, improvements in central macular thickness were seen with BVZ at one year and were maintained over the second year with a mean of four injections.

Table Continued on next page

TABLE 4 *(Continued)*
Clinical Studies of Anti-VEGF Agents

Study name / study type	Evidence grade	Background	Results
BOLT Study[326,327] RCT	B	Provided a post hoc analysis of patients to assess the factors that may determine the injection frequency at 12 and 24 months.	Good long-term response from treatment with BVZ was predicted based on resolution of macular edema by four months; however, approximately 20 percent of patients with persistent edema at 12 months achieved a dry macula and 50 percent gained more than 15 letters at 24 months with sustained treatment, suggesting that edema at 4 or 12 months should not be used as a stopping criterion for treatment. The overall outcomes of mean change in BCVA and central macular thickness in participants treated with BVZ were comparable to those reported in association with RBZ at 12 and 24 months.
Bevordex Study[328] RCT	B	Evaluated the use of intravitreous BVZ versus intravitreous dexamethasone for central-involved DME.	Twelve-month results found the dexamethasone implant achieved similar rates of visual acuity improvement compared with BVZ for DME, with superior anatomic outcomes and fewer injections. Both treatments were associated with improvement in visual quality-of-life scores; however, more dexamethasone implant-treated eyes lost vision, mainly because of cataract.
DAVINCI Study[329,330] RCT	B	Compared five different aflibercept regimens to laser therapy to determine whether different doses and dosing regimens of intravitreous VEGF Trap-Eye (aflibercept) are superior to focal/grid photocoagulation in eyes with DME.	Intravitreous aflibercept produced a statistically significant and clinically relevant improvement in visual acuity when compared with macular laser photocoagulation in patients with DME. Eyes receiving aflibercept experienced improvements in BCVA compared with laser treatment at 6 months and results were maintained or improved through 12 months.
VISTA and VIVID Studies[331] RCT	A	Assessed the efficacy and safety of aflibercept in treating DME when comparing two dosing regimens of intravitreous aflibercept with macular laser photocoagulation for DME.	Intravitreous aflibercept was associated with significant BCVA gains from baseline over 100 weeks compared with laser treatment. This study indicated the potential for a therapeutic option with a longer injection interval and subsequently a reduced number of injections and monitoring visits.

BCVA – best corrected visual acuity
BVZ – bevacizumab
CSME – clinically significant macular edema
DME – diabetic macular edema
ETDRS – Early Treatment Diabetic Retinopathy Study
PDR – proliferative diabetic retinopathy
PRP – panretinal photocoagulation
RBZ – ranibizumab
RCT – randomized clinical trial

Safety of Anti-VEGF Agents

Intravitreous anti-VEGF therapy is generally safe with relatively low side effects; however, ocular adverse events resulting from the intravitreous injection can include endophthalmitis, ocular inflammation, retinal detachment, vitreous hemorrhage, and traumatic cataract. Anti-VEGF drugs can also pass into systemic circulation; therefore, vascular endothelial growth factor inhibitors for DME should be used with caution due to potential systemic adverse events.[315]

An analysis of patients with DME at high risk for vascular disease who received two years of monthly anti-VEGF treatment (aflibercept or ranibizumab) revealed a possible increased risk for death and potentially for cerebrovascular accidents; however, concern about a potential increased risk of death may not apply to most patients who are undergoing less intensive anti-VEGF therapy.[332] (Evidence Grade: A) Ranibizumab for DME is considered safe when the patients are carefully selected based on systemic vascular conditions and it is used on an as needed basis.[333] (Evidence Grade: A)

A study to assess the risk of sustained IOP elevation following repeated intravitreous injections of RBZ found that in eyes with central-involved DME and no prior open-angle glaucoma, repeated injections may increase the risk of sustained IOP elevation or the need for ocular hypotensive treatment.[81] (Evidence Grade: B)

Clinical note: *Clinicians should consider the risk of elevated IOP in patients who have received intravitreous injections of anti-vascular endothelial growth factor (anti-VEGF) for the treatment of DME.*

Cost-effectiveness Studies

A number of studies have looked at the cost-effectiveness of treatment options for patients with DME. One study assessed the incremental, comparative effectiveness (patient value gain) and cost effectiveness (financial value gain) associated with 0.3 mg intravitreous RBZ injection therapy versus sham therapy for DME. It concluded that intravitreous RBZ therapy for the treatment of DME confers considerable patient (human) value gain. It also accrues financial value to patients, public and private insurers, and society.[334]

The cost-effectiveness of RBZ monotherapy or combination therapy (RBZ plus laser photocoagulation) was compared with laser monotherapy for the treatment of visual impairment due to DME. From a societal perspective, RBZ monotherapy and combination therapy provided greater benefits at lower costs than laser monotherapy.[335]

Another study evaluated the most cost-effective treatment option for patients with newly diagnosed central-involved DME. It compared focal laser photocoagulation alone, focal laser plus intravitreous RBZ, focal laser plus intravitreous BVZ, or focal laser plus intravitreous triamcinolone injections.[336] With BVZ and RBZ assumed to have equivalent effectiveness and similar safety profiles when used in the management of CSME, BVZ therapy was reported to confer the greatest value among the different treatment options for CSME.

A follow-up study to the DRCR.net Protocol S clinical trial reported on the relative cost-effectiveness of PRP and RBZ treatment when managing PDR, with or without concomitant baseline DME. Over two years, compared with PRP, 0.5 mg RBZ was cost-effective for eyes presenting with PDR and vision-impairing DME, but not for those with PDR without vision-impairing DME.[337]

An evaluation of the incremental cost-effectiveness ratios of aflibercept, BVZ, and RBZ for the treatment of DME[338] concluded that aflibercept (2.0 mg) and RBZ (0.3 mg) are not cost-effective relative to BVZ for treatment of DME unless their prices decrease substantially.

Patients with DME receiving anti-VEGF therapy in a clinical practice setting may undergo less frequent monitoring and intravitreous injections and achieve inferior vision outcomes compared to patients in clinical trials.[339]

EVIDENCE-BASED ACTION STATEMENT: Patients with central-involved diabetic macular edema (DME) should be referred to an ophthalmologist experienced in the management of diabetic retinal disease for treatment with anti-VEGF agents and/or subsequent or deferred focal/grid macular laser therapy.[65,69,71,72,74,75,77,82,298,300,311,313-317,319-324,327,329]

Evidence Quality: Grade A. Randomized Clinical Trials, Systematic Reviews, Cohort-prospective Studies, Cohort-retrospective Study, Case Series

Level of Confidence: High

Clinical Recommendation Strength: Strong Recommendation. This recommendation should be followed unless clear and compelling rationale for an alternative approach is present.

Evidence Statements: Clinical studies to evaluate the efficacy of aflibercept, bevacizumab (BVZ), or ranibizumab (RBZ) for the treatment of central-involved DME have concluded that all three agents improved vision and were equally or more effective than focal/grid photocoagulation or sham treatment.[65,74,298,300,314-316,317,319,320,321,324] (All Evidence Grade: A)[322,327,329] (All Evidence Grade: B)

A study of long-term outcomes of ranibizumab (RBZ) injections given as needed based on functional and anatomical responses for 48 months in an ordinary clinical setting reported a substantial and continuous visual benefit in patients with DME.[313] (Evidence Grade: C)

Patients with DME who have early response (after one injection) to anti-VEGF treatment by reduction in central retinal thickness will have significant response to treatment by three months.[311] (Evidence Grade: D)

In eyes with initial visual acuity of 20/40 or better at baseline, there was no significant difference among aflibercept, bevacizumab (BVZ), or ranibizumab (RBZ) for the treatment of central-involved DME. In eyes with 20/50 visual acuity or worse, aflibercept provided greater average gains in visual acuity compared to BVZ and RBZ.[71] (Evidence Grade: A) [75] (Evidence Grade: A) [77] (Evidence Grade: B) [82] (Evidence Grade: A)

Most eyes treated with ranibizumab (RBZ) and either prompt or deferred laser maintain vision gains obtained by the first year through five years with little additional treatment after three years.[72] (Evidence Grade: A)

The use of focal/grid laser treatment at the time of initiation of intravitreous RBZ is not better, and possibly worse, for vision outcomes than deferring laser treatment for 24 weeks or more in eyes with DME involving the fovea.[69] (Evidence Grade: A)

Patients treated with RBZ experienced fewer complications such as vitreous hemorrhage and fewer developed proliferative diabetic retinopathy (PDR) or underwent panretinal photocoagulation (PRP).[323] (Evidence Grade: A)

Potential Benefits: Preservation of vision	**Potential Risks/Harms:** Complications from intravitreous injections or laser treatment

Benefit and Harm Assessment: Benefits significantly outweigh harms

Potential Costs: Direct cost of treatment

Value Judgments: None

Role of Patient Preferences: Moderate

Intentional Vagueness: None

Gaps in Evidence: None identified

Intraocular Steroids

The DRCR.net (Protocol B) study evaluated the efficacy and safety of 1 mg and 4 mg doses of intravitreous triamcinolone acetonide (IVTA) in comparison with focal/grid photocoagulation for the treatment of DME. Focal/grid photocoagulation was found to be more effective with respect to both visual acuity and OCT-measured retinal thickening and has fewer side effects, particularly elevation of intraocular pressure (IOP) and lens changes, than IVTA for most patients with DME at two-[62] (Evidence Grade: A) and three-year follow-ups.[80]

In the DRCR.net (Protocol I) study, IVTA combined with prompt focal/grid laser therapy was reported to be equally effective as RBZ monotherapy at improving visual acuity and reducing retinal thickening in pseudophakic persons, but was less effective in those who had not had cataract surgery.[65] (Evidence Grade: A)[68] (Evidence Grade: A) In addition, the treatment effects wane and patients require repeated injections that increase the risk of glaucoma and cataract development.

Some eyes have persistent DME following anti-VEGF therapy for DME. Subsequently, adding intravitreous corticosteroids to the treatment regimen was studied to determine if it might result in better outcomes than continued anti-VEGF therapy alone. Although its use is more likely to reduce retinal thickness and increase IOP, the addition of intravitreous dexamethasone implant to continued RBZ therapy did not improve visual acuity at 24 weeks more than continued RBZ therapy alone among eyes with persistent DME following anti-VEGF therapy.[340] (Evidence Grade: A)

Results of a meta-analysis of studies that evaluated the efficacy of IVTA for the treatment of DME refractory to laser photocoagulation reported a temporary improvement of visual acuity in patients with DME, with a peak benefit of approximately three lines of visual acuity one month post injection.[302] (Evidence Grade: A)

A study evaluating the efficacy of combined BVZ-IVTA injection in the treatment of DME compared to monotherapy found mono- or combination therapy was effective for DME treatment. No synergistic effects were observed; however, triamcinolone alone or a drug combination may reduce the number of injections required when compared to BVZ alone.[341] (Evidence Grade: B)

The use of IVTA is associated with a substantial risk of adverse events. In particular, the risk of elevated IOP and the rates of visually significant cataracts were substantially higher compared to eyes receiving focal/grid laser treatment.[62] (Evidence Grade: A)[342] As a result of these potential side effects, the use of corticosteroids for the treatment of DME has become more of a second line therapy.

Intravitreous steroid implants provide low dose delivery that may avoid or reduce the complications resulting from repeat injections of IVTA and may have a more sustained effect; however, they also increase the risk of cataract progression and elevated IOP.[301] Intravitreous treatment with dexamethasone implant has been shown to safely reduce DME and improve visual acuity in difficult to treat and long-standing DME.[343,344] In addition, one injection of dexamethasone was found to provide anatomical and functional effectiveness for the treatment of DME as reported in a six-month study. Side effects were reported to be rare and manageable.[345] (Evidence Grade: B)

Clinical note: *Intraocular pressure (IOP) should be monitored for persons receiving treatment with intraocular steroids.*

A study to assess the long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for DME found that both low- and high-dose inserts significantly improved BCVA in patients with DME over two years, and the risk-to-benefit ratio was superior for the low-dose insert.[346] (Evidence Grade: A)

In patients with diffuse DME, sustained release drug delivery with dexamethasone intravitreous implant in combination with laser therapy was found to reduce vascular leakage and retinal edema and improve visual acuity more than laser surgery at one month and nine months, but the difference was not statistically significant at twelve months.[347] (Evidence Grade: A)

A study evaluating the long-term anatomical and functional outcomes in patients with DME treated with intravitreous dexamethasone implant reported it to be a safe and effective treatment for DME in patients' refractory to previous anti-VEGF injections. There was a mean improvement of 5.2 letters at the end of follow-up, while 87 percent of the patients presented an improvement in or stabilization of visual acuity. Total resolution of DME was observed in 57.4 percent of patients at twelve months;[348] (Evidence Grade: B) however, cataract development or progression is probable with dexamethasone implants. Prompt diagnosis and cataract extraction are needed for optimal visual outcomes.[349] (Evidence Grade: B)

EVIDENCE-BASED ACTION STATEMENT: Persons who experience persistent diabetic macular edema (DME) following laser and/or anti-vascular endothelial growth factor (anti-VEGF) therapy for DME should be referred to an ophthalmologist experienced in the management of diabetic retinal disease for possible treatment with intraocular steroids.[62,65,302,345,346,348]

Evidence Quality: Grade A. Randomized Clinical Trials, Systematic Review, Cohort-prospective Studies

Level of Confidence: High

Clinical Recommendation Strength: Strong Recommendation. This recommendation should be followed unless clear and compelling rationale for an alternative approach is present.

Evidence Statements: Intravitreous triamcinolone acetonide (IVTA) combined with prompt focal/grid laser therapy was reported to be equally effective as ranibizumab monotherapy at improving visual acuity and reducing retinal thickening in pseudophakic persons, but was less effective in those who had not had cataract surgery.[65] (Evidence Grade: A)

The use of IVTA injections and intraocular corticosteroid sustained-release drug delivery systems for the treatment of DME have been shown effective in decreasing macular thickness and improving visual acuity. Results of a meta-analysis of studies that evaluated the efficacy of IVTA for the treatment of DME refractory to laser photocoagulation reported a temporary improvement of visual acuity, with a peak benefit of approximately three lines of visual acuity one month post injection.[302] (Evidence Grade: A)

An evaluation of the efficacy and safety of 1 mg and 4 mg doses of IVTA in comparison with focal/grid photocoagulation for the treatment of DME found focal/grid photocoagulation to be more effective with respect to both visual acuity and retinal thickening and has fewer side effects, particularly elevation of intraocular pressure and lens changes, than IVTA for most patients with DME at two years.[62] (Evidence Grade: A)

Intravitreous treatment with dexamethasone implant has been shown to safely reduce DME and improve visual acuity in difficult to treat and long-standing DME. One injection of dexamethasone was found to provide anatomical and functional effectiveness for the treatment of DME as reported in a six-month study and side effects were reported to be rare and manageable.[345] (Evidence Grade: B)

A study to evaluate the long-term anatomical and functional outcomes in patients with DME treated with intravitreous dexamethasone implant reported it to be a safe and effective treatment for DME in patients' refractory to previous anti-VEGF injections.[348] (Evidence Grade: B)

An assessment of the long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for DME found that both low- and high-dose inserts significantly improved best corrected visual acuity in patients with DME over two years, and the risk-to-benefit ratio was superior for the low-dose insert.[346] (Evidence Grade: A)

Potential Benefits: Preservation of vision	**Potential Risks/Harms:** Development of cataracts and increased intraocular pressure, complications of intravitreous injections

Benefit and Harm Assessment: Balance of benefits and harms

Potential Costs: Direct cost of treatment

Value Judgments: None

Role of Patient Preferences: Moderate

Intentional Vagueness: None

Gaps in Evidence: None identified

Vitrectomy

Vitrectomy is a treatment option for patients with severe complications from diabetic retinopathy. It is used for treating vitreous hemorrhage and PDR with non-clearing vitreous hemorrhage or fibrosis, areas of traction threatening the macula, and persistent DME with vitreous traction.[303]

Vitrectomy performed for DME and vitreomacular traction can result in a reduction in macular thickening and has been shown to improve vision with a low surgical complication rate;[66] (Evidence Grade: B) however, the role of vitrectomy compared with other approaches in the management of DME remains uncertain as the potential benefits and risks have not been clearly defined by long-term, adequately-sized randomized clinical trials.[304] (Evidence Grade: B) There is little evidence to support the use of vitrectomy as an intervention for DME in the absence of epiretinal membrane or vitreomacular traction. Although vitrectomy appears to be superior to laser in its effects on retinal structure at six months, no such benefit has been proved at twelve months. Furthermore, there is no evidence to suggest a superiority of vitrectomy over laser in terms of functional outcomes.[305] (Evidence Grade: B)

In a randomized clinical trial evaluating RBZ or saline for vitreous hemorrhage from PDR, vitrectomy rates were lower than expected in both groups. This study suggested little likelihood of a clinically important difference between RBZ and saline on the rate of vitrectomy by sixteen weeks in eyes with vitreous hemorrhage from PDR. Short-term secondary outcomes including visual acuity improvement, increased PRP completion rates, and reduced recurrent vitreous hemorrhage rates suggest biologic activity of RBZ. Long-term benefits remain unknown.[70] (Evidence Grade: A)

EVIDENCE-BASED ACTION STATEMENT: Persons with vitreous hemorrhage, traction retinal detachment, macular traction, or an epiretinal membrane should be referred to an ophthalmologist experienced in the management of diabetic retinal disease for possible vitrectomy.[66,304,305]
Evidence Quality: Grade B. Systematic Review, Cohort-prospective Studies **Level of Confidence:** Medium **Clinical Recommendation Strength:** Recommendation. This recommendation should generally be followed, but remain alert for new information.
Evidence Statements: Vitrectomy performed for diabetic macular edema (DME) and vitreomacular traction has been shown to improve vision with a low surgical complication rate.[66] (Evidence Grade: B) Vitrectomy can result in a reduction in macular thickening[66] and can improve visual acuity in DME when the pre-operative acuity is <20/80 and there is an epiretinal membrane or vitreoretinal adhesion.[304] (Evidence Grade: B) There is little evidence to support the use of vitrectomy as an intervention for DME in the absence of epiretinal membrane or vitreomacular traction. Furthermore, there is no evidence to suggest a superiority of vitrectomy over laser in terms of functional outcomes.[305] (Evidence Grade: B)
Potential Benefits: Preservation of vision / **Potential Risks/Harms:** Complications from vitrectomy surgery
Benefit and Harm Assessment: Benefits significantly outweigh harms
Potential Costs: Direct cost of treatment
Value Judgments: None
Role of Patient Preferences: Large
Intentional Vagueness: None
Gaps in Evidence: None identified

At the time of publication of this guideline, there are other diagnostic and treatment developments that do not have sufficient evidence to form clinical recommendations. It is anticipated that with time there will be evidence to include them in future guidelines.

4. Prognosis and Follow-Up

Disability and premature death are not inevitable consequences of diabetes.[20] Lifestyle and behavioral modification and pharmacotherapy can delay progression to type 2 diabetes among persons with prediabetes;[112] (Evidence Grade: A) however, all patients with diabetes mellitus are at risk for the development of ocular-related complications. Adherence to treatment recommendations to maintain optimal control of blood glucose levels is a substantial factor in slowing the development and progression of complications of diabetes.

Studies indicate that the rates of progression to PDR and severe vision loss are substantially lower, especially in patients with type 1 diabetes, than reported thirty or more years ago. These findings may be due to improvements in the management of risk factors (hyperglycemia, hypertension and hyperlipidemia) and overall diabetes care, along with earlier identification of diabetes.[350] Regular eye examinations can identify diabetic retinopathy before it causes

visual loss. Epidemiological studies have shown that the major predictors of retinopathy progression are the presence and severity of retinopathy at the time of the patient's initial eye examination.[351]

Appropriate communication with the patient's primary care physician (as with any referral consultant) is critical for proper coordination of the patient's care. Due to the nature of diabetes, a multidisciplinary approach to patient management of individuals with diabetes is essential. All health care personnel involved with an individual's care should be aware of his or her overall medical status. Written letters or reports are useful in accomplishing this task. These letters also provide permanent documentation for the patient's record.

5. Quality of Life

Individuals with diabetic retinopathy may have a measurable decline in health-related quality of life early in the disease process. This decline is much greater and more rapid in persons with bilateral moderately severe NPDR, or worse compared with those with no diabetic retinopathy or less severe diabetic retinopathy;[352] therefore, it is important to also consider psychological and emotional support for patients with diabetes mellitus, especially those with longer diabetes duration or diabetes complications, to maximize the effectiveness of diabetes education. Diabetes "burn-out" or diabetes-related stress influences patient self-care behaviors.[353] Special care is also indicated in counseling children and elderly patients. Their risks and benefits may be different; therefore, as with all patients, the discussion and instruction should be individualized.

The National Eye Institute 25 Item Visual Function Questionnaire (NEI VFQ-25) is a health-related quality of life instrument designed to measure vision-related function and the influence of vision problems on performance of daily activities. The NEI VFQ-25 near and distance activities subscales demonstrate utility as measures of central vision function in persons with type 1 and type 2 diabetes. Low scores on the NEI VFQ-25 may reflect poor central visual fields and contrast sensitivity in addition to poor visual acuity.[354] (Evidence Grade: D) Loss of visual acuity is the most important factor related to negative changes in the NEI VFQ-25 scores in individuals with type 1 diabetes.[355] (Evidence Grade: B)

Vision-related quality of life is also influenced strongly by nonvisual factors, particularly physical and mental health.[356] The fear of vision loss associated with diabetic retinopathy can result in a high level of anxiety for any individual with diabetes, and for their family members, regardless of the level of visual impairment.[357,358] Even those without retinopathy or other ocular complications may have personal concerns about diabetes (e.g., problems accepting the disease, adapting to it, and adjusting to emotional and social changes). An early counseling visit may be beneficial for a family with a child who has diabetes.

B. ACCESS, EDUCATION, AND COMMUNICATION

1. Telehealth Programs

The use of telehealth programs for delivering health care is increasing and has the potential to address disparities related to access by overcoming barriers of distance, time, and possibly expense.[359] Ocular telehealth programs can be an integral component of primary care for patients with diabetes and can increase access and adherence to demonstrated standards of care.[360]

Studies across multiple populations demonstrate that the prevalence of blindness and visual impairment among patients with diabetes is lowest among populations with a national program that provides retinal evaluations for all patients with diabetes.[361-363] Telehealth programs have been largely used in these initiatives and rely on the digital capture and transmission of standardized ocular images and patient health information for interpretation and evaluation by trained observers who can generate a treatment and care plan.[360]

Diabetic retinopathy telehealth programs in remote and resource-poor settings using imagers without specialist medical or eye qualifications have been shown to be an effective alternative to onsite examinations; however, they

yield a significantly greater false positive rate than telehealth programs involving imagers with specialist medical or eye qualifications, particularly when mydriasis is not used.[364] (Evidence Grade: A) In addition, diabetic retinopathy telehealth programs are not likely to be successful without incorporation of eye health education initiatives that promote adherence to recommended comprehensive eye care for preventing vision loss.[365] (Evidence Grade: B)

Artificial intelligence (AI)-based grading systems have been studied for screening fundus photographs obtained from patients with diabetes and show high sensitivity and specificity for detecting referable diabetic retinopathy;[366] (Evidence Grade: B),[367] (Evidence Grade: B) however, further research is necessary to determine the feasibility of applying an algorithm in the clinical setting and to determine whether its use could lead to improved care and outcomes compared with current methods of assessment.[368] The FDA has authorized the use of an AI-based system for detecting more than mild diabetic retinopathy and DME in primary care offices.[369] Primary care clinics could use telehealth programs to triage and monitor patients for diabetic retinopathy. When patients are offered both traditional and telehealth diabetic monitoring examinations, approximately 30 percent will use only telehealth programs.[370] (Evidence Grade: A)

Ocular telehealth programs for diabetic retinopathy have the potential to deliver economical, high quality eye care locally, nationally, and internationally;[371,372] (Evidence Grade: C) however, telehealth-based retinal evaluations are not a substitute for a comprehensive eye examination, which should be performed at least initially and at intervals thereafter as recommended by an eye care professional.[106,373] While telehealth programs using digital imaging are not a replacement for a comprehensive eye examination, with advancements in technology, their usage may be a cost effective way of monitoring eye care for persons with diabetic retinopathy or DME.[374] (Evidence Grade: D)

EVIDENCE-BASED ACTION STATEMENT: Ocular telehealth programs for diabetic retinopathy can be used to increase access to evaluation, educate patients, and promote appropriate follow-up and treatment, but they are not a replacement for a comprehensive eye examination.[364,365,370,372,374]

Evidence Quality: Grade B. Randomized Clinical Trial, Meta-analysis, Cohort-prospective Study, Cohort-retrospective Study, Review
Level of Confidence: Medium
Clinical Recommendation Strength: Strong Recommendation. This recommendation should be followed unless clear and compelling rationale for an alternative approach is present.

Evidence Statements: Diabetic retinopathy telehealth programs in remote and resource-poor settings using imagers without specialist medical or eye qualifications have been shown to be an effective alternative to onsite examinations; however, they yield a significantly greater false positive rate than telehealth programs involving imagers with specialist medical or eye qualifications, particularly when mydriasis is not used.[364] (Evidence Grade: A)

Telehealth programs can increase the percentage of persons receiving diabetic retinopathy surveillance examinations, at least initially. When patients are offered both traditional and telemedicine diabetic monitoring examinations, approximately 30 percent will use only telehealth programs.[370] (Evidence Grade: A)

Diabetic retinopathy telehealth programs are not likely to be successful without incorporation of eye health education initiatives that promote adherence to recommended comprehensive eye care for preventing vision loss.[365] (Evidence Grade: B)

Telehealth has the potential to deliver economical, high quality eye care locally, nationally and internationally.[372] (Evidence Grade: C)

Telehealth programs using digital imaging are not a replacement for a comprehensive eye examination, but with advancements in technology, their usage may be a cost effective way of monitoring eye care for persons with diabetic retinopathy or diabetic macular edema.[374] (Evidence Grade: D)

Potential Benefits: Increased access to care, preservation of vision	**Potential Risks/Harms:** Persons may mistakenly confuse telehealth screening with a comprehensive eye examination

Benefit and Harm Assessment: Benefits equal harms

Potential Costs: Costs of testing

Value Judgments: None

Role of Patient Preferences: Moderate

Intentional Vagueness: None

Gaps in Evidence: None identified

2. Patient Education and Counseling

The vast majority of persons with diabetes will develop diabetic retinopathy at some point during the course of the disease; therefore, it is important for them to learn about the disease process and the risks for developing ocular complications from diabetes, which may result in vision loss. Individuals need to be aware that retinopathy may exist even when vision is good and there is an absence of any symptoms.

Clinical note: *A patient-centered communication style that uses active listening, elicits patient preferences and beliefs, and assesses potential literacy barriers to care can be used to optimize patient health outcomes.*

Patients should be encouraged to report all ocular symptoms (e.g., blurred vision, flashes, floaters). Doctors of optometry should help their patients understand that timely follow-up examinations and management are critical for early diagnosis and intervention, when indicated, to reduce the risk of vision loss from diabetic retinopathy. Individuals should also be informed about their higher risk for other nonretinal ocular complications, such as cataracts and glaucoma, and informed about available optometric vision rehabilitation care to address loss of visual function.

CONSENSUS-BASED ACTION STATEMENT: Persons with diabetes should be educated about the ocular signs and symptoms of diabetic retinopathy and other nonretinal ocular complications of diabetes, and encouraged to comply with recommendations for follow-up eye examinations and care.
Evidence Quality: There is a lack of published research to support or refute the use of this recommendation.
Benefit and Harm Assessment: Implementation of this recommendation is likely to result in increased adherence to recommendations for regular eye care. The benefits of this recommendation were established by expert consensus opinion.

Individuals should also be encouraged to participate in diabetes self-management education programs. Despite substantial improvement in recent years, achievement of the diabetes ABCs recommendations (A1C, blood pressure, cholesterol, smoking cessation) remains suboptimal among adults, particularly in some minority groups (Mexican Americans and non-Hispanic Blacks). Substantial opportunity exists to further improve diabetes control and, thus, to reduce diabetes-related morbidity and mortality.[375]

A structured, group-based educational program focusing on self-management can further improve A1C levels, even in patients who are well controlled and should be part of routine care for patients with diabetes.[376] (Evidence Grade: B) In addition, an active-learning team-based empowerment approach to diabetes education can lead to greater understanding and knowledge retention.[377] (Evidence Grade: B) Intensive diabetes education, defined as adoption of behaviors that allow for active engagement in diabetes self-management, is more effective in bringing about lifestyle behavior modification and glycemic control in newly or recently diagnosed patients with diabetes as compared to outcomes for patients with a longer duration of diabetes prior to education.[353] (Evidence Grade: B)

Studies show that most lifestyle education and diabetes self-management programs that involve eleven or more contact hours can lead to clinically important improvement in glycemic control; however, these programs seem to benefit persons with suboptimal glycemic control more than those with good control.[378] (Evidence Grade: A) The effects of lifestyle counseling were particularly pronounced in patients who were counseled at least once a month;[379] (Evidence Grade: A) however, the benefit may decline over one to three months after the intervention ceases, suggesting that learned behaviors change over time.[380] (Evidence Grade: A)

In rural areas, the distance from health care providers and educational classes may make access to educational programs difficult; therefore, education needs to be tailored to the needs of the specific population and provided in a culturally competent manner. Motivational counseling should also be included to encourage and empower patients to take control of their lives and the disease process and make informed choices.[381] (Evidence Grade: B)

EVIDENCE-BASED ACTION STATEMENT: Patients with diabetes should be encouraged to participate in lifestyle education and diabetes self-management programs.[353,376-381]

Evidence Quality: Grade B. Randomized Clinical Trial, Systematic Reviews, Cohort-prospective Study, Case Control Study

Level of Confidence: Medium

Clinical Recommendation Strength: Recommendation. This recommendation should generally be followed, but remain alert for new information.

Evidence Statements: Most lifestyle education and diabetes self-management programs that involve eleven or more contact hours can lead to clinically important improvement in glycemic control; however, these programs seem to benefit persons with suboptimal glycemic control more than those with good control.[378] (Evidence Grade: A)

The effects of lifestyle counseling were particularly pronounced in patients who were counseled at least once a month;[379] (Evidence Grade: A) however, the benefit may decline over one to three months after the intervention ceases, suggesting that learned behaviors change over time.[380] (Evidence Grade: A)

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An active-learning team-based empowerment approach to diabetes education can lead to greater understanding and knowledge retention.[377] (Evidence Grade: B)

Potential Benefits: Better management of diabetes	**Potential Risks/Harms:** None

Benefit and Harm Assessment: Benefits significantly outweigh harms

Potential Costs: Time for counseling

Value Judgments: None

Role of Patient Preferences: Large

Intentional Vagueness: None

Gaps in Evidence: None identified

Electronic personal health records (PHRs), which provide the opportunity for individuals to access, manage, and share their health information in a confidential environment, have the potential to empower patients in self-management of chronic diseases like diabetes. PHRs can include patient-doctor communications, patient education materials, and web-based resources. There is evidence to support better health outcomes of persons with diabetes who access and engage with their PHR. Frequency of use does not appear to be a factor.[382] (Evidence Grade: B)

Automated telephone communication systems can also be used to deliver voice messages and collect health-related information from patients using either their telephone's touch-tone keypad or voice recognition software. These types of interventions for persons with diabetes may have a small effect on their health behaviors, as compared with usual or no calls.[383] (Evidence Grade: A)

Improved A1C control is associated with more effective communication between health care providers and their patients who have type 2 diabetes.[384] Providing patients with personalized clinical information during a consultation can increase their involvement and make them more likely to take the lead in discussing aspects of their diabetes care without significantly increasing the length of the consultation.[385] (Evidence Grade: C)

There is also a clear need to increase the frequency of smoking cessation counseling for patients with diabetes, given the association between smoking and diabetes complications.[386] Cigarette smoking is thought to be a modifiable risk factor for the development of cardiovascular disease in persons with type 2 diabetes mellitus;[387] however, its relationship with microvascular complications, including diabetic retinopathy, may be more limited.[388]

Systematic reviews of studies assessing the association between smoking and incidence of diabetes have concluded that active and passive smoking are associated with an increased risk of type 2 diabetes.[389] (Evidence Grade: A)[390] (Evidence Grade: A) A meta-analysis of observational studies in Japan found that current smoking is associated with an increased risk of type 2 diabetes mellitus and although the risk of diabetes remains high after short-term smoking cessation, the risk decreases substantially in the long run.[391] (Evidence Grade: A) National Health and Nutrition Examination Survey data also provide some evidence that early onset smoking increases type 2 diabetes risk among men in the United States and South Korea and type 2 diabetes risk increases with higher pack-years in men in the United States.[392] (Evidence Grade: D) In the Multi-Ethnic Study of Atherosclerosis, there was no consistent association found between tobacco use and insulin resistance or the development of type 2 diabetes.[393] (Evidence Grade: B) This finding seems to indicate that the role smoking plays in causing diabetes may be more complicated than originally thought and warrants more study.

EVIDENCE-BASED ACTION STATEMENT: Individuals should be advised by their health care providers of the risks of smoking and encouraged to quit smoking and/or seek smoking cessation assistance.[389-392]
Evidence Quality: Grade A. Systematic Reviews, Cross-sectional Study **Level of Confidence:** High **Clinical Recommendation Strength:** Strong Recommendation. This recommendation should be followed unless clear and compelling rationale for an alternative approach is present.
Evidence Statements: Systematic reviews of studies assessing the association between smoking and incidence of type 2 diabetes have concluded that active and passive smoking are associated with an increased risk of type 2 diabetes.[389] (Evidence Grade: A)[390] (Evidence Grade: A) A meta-analysis of observational studies in Japan found that current smoking is associated with an increased risk of type 2 diabetes mellitus and although the risk of diabetes remains high after short-term smoking cessation, the risk decreases substantially in the long run.[391] (Evidence Grade: A) National Health and Nutrition Examination Survey data provides some evidence that early onset smoking increases type 2 diabetes risk among men in the United States and South Korea and type 2 diabetes risk increases with higher pack-years in men in the United States.[392] (Evidence Grade: D)

Potential Benefits: Improved overall health and reduced risk for diabetes	**Potential Risks/Harms:** None

Benefit and Harm Assessment: Benefits significantly outweigh harms
Potential Costs: Time for counseling
Value Judgments: None
Role of Patient Preferences: High
Intentional Vagueness: None
Gaps in Evidence: None identified

3. Interdisciplinary Collaboration and Communication

The use of a patient-centered interprofessional team approach to providing supportive care for people with diabetes can help reduce risk factors for type 2 diabetes, improve diabetes management, and lower the risk for chronic complications.[394] (Evidence Grade: D) Collaboration and communication are of crucial importance among all providers in helping patients to manage their diabetes and take the needed steps to lower their risk of complications. Optometrists, as well as dentists, podiatrists, and pharmacists, are well positioned to deliver key diabetes prevention and management messages, communicate the need for metabolic control, and encourage patients with diabetes to seek appropriate care.

Steps doctors of optometry can take include:

- Getting to know other providers in their community and creating a referral network for preventive and urgent care needs

- Educating patients with diabetes about maintaining a healthy weight, getting moderate-intensity physical exercise, avoiding smoking, and encouraging self-monitoring of blood pressure
- Reminding patients at each encounter of the risk of developing diabetes-related complications, especially as they relate to their eyes and vision.

(See Working Together to Manage Diabetes: A Toolkit for Pharmacy, Podiatry, Optometry and Dentistry https://www.cdc.gov/diabetes/ndep/toolkits/ppod.html for more information)

C. MANAGEMENT OF PERSONS WITH VISUAL IMPAIRMENT

Vision plays an important role in the ability of people to participate in everyday activities such as reading, working, walking, driving, and interacting with others. As the population increases and ages, vision loss from diabetic retinopathy and DME will also increase.[395] (Evidence Grade: A) Approximately 11 percent of adults in the United States with diabetes have some form of visual impairment.[396] They can face challenges in managing their diabetes and completing many other activities of daily living, which may lead to depression, anxiety, social isolation, and difficulties at home, in school, or at work.[352]

Diabetic retinopathy ranks as the fifth most common cause of global blindness and moderate and severe vision impairment.[178] Common visual impairments associated with diabetic retinopathy include:

- Reduced central visual acuity affecting near, intermediate, and distance visual function
- Central or para-central scotoma from diabetic maculopathy
- Loss of peripheral and mid-central visual field, secondary to retinal ischemia or PRP
- Reduced dark adaptation and increased lag times in seeing in dim light
- Difficulty with glare
- Vision loss resulting from VH, PRH, or traction retinal detachment
- Decreased contrast sensitivity.

In addition, important functional sequelae of diabetes-related vision loss can include:

- Inability to self-manage diabetes care, including monitoring of blood glucose
- Difficulty with addressing dietary, medical, and other health-related issues
- Difficulty with other health care tasks (such as checking feet and trimming nails)
- Loss of, or restriction in, driver's license and subsequent limitations on independent transportation
- Inability to maintain wellness and comply with preventive health measures.

Persons with diabetes-related vision loss should be evaluated to determine their potential to benefit from comprehensive vision rehabilitation. This process provides the only currently available treatment option for patients with chronic vision loss. Vision rehabilitation can help individuals with vision loss attain maximum function, independence, and quality of life.

Individuals with diabetes are at increased risk of chronic vision loss, subsequent functional impairment, and resultant disability. Visual impairment has physical, psychological, behavioral, and social consequences that affect patients, their family, friends, and caregivers. Health care providers and stakeholders may be unaware of the overall impact of vision loss on the health and well-being of the patient.

The Veterans Affairs model for treatment of vision impairment has demonstrated effectiveness in patients with vision impairment resulting from macular diseases. Outpatient low vision rehabilitation services provided for veterans significantly improved the functional visual ability of patients moderately and severely impaired by low vision. The

Veterans Affairs model involves at least 10 hours of low-vision therapy, including a home visit and assigned homework to encourage practice, for patients with moderate and severe vision loss from macular diseases.[397]

CONSENSUS-BASED ACTION STATEMENT: Persons who experience vision loss from diabetes should be counseled on the availability and scope of vision rehabilitation care and provided, or referred for, a comprehensive examination of their visual impairment by a practitioner trained or experienced in vision rehabilitation.
Evidence Quality: There is a lack of published research to support or refute the use of this recommendation.
Benefit and Harm Assessment: Implementation of this recommendation is likely to enhance visual abilities and quality of life for individuals suffering from vision loss due to diabetes. The benefits of this recommendation were established by expert consensus opinion.

The burden of managing a chronic disease like diabetes for a visually impaired individual can be demanding. One way of improving health in visually impaired individuals with diabetes could be the use of patient empowerment programs to increase their feelings of control and power. Those persons who experience power, based upon their knowledge, values, situation, self-efficacy, and improved metabolic control, report better emotional and general health.[398] (Evidence Grade: D)

CONSENSUS-BASED ACTION STATEMENT: Referral for counseling is indicated for any individual experiencing difficulty dealing with vision and/or health issues associated with diabetes or diabetic retinopathy. Educational literature and a list of support agencies and other resources should be made available to these individuals.
Evidence Quality: There is a lack of published research to support or refute the use of this recommendation.
Benefit and Harm Assessment: Implementation of this recommendation is likely to assist individuals in handling any emotional or psychological difficulties associated with diabetes-related complications. The benefits of this recommendation were established by expert consensus opinion.

D. MANAGEMENT OF HYPOGLYCEMIA

Intensive glycemic control increases the risk of hypoglycemia (a plasma glucose level below 70 mg/dL) by 30 percent compared to conventional glycemic control.[399] (Evidence Grade: A) The classic symptoms of hypoglycemia are hunger, shakiness, nervousness, confusion, sweating, or weakness.[400] While hypoglycemia is more common in type 1 diabetes, the incidence is also high in type 2 patients who use insulin or secretagogues, particularly persons with longer duration of diabetes.[401]

To help identify persons experiencing hypoglycemia, the optometric office staff should be alert for neuroglycopenic symptoms such as slow cognitive response, light-headedness, sleepiness, confusion, difficulty speaking, and anxiety. It may be prudent for doctors of optometry offices to maintain a blood glucose meter and single use lancet devices for confirming hypoglycemia and its resolution, where state laws permit.

The treatment of a hypoglycemic episode may include the following steps:[401,402]

1. Check blood glucose to confirm hypoglycemia (blood glucose <70 mg/dL).
2. Treat mild or moderate hypoglycemia (54-70 mg/dL) by giving 15-20 g of simple carbohydrates orally as immediate treatment. Options include 4 oz of fruit juice, 5 to 6 oz regular soda, 1 tablespoon of table sugar or honey, 2 tablespoons of raisins, or 3 to 4 glucose tablets. If initial blood glucose is ≤54 mg/dL, give 20-30 g of simple carbohydrates.
3. Re-check blood glucose after 15 minutes. If blood glucose does not return to normal range, repeat the treatment (step 2) until blood glucose returns to at least 90 mg/dL.
4. Provide a snack, if the patient's next meal is more than one hour away, such as 6 saltine crackers, 3 graham cracker squares, or 1/2 peanut butter sandwich. Further glucose monitoring may be necessary.
5. Dial 911, if patient is unconscious. Treat with glucagon and/or intravenous glucose, if it is available in the office.
6. When patient is alert enough to swallow, give fruit, fruit juice, or sugar-sweetened soda immediately and follow steps 2 to 4.

Clinical note: *Doctors of optometry should have a rapid-acting carbohydrate (e.g., glucose gel or tablets, sugar-sweetened beverage, or fruit juice) in their office for use by patients with diabetes who experience acute hypoglycemia during an eye examination.*

E. CONCLUSION

Vision impairment from diabetes is a significant public health problem which affects the health, economic well-being, and productivity of individuals, families, and society as a whole. Good vision is vital to persons with diabetes in order to retain their independence and manage their disease. Steps to prevent visual impairment in persons with diabetes include optimal glycemic control, the treatment of ancillary risk factors such as obesity, hypertension, and high cholesterol levels, and ongoing comprehensive eye examinations for the early detection and, when needed, treatment of eye and vision problems.

All persons with diabetes should be informed of the possibility of developing retinopathy or other nonretinal ocular complications, with or without symptoms, and of the associated threat of vision loss. The natural course and treatment of diabetic retinopathy should be discussed with the person, and the importance of lifelong eye examinations should be stressed. They should be made aware of the benefits of early diagnosis and available treatment options in preserving vision. In addition, they should be advised of the availability of vision rehabilitation services to address functional vision issues and provided with referral or treatment for diabetes-related vision loss.

Until therapies are available to prevent or cure diabetic retinopathy and other ocular complications of diabetes, emphasis must be placed on diagnosis, careful follow-up, and timely treatment. Doctors of optometry may be the first to examine persons with signs of diabetes or diabetic retinopathy; therefore, they have a key role in identifying individuals with undiagnosed diabetes and reinforcing the importance of diabetes control and appropriate follow-up care to lower the risk for vision loss.

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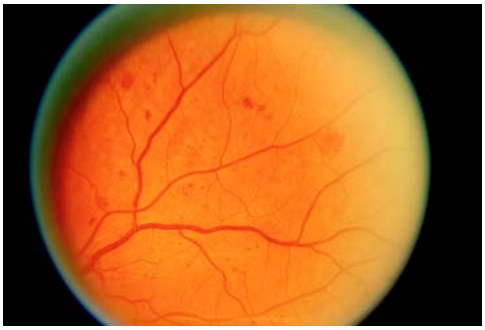
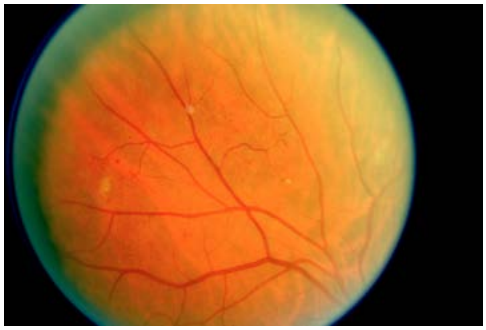
VII. APPENDICIES

Appendix 1
Selected Airlie House Classification of Diabetic Retinopathy Standard Photographs

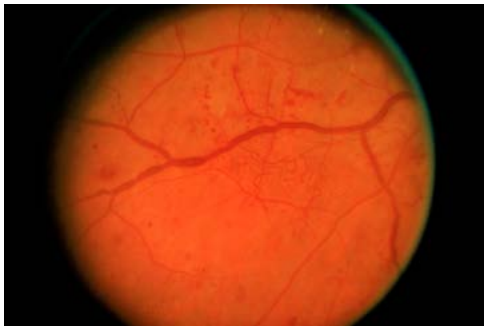
Standards for nonproliferative diabetic retinopathy lesions



Standard Photo 2A
Severe hemorrhages and/or microaneurysms

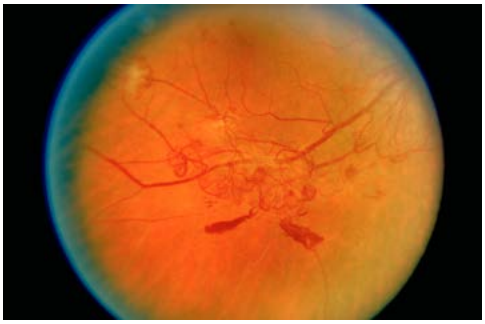


Standard Photo 8A
Severe intraretinal microvascular abnormalities

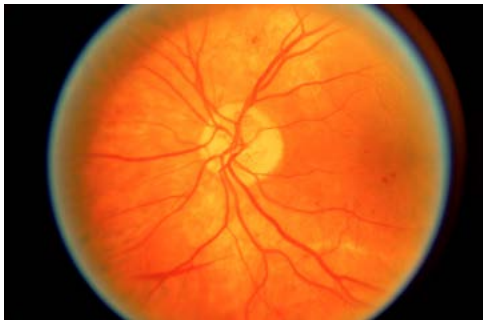


Standard Photo 6B
Severe venous beading

Standards for proliferative diabetic retinopathy lesions



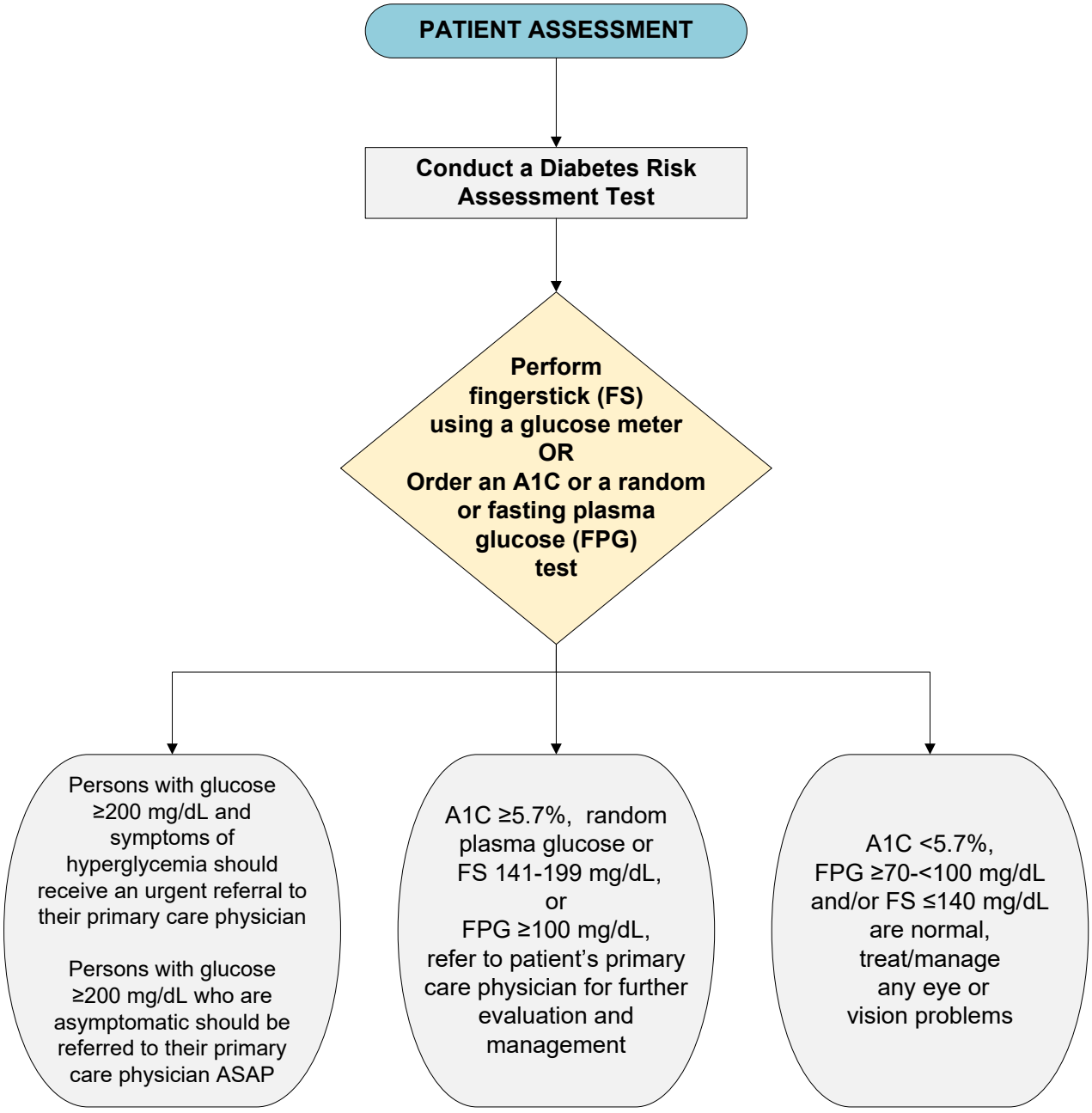
Standard Photo 7
New vessels on the retina



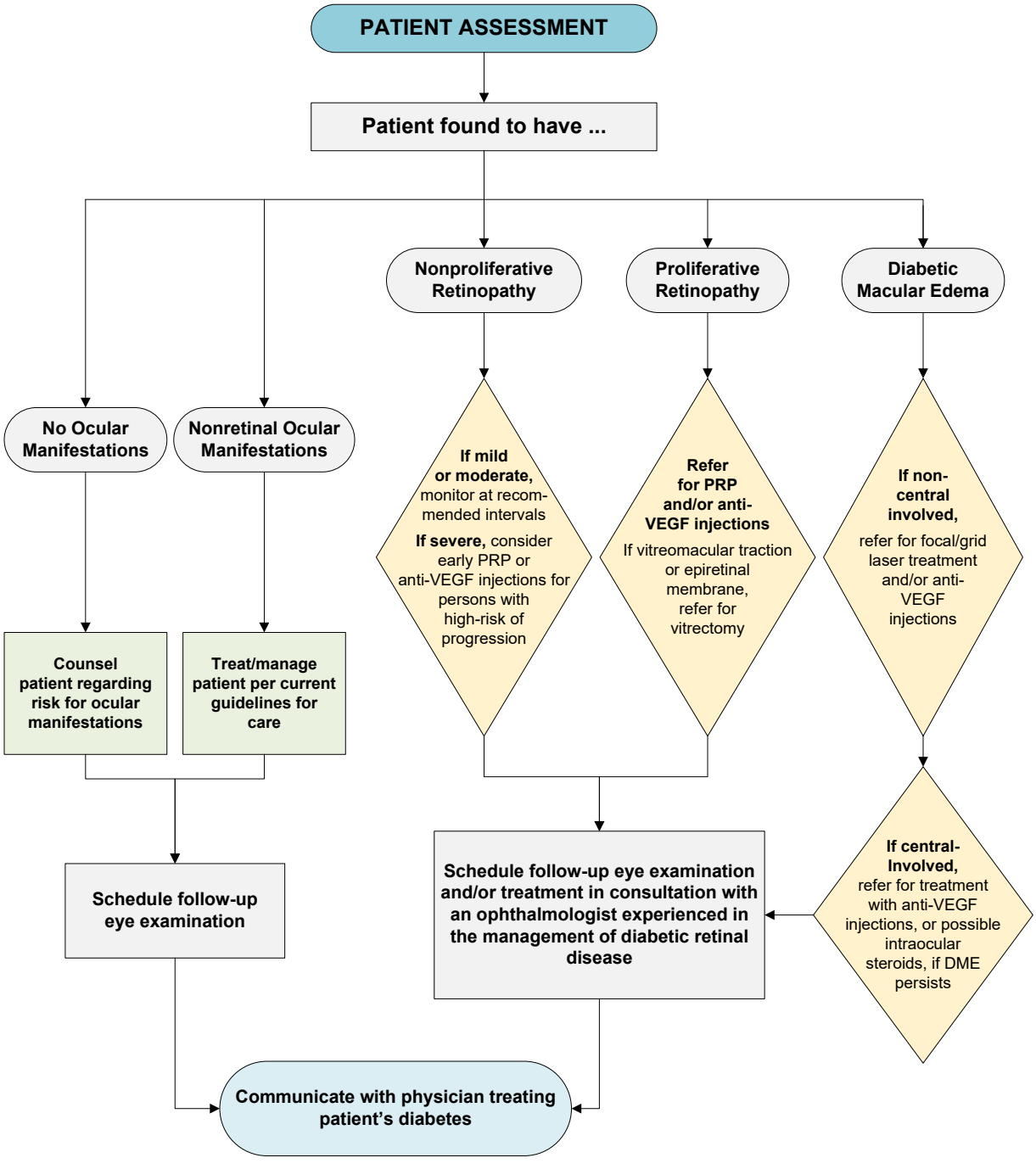
Standard Photo 10A
New vessels on the disc

Source: Fundus Photograph Reading Center, University of Wisconsin - Madison

Appendix 2
Optometric Management of the Patient with Undiagnosed or Suspected Diabetes Mellitus: A Flowchart



Appendix 3
Optometric Management of the Patient Diagnosed with Diabetes Mellitus: A Flowchart



Appendix 4
Effects of Systemic Medications on the Onset and Progression of Diabetic Retinopathy

Table 1: Systemic medications and their implications for diabetes eye care*

Systemic agents	Prototypical Drugs	Systemic Effects	Specific Ocular Mechanism	Key Studies** (Author/ Study Group)	Implications for Diabetes Eye Care
Agents for glycemic control					
Insulin	Various types of insulin	Regulates carbohydrate, lipid and protein metabolism	• Increased VEGF gene expression[1] • Alterations in retinal blood flow with sudden improved glycemic control	• UKPDS • DCCT • EDIC	• Glycemic control with HbA1C targets of <7% significantly reduces the risk of developing or worsening of retinopathy • EW following initiation of intensive control and associated with rapid reduction in HbA1C; poorly controlled long-standing DM with moderate NPDR or worse. • Potentially angiogenic at very high non-physiologic doses
Thiazolidinediones	Rosiglitazone Pioglitazone	Improves insulin sensitivity	• PPAR-γ agonist activity • Decreased VEGF production	• Shen, et al. • Fong, et al	• Delays the onset of PDR • May cause DME
Biguanides	Metformin	Improves glycemic control; Cardioprotective effects	• Decreased concentrations of PAI-1 • Inhibition of NF-kB and TSP-1	• UKPDS	• First line oral hypoglycemic agent particularly beneficial in overweight or obese type 2 patients with cardiovascular risk factors • Clinical implications independent of glycemic control have yet to be fully determined
Agents for lipid control					
Fibrates	Fenofibrate, Clofibrate, Etofibrate	Improves lipid parameters (↑HDL, ↓Total and LDL, cholesterol, ↓↓Triglycerides)	• PPAR α agonist activity	• FIELD Study	• Reduces the need for laser treatment by 31% • May reduce the rate of progression in patients with retinopathy • Control of lipid parameters in patients with DME may result in improved visual outcomes
Statins	Atorvastatin, Simvastatin	Improves lipid parameters (↓↓LDL and Total cholesterol)	• Potential anti-inflammatory effects through NF-kB inhibition • Decreased TNF-α-induced ICAM-1 expression	• Steno-2 Study • CARDS	• Evidence still insufficient to support primary use to prevent retinopathy progression • Control of lipid parameters in patients with DME may result in improved visual outcomes

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Appendix 4 *(Continued)*
Effects of Systemic Medications on the Onset and Progression of Diabetic Retinopathy

Systemic agents	Prototypical Drugs	Systemic Effects	Specific Ocular Mechanism	Key Studies** (Author/ Study Group)	Implications for Diabetes Eye Care
Agents for hypertensive control					
Angiotensin converting enzyme inhibitors	Captopril, Enalapril, Lisinopril	Blocks the conversion of angiotensin I to angiotensin II	• Renin-angiotensin system blockade • Vitreous activity of ACE is correlated with VEGF levels	• UKPDS • EUCLID • RASS	• Tight blood pressure control reduces the risk for 2-step DR progression by 34% and 3-line visual loss by 47% • Treatment with enalapril in normotensive type 1 patients has been shown to reduce the risk for 2-step or more progression by 65%
Angiotensin II receptor blockers	Candesartan Telmisartan Losartan	Blocks the activation of angiotensin II	• Renin-angiotensin system blockade • PPAR-γ agonist activity	• RASS • DIRECT (Prevent 1; Protect 1 and 2)	• Treatment with losartan in normotensive type 1 patients has been shown to reduce the risk for 2-step or more progression by 65% • Type 2 patients with retinopathy may benefit from candesartan treatment as this has been associated with higher rates of DR regression
Agents for cardiac complications					
Antiplatelet agent	Aspirin	Decreased platelet activation and aggregation; Decreased prostaglandin production	• Low doses: inhibits COX and thromboxane A2 production • Intermediate-High doses: inhibit COX, prostaglandin production and NF-kB mediated pathways	• ETDRS • DAMAD • TIMAD	• Does not worsen DR or predispose to developing vitreous hemorrhage • At intermediate to high dose, may potentially slow the progression of early retinopathy but further studies have to be conducted
Anticoagulants	Warfarin Heparin	Inhibits synthesis of clotting factors	• Inhibits synthesis of clotting factors	• Dayani, et al • Jamula, et al • Fu, et al	• If maintained at the therapeutic range, it is not a contraindication to ocular surgery • Does not increase the risk for significant intraocular hemorrhage
Cardiac glycosides	Digoxin Digitoxin	Antiarrhythmic agent; Inhibits Na-K ATPase	• Inhibits the expression of kallikrein • Reduces HIF- α levels	• Prassas, et al • Phipps, et al	• Potentially can inhibit neovascularization • Studies are being considered to determine a safe dose effective in preventing ocular neovascularization

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Appendix 4 *(Continued)*
Effects of Systemic Medications on the Onset and Progression of Diabetic Retinopathy

Systemic agents	Prototypical Drugs	Systemic Effects	Specific Ocular Mechanism	Key Studies** (Author/ Study Group)	Implications for Diabetes Eye Care
Agents for the treatment of anemia					
Erythropoietin	Erythropoietin	Stimulates increased RBC production	• VEGF independent angiogenic factor	• Watanabe, et al	• Patients requiring treatment with erythropoietin should be monitored closely for the development or worsening of DR particularly in the setting of chronic renal disease and anemia.
Anti-inflammatory agents					
Salicylates and COX-2 inhibitors	Salsalate Celecoxib	Inhibit prostaglandin synthesis	• •Inhibits COX and prostaglandin production • •Suppresses NF-kB mediated pathways	• Fleischman, et al • Chew, et al	• Concern on cardiovascular safety with long-term use and higher doses • Potentially may slow the progression of early retinopathy but further studies have to be conducted
Corticosteroids	Prednisone, Triamcinolone	Modulation of inflammatory response	• Inhibits prostaglandin release • Inhibits VEGF and VEGF gene expression	DRCR.net	• An independent beneficial or deleterious effect of systemic corticosteroids on the development or progression of DR and/or DME has not been reported and is likely overshadowed by the resultant changes in metabolic control
Chemotherapeutic agents	Bevacizumab, Ranibizumab	Inhibits tumor growth and angiogenesis	• Inhibits all VEGF isoforms	Multiple Ophthalmic Bevacizumab/ Ranibizumab trials	• Limited by systemic side-effect to local intravitreal administration • Highly effective in causing the regression of PDR and hastening the resolution of DME

ACE *- angiotensin converting enzyme* ***ARB*** *- angiotensin II receptor blocker* ***CARDS*** *- Collaborative Atorvastatin Diabetes Study* ***COX*** *- cyclooxygenase* ***DAMAD*** *- Dipyridamole Aspirin Micro Angiopathic Diabetique* ***DCCT*** *- Diabetes Control and Complications Trial* ***DIRECT*** *- Diabetic Retinopathy Candesartan Trials* ***DM*** *- diabetes mellitus* ***DME*** *- diabetic macular edema* ***DR*** *- diabetic retinopathy* ***EDIC*** *- Epidemiology of Diabetes Interventions and Complications* ***ETDRS*** *- Early Treatment Diabetic Retinopathy Study* ***EUCLID*** *- EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes* ***EW*** *- early worsening* ***HbA1C*** *- hemoglobin A1C* ***HDL*** *- high density lipoprotein* ***HIF*** *- hypoxia induced factor* ***ICAM -1*** *- intracellular adhesion molecule -1* ***LDL*** *- low density lipoprotein* ***Na-K ATPase*** *- sodium-potassium adenosine triphosphate pump* ***NF-Kβ*** *- nuclear factor* Kβ ***NPDR*** *- nonproliferative diabetic retinopathy* ***PAI-1*** *- plasminogen-activator inhibitor type 1* ***PDR*** *- proliferative diabetic retinopathy* ***PPAR-α*** *- peroxisome proliferative activated receptor alpha* ***PPAR-γ*** *- peroxisome proliferative activated receptor gamma* ***RASS*** *- renal and retinal effects of enalapril and losartan in type 1 diabetes* ***TIMAD*** *- Ticlopidine Microangiopathy of Diabetes Study* ***TNF-α*** *- tumor necrosis factor alpha* ***TSP-1*** *- thrombospondin-1* ***UKPDS*** *- United Kingdom Prospect Diabetes Study* ***VEGF*** *- vascular endothelial growth factor*

**Source: Silva PS, Cavallerano JD, Sun JK, et al. Effect of systemic medications on onset and progression of diabetic retinopathy. Nat Rev Endocrinol 2010;6:494-508*

***Refer to source above for study references*

Appendix 5
Comparison of ETDRS and International
Clinical Diabetic Retinopathy and Macular Edema Severity Scales

Diabetic Retinopathy	ETDRS	International Scale
No apparent DR		No abnormalities
Mild NPDR	At least one Ma	Ma only
Moderate NPDR	H/Ma >standard photo 2A or soft exudates, VB, and IRMA present	More than just Ma, but less than severe NPDR
Severe NPDR	One of the following: • H/Ma ≥standard photo 2A in all 4 quadrants; • VB present in at least 2 quadrants; • IRMA ≥standard photo 8A in at least 1 quadrant	No signs of PDR, with any of the following: • >20 intraretinal hemorrhages in each of 4 quadrants; • Definite VB in ≥2 quadrants; • Prominent IRMA in ≥1 quadrant
PDR		Severe NPDR and one or both of the following: • Neovascularization; • Vitreous/preretinal hemorrhage
Mild PDR	One or more of the following: • NVE; FPD or FPE present; • NVD and NVE present	
Moderate PDR	One or more of the following: • NVE elevated; • NVD <standard photo 10A; • VH/PRH and NVE <½ DA; • NVD absent	
High-Risk PDR	One or more of the following: • NVD ≥1/4 to 1/3 DA (standard photo 10A); • NVD and VH/PRH; • NVE ≥½ DA and VH/PRH	

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Appendix 5 *(Continued)*
Comparison of ETDRS and International
Clinical Diabetic Retinopathy and Macular Edema Severity Scales

Diabetic Macular Edema	ETDRS	International Scale
DME apparently absent		No apparent retinal thickening or HE in posterior pole
DME apparently present		Some apparent retinal thickening or HE in posterior pole
Mild DME	Retinal thickening within 2 DD of center of the macula	Some retinal thickening or HE in posterior pole, but distant from center of the macula
Moderate DME		Retinal thickening or HE approaching, but not involving, the center of the macula
Severe DME		Retinal thickening or HE involving the center of the macula
CSME (non-central involved) **CSME (central-involved)**	One or more of the following: • A zone or zones of retinal thickening ≥1 DA in size, any portion of which is ≤1 DD from the center of the macula • Thickening of the retina ≤500 microns from the center of the macula; • HE ≤500 microns from the center of the macula with thickening of the adjacent retina	

CSME *- clinically significant macular edema* ***DA*** *- disc area* ***DD*** *- disc diameter* ***DME*** *- diabetic macular edema* ***DR*** *- diabetic retinopathy* ***FPD*** *- fibrous proliferation on or within 1 DD of disc margin* ***FPE*** *- fibrous proliferation elsewhere* ***HE*** *- hard exudates* ***H/MA*** *- hemorrhage(s) and/or microaneurysm(s)* ***IRMA*** *- intraretinal microvascular anomaly* ***Ma*** *- microaneurysms* ***NPDR*** *- nonproliferative diabetic retinopathy* ***NVD*** *- new vessels on or within 1 DD of disc margin* ***NVE*** *- new vessels elsewhere* ***PDR*** *– proliferative diabetic retinopathy* ***PRH*** *- preretinal hemorrhage* ***VB*** *- venous beading* ***VH*** *- vitreous hemorrhage*

Sources: 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 and Wilkinson CP, Ferris FL 3rd, Klein RE, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 2003;110:1677-82

Appendix 6
A Summary of Major Studies on Diabetes Prevention and Treatment

Study	Background	Methods	Results
Action to Control Cardiovascular Risk in Diabetes (**ACCORD**)[132] (2010),[148] (2010),[151] (2011)	1. Does a therapeutic strategy that targets A1C <6.0% reduce the rate of CVD events more than a strategy that targets an A1C of 7.0% to 7.9%? 2. With good glycemic control, does a therapeutic strategy that uses a fibrate to raise HDL/lower triglyceride levels and uses a statin for treatment of LDL reduce the rate of CVD events compared to a strategy that only uses a statin for treatment of LDL? 3. With good glycemic control, does a therapeutic strategy that targets a systolic blood pressure (SBP) of <120 mmHg reduce the rate of CVD events compared to SBP of <140 mmHg?	10,251 people 40-79 years of age (mean age 62) with type 2 diabetes and at high risk of cardiovascular disease were randomly assigned to receive intensive glucose therapy (targeting an A1C level below 6.0%) or standard therapy (targeting a level of 7 to 7.9%). In addition, one arm of the trial addressed lipid control in 5,518 of the participants being treated with simvastatin. Another arm addressed blood pressure control in 4,733 of the participants.	1. Aiming to achieve an A1C level of <6% (as opposed to a less strict A1C goal between 7 to 7.9 %) unexpectedly increased the risk of death from cardiovascular disease. 2. The combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke, as compared with simvastatin alone. 3. In patients with type 2 diabetes at high risk for cardiovascular events, targeting a systolic blood pressure of <120 mmHg, as compared with <140 mmHg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events.
Action in Diabetes and Vascular Disease: PreterAx and DiamicroN MR Controlled Evaluation (**ADVANCE**)[122] (2008)	1. Would intensifying glucose control to achieve an A1C of <6.5% provide additional benefit in reducing the risk of both micro- and macrovascular disease? 2. A separate arm of the study sought to establish whether routine provision of blood pressure (BP) lowering therapy produced additional benefits in terms of macro- and microvascular disease, irrespective of baseline BP, and added to the benefits produced by other cardiovascular preventive therapies, including ACE inhibitors.	11,140 people (age 55 or older) with type 2 diabetes and at high risk for cardiovascular disease were randomly assigned to undergo either standard glucose control or intensive glucose control, defined as the use of gliclazide (modified release) plus other drugs as required to achieve a glycated hemoglobin value of 6.5% or less.	1. Intensive glucose control, involving gliclazide (modified release) and other drugs as required, that lowered the glycated hemoglobin value to 6.5% yielded a 10% relative reduction in the combined outcome of major macrovascular and microvascular events, primarily as a consequence of a 21% relative reduction in nephropathy. 2. Routine administration of a fixed combination of perindopril (ACE inhibitor) and indapamide (diuretic) to patients with type 2 diabetes was well tolerated and reduced the risks of major vascular events, including death.

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Appendix 6 *(Continued)*
A Summary of Major Studies on Diabetes Prevention and Treatment

Study	Background	Methods	Results
Diabetes Control and Complications Trial (**DCCT**)[7] (1993),[60] (1995) **and** Epidemiology of Diabetes Interventions and Complications (**EDIC**)[10] (2015)	1. Does an intensive treatment regimen directed at maintaining blood glucose concentrations as close to normal as possible prevent or delay the appearance or progression of early vascular complications in patients with type 1 diabetes mellitus? 2. An observational follow-up study to the DCCT Study evaluated the durability of the DCCT effects on the more advanced stages of diabetes complications including cardiovascular disease (CVD).	1,441 people with type 1 diabetes (726 with no retinopathy at base line and 715 with mild retinopathy) ages 13 to 40 years were randomly assigned to intensive therapy administered either with an external insulin pump or by three or more daily insulin injections and guided by frequent blood glucose monitoring or to conventional therapy with one or two daily insulin injections. 1,394 people with type 1 diabetes (97% of the original DCCT cohort)	1. Although intensive therapy does not prevent retinopathy completely, the study, conducted over 6.5 years, found that diabetic retinopathy could be dramatically reduced by maintaining healthy blood sugar levels. Tight blood sugar control also reduced development of kidney disease and cardiovascular disease; however, patients with tight blood sugar control were more likely than others to have hypoglycemic events. 2. After 30 years of follow-up (EDIC Study), the group that had tightly controlled blood glucose levels from the beginning of the study had a 32% reduction in major cardiovascular events (nonfatal myocardial infarction; stroke or cardiovascular death) suggesting that better control early in type 1 diabetes can prevent cardiovascular disease.
Diabetes Prevention Program (**DPP**)[111] (2002),[112] (2015)	1. Does a lifestyle modification program with the goals of a minimum of 7% weight loss/weight maintenance and a minimum of 150 minutes of physical activity similar in intensity to brisk walking reduce the risk of diabetes? 2. Would taking metformin delay or prevent type 2 diabetes?	A randomized study of 3,234 middle-age adults with prediabetes comparing an intensive lifestyle intervention or masked metformin with a placebo. The lifestyle intervention included: individual case managers or "lifestyle coaches;" a 16-session curriculum that taught self-management strategies for weight loss and physical activity; supervised physical activity sessions; tailoring of materials and strategies to address ethnic diversity; and an extensive network of training, feedback, and clinical support.	1. Intensive lifestyle counseling (which included dietary changes and 150 minutes of exercise per week) was found to reduce the onset of diabetes by 58% compared to usual care. 2. Metformin treatment reduced the onset of diabetes by 31%. These benefits persisted throughout the study's 15-year follow-up period.

Table Continued on next page

Appendix 6 *(Continued)*
A Summary of Major Studies on Diabetes Prevention and Treatment

Study	Background	Methods	Results
United Kingdom Prospective Diabetes Study (**UKPDS**)[8] (1998), [56] (1998)[57] (1998)	1. Does improved blood glucose control in persons with type 2 diabetes prevent the complications of diabetes? 2. Is any specific therapy advantageous or disadvantageous? 3. Does tight control of blood pressure prevent macrovascular and microvascular complications in patients with type 2 diabetes?	3,867 patients with newly diagnosed type 2 diabetes, were randomly assigned to intensive glucose control with a sulphonyl urea or with insulin (2,729 patients), or to conventional control with diet (1,138 patients). Of 753 obese patients, 411 were allocated to conventional therapy and 342 allocated to intensive therapy with metformin. The aim in the intensive group was FPG <6 mmol/L. In the conventional group, the aim was the best achievable FPG with diet alone; drugs were added only if there were hyperglycemic symptoms or FPG >15 mmol/L. In the blood pressure arm of the study, a total of 1,148 hypertensive patients with type 2 diabetes (mean blood pressure at entry 160/94 mmHg) were randomized to one of two groups; 758 patients were allocated to tight control of blood pressure (<150/85 mmHg) and 390 patients to less tight control (<180/105 mmHg).	1. Intensive therapy leading to tighter glucose control (A1C <7%) lowered the risk of diabetes complications, mainly related to eye and kidney disease, over a 10-year period. 2. Intensive glucose control with metformin appears to decrease the risk of diabetes-related endpoints in overweight diabetic patients, and is associated with less weight gain and fewer hypoglycemic attacks than are insulin and sulphonylureas. 3. Tight blood pressure control in patients with hypertension and type 2 diabetes achieves a clinically important reduction in the risk of deaths and complications related to diabetes, progression of diabetic retinopathy, and deterioration in visual acuity.

Appendix 7
Abbreviations/Acronyms

ACCORD -	Action to Control Cardiovascular Risk in Diabetes
ADVANCE –	Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation
ADA -	American Diabetes Association
AI -	Artificial intelligence
ASCVD -	Atherosclerotic cardiovascular disease
A1C -	Glycated hemoglobin
BCVA -	Best corrected visual acuity
BMI -	Body mass index
BVZ -	Bevacizumab
CRT -	Central retinal thickness
CSME -	Clinically significant macular edema
CVD -	Cardiovascular disease
DA -	Disc area
DD -	Disc diameter
DCCT -	Diabetes Control and Complications Trial
DME -	Diabetic macular edema
DPP -	Diabetes Prevention Program
DPP-4 -	Dipeptidyl peptidase 4
DRCR.net -	Diabetic Retinopathy Clinical Research Network
DRS -	Diabetic Retinopathy Study
ETDRS -	Early Treatment Diabetic Retinopathy Study
EDIC -	Epidemiology of Diabetes Interventions and Complications
EHR -	Electronic health record
FA -	Fluorescein angiography
FAF -	Fundus autofluorescence
FDA -	Food and Drug Administration
FIELD -	Fenofibrate Intervention and Event Lowering in Diabetes
FPD -	Fibrous proliferations of the disc, on or within 1 DD of disc margin
FPE -	Fibrous proliferations elsewhere, not FPD
FPG -	Fasting plasma glucose
FS -	Fingerstick
GAD65 -	Glutamic acid decarboxylase
GDM-	Gestational diabetes mellitus
GLP-1-	Glucagon-like peptide
HDL -	High density lipoprotein
HE -	Hard exudates
HLA -	Human leukocyte antigen
H/Ma -	Hemorrhage(s) and/or microaneurysm(s)
IAA -	Insulin autoantibodies
ICA -	Islet cell antibodies
IFG -	Impaired fasting glucose
IGT -	Impaired glucose tolerance
IOP -	Intraocular pressure
IRMA -	Intraretinal microvascular abnormality
IVTA -	Intravitreous triamcinolone acetonide
mETDRS -	Modified ETDRS (laser therapy)
MetS -	Metabolic syndrome

Appendix 7 *(Continued)*
Abbreviations/Acronyms

Ma -	Microaneurysms
MODY -	Maturity-onset diabetes of the young
NAION -	Nonarteritic anterior ischemic optic neuropathy
NEI -	National Eye Institute
NPDR -	Nonproliferative diabetic retinopathy
NV -	New vessels
NVD -	New vessels on or within 1 DD of disc margin
NVE -	New vessels elsewhere in the retina outside of disc and 1 DD from disc margin
NVG -	Neovascular glaucoma
NVI -	Neovascularization of the iris
OAG -	Open angle glaucoma
OCT -	Optical coherence tomography
OCTA -	Optical coherence tomography angiography
OGTT -	Oral glucose tolerance test
PDR -	Proliferative diabetic retinopathy
PHR -	Personal health record
PRH -	Preretinal hemorrhage
PRN -	Pro re nata (as needed)
PRP -	Panretinal photocoagulation
PVD -	Posterior vitreous detachment
RAS -	Renin-angiotensin system
RBZ -	Ranibizumab
SDM -	Subthreshold diode micropulse (laser)
SGLT-2 -	Sodium-glucose cotransporter – 2
TZDS -	Thiazolidinediones
UKPDS -	United Kingdom Prospective Diabetes Study
VB -	Venous beading
VEGF -	Vascular endothelial growth factor
VH -	Vitreous hemorrhage

Appendix 8
Gaps in Research Evidence

During the course of the development of this guideline, the Evidence-Based Optometry Guideline Development Group identified the following as potential areas for future research:

- When is the most appropriate/effective time for initial ocular examination of persons newly diagnosed with type 1 diabetes?
- What is the potential role of anti-VEGF agents in the treatment of nonproliferative diabetic retinopathy?
- What are the mechanisms of action and potential benefits/harms of the use of nutritional and/or anti-oxidant supplements in reducing the risk of development or progression of diabetic retinopathy?
- Is there a correlation between a lack of physical activity and the risk for development of diabetic retinopathy?

VIII. METHODOLOGY FOR GUIDELINE DEVELOPMENT

This guideline was developed by the AOA Evidence-Based Optometry Guideline Development Group (GDG). Clinical questions to be addressed in the guideline were identified and refined during an initial meeting of the GDG and served as the basis for a search of the clinical and research literature.

An English language search of the medical literature for the diagnosis, treatment, and management of diabetes-related eye and vision problems for the time period January 1976 through January 2019 was conducted by trained researchers.

Search Inclusion Criteria (must meet *all*):

1. English Studies
2. Study addresses the clinical question(s)
3. Paper meets the age group being addressed
4. Searched by question(s) formulated at the AOA Call to Question Meeting attended by the Guideline Development Group (GDG)
5. Using all similar and relevant terms as defined by the GDG

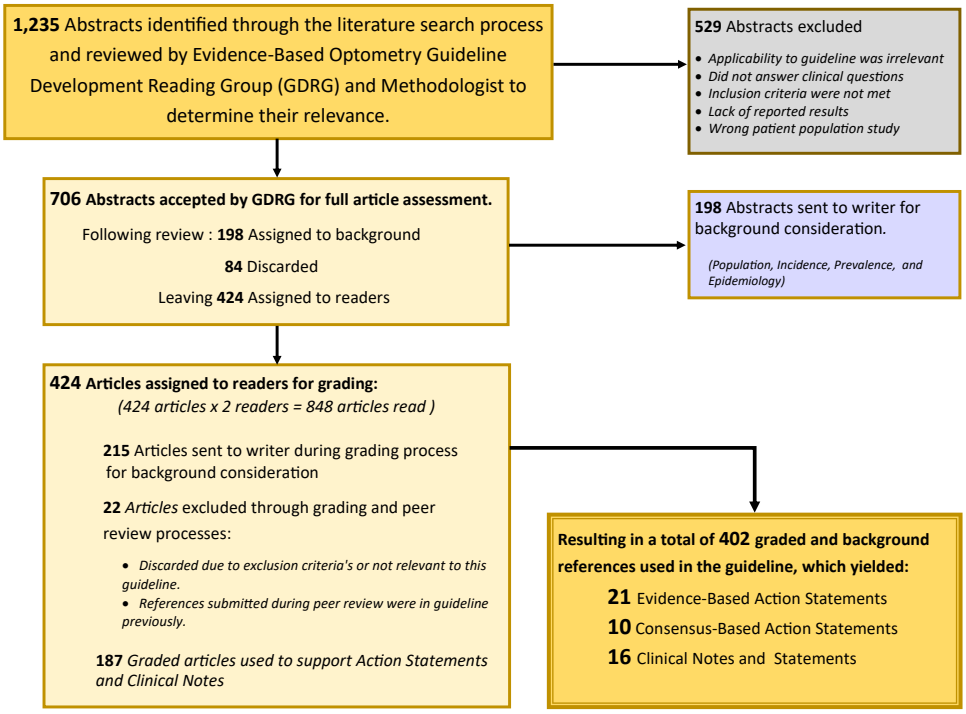
Exclusion Criteria (meeting *any* of the below):

6. Non-English studies
7. Animal studies
8. Studies outside of the patient age range
9. Studies not addressing any topic of the clinical questions searched

In addition, a review of selected earlier research publications was conducted based on previous versions of this guideline. The literature search was conducted using the following electronic databases:

- *American Diabetes Association*
- *Centers for Disease Control and Prevention, National Center for Health Statistics*
- *Cochrane Library*
- *Diabetes Care*
- *Google Scholar*
- *Healthy People 2020*
- *Investigative Ophthalmology and Visual Science*
- *JAMA Ophthalmology*
- *Medline Plus*
- *National Eye Institute*
- *PLoS One*
- *PubMed*
- *Retina*

The literature search resulted in the retrieval of the number of references shown in the following chart.



All references meeting the criteria were reviewed to determine their relevance to the clinical questions addressed in the guideline. Each article was assigned to two clinicians who independently reviewed and graded the quality of evidence and the clinical recommendations derived from the article, based on a previously defined system for grading quality. If discrepancies were found in the grading results, the article was assigned to an independent third reader for review and grading.

During articulation meetings (two face-to-face and six using a video conferencing platform) of the Evidence-Based Optometry Guideline Development Reading Group (GDRG), all evidence was reviewed and clinical recommendations were developed. The strength level of clinical recommendations was based on the quality grade of the research and the potential benefits and harms of the procedure or therapy recommended. Where high quality evidence to support a recommendation was weak or lacking, a group consensus was required to approve any consensus recommendations.

Review and editing of the draft guideline by the Evidence-Based Optometry GDG required one face-to-face meeting and three additional Draft Reading Meetings using a video conferencing platform. The final Peer Review draft was reviewed and approved by the GDG by video conferencing platform, then made available for peer and public review for 30 days for numerous stakeholders (individuals and organizations). Comments were promoted and encouraged. All suggested revisions were reviewed and, if accepted by the GDG, incorporated into the guideline. All peer and public comments and all actions (and inactions) were recorded.

Clinical recommendations in this guideline are evidence-based statements regarding patient care that are supported by the scientific literature or consensus of professional opinion when no quality evidence was discovered. The guideline will be periodically reviewed for new scientific and clinical evidence and updated within 3 to 5 years.

IX. EVIDENCE-BASED OPTOMETRY GUIDELINE DEVELOPMENT GROUP

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