PRACTICAL GUIDELINES

The Modern Fundamentals of Diabetic Retinopathy Management in Primary Eye Care

1. **<u>DETECT</u>: Approach diabetic retinopathy as a chronic progressive disease. Being a chronic progressive disease implies that you can detect it before it becomes advanced disease. This can be achieved using both structural and functional testing.**

   Structural assessment for diabetic retinopathy should consist of any or all of the following:

   - Stereoscopic assessment of the retina and optic nerve through dilated pupils, including evaluation of both the posterior pole and mid-peripheral retina.
   - Retinal photography to document baseline retinal status. Utilize a red-free filter to improve visibility and detect subtle retinopathy.
   - Wide-field or ultrawide-field retinal imaging, when possible.
   - Spectral domain optical coherence tomography (SD-OCT) when any DR is detected to assess for DME and also consider at baseline for future comparison.
   - OCTA at baseline exam should be considered for future comparison to assess degree of retinal non-perfusion.
   - SD-OCT on patients with diabetes mellitus duration > 5-10 years to assess for retinal diabetic neuropathy (RDN – defined as abnormal thinning of the retinal nerve fiber layer [RNFL] and ganglion cell complex [GCC] that portends functional vision loss and autonomic neuropathy).

   Although the standard of care for the assessment of vision loss due to diabetic retinopathy is high-contrast visual acuity, evidence shows it is insufficient and workup should include any or all of the following:

   - Electro-diagnostic testing (ffERG) is recommended. Electro-diagnostic testing (ffERG), preferably utilizing the additional measure of pupillometry, as in the DR score, offers a direct reading of retinal health. ERG is a measure of the function of the retina, the health of the cells and the risk of disease progression.
   - Other technologies that may be considered include visual fields, MPOD, color contrast threshold sensitivity testing and low-contrast visual acuity testing.

2. **<u>GRADE</u>: Grade diabetic retinopathy at the time of diagnosis and at each subsequent visit. Chart structural retinal damage and quantify retinal cell function.**

   Diabetic retinopathy grading should adhere to accepted standards from the Early Treatment Diabetic Retinopathy (ETDRS) severity scale or International DR Severity scale, with particular attention to the following:

- Characteristics of severe NPDR, which include any one or more of the following:
    - 20+ intra-retinal hemorrhages/microanuerysms (Hm/ma) in all four retinal quadrants centered on the fovea
    - Venous beading (VB) in two or more quadrants
    - Any prominent intra-retinal microvascular anomalie(s) (IRMA)
- Characteristics of moderately severe NPDR include any of the following:
    - Venous beading
    - Severe intra-retinal hemorrhage in any quadrant

Be sure to make specific reference to recognized grading criteria as follows:

- Mild Non-Proliferative Diabetic Retinopathy (NPDR)
- Moderate NPDR
- Moderately severe or severe NPDR
- Proliferative Diabetic Retinopathy (PDR)
- Any Center-involved Diabetic Macular edema (CI-DME) or non-center involved DME based on SD-OCT subfield analysis

3. **<u>ASSESS RISK</u>: To assess risk of progression, monitor diabetic retinopathy patients over time using both structural and objective functional measures.**
   Risk of progression should be based on ETDRS findings, long-term metabolic control, diabetes subtype and treatment, established risk factors for DR progression, and worsening DR severity over time using both structural and objective functional measures. Note that retinal function does not always align with structure because DR is a neurovascular disease. Functional loss may precede identifiable structural damage when using objective tests, such as ERG. Importantly, notate the probable need for pharmacologic or laser treatment within 3 years based on ffERG DR score.

   Retinal imaging at baseline identification of any diabetic retinopathy is recommended to assess for structural change over time (i.e., worsening of diabetic retinopathy severity) at appropriate intervals, as follows:
   - Minimal or mild NPDR – annually
   - Moderate NPDR – every 4-6 months
   - Moderately severe or severe NPDR – every 3-4 months or refer to retina specialist (see below for risk stratification using RET*eval*)
   - Referral to a retina specialist or ophthalmologist experienced with the management of diabetic retinal disease should be made if CI-DME or proliferative diabetic retinopathy (PDR) is detected (within 2-4 weeks)
   - High-risk PDR should be referred to a retinal specialist within 48 hours (NVD > ¼ disk diameter, pre-retinal hemorrhage and/or vitreous hemorrhage)

Initial ffERG is recommended for patients with any diabetic retinopathy at baseline to establish a comparator if future DR worsening is detected subsequently. The ffERG is recommended for patients who demonstrate structural DR worsening over time (via clinical exam or imaging) equivalent to a 2-step DRSS change (e.g., going from mild to moderate NPDR, or moderate to moderately severe or severe NPDR) as follows:

- Patients with any DR who demonstrate a RET*eval* score ≥ 23.5 should be referred to a retina specialist, particularly if NPDR severity is moderate or worse
- Patients with RET*eval* score ≥ 23.5 with what appears, clinically, to be mild NPDR, should be monitored closely or considered for referral to a retinal specialist to confirm appropriate staging of DR severity
- Patients with a RET*eval* score ≥ 26 should be referred to a retina specialist
- Patients with a RET*eval* score ≤ 23.5 with mild or moderate NPDR should have repeat examination as indicated above under 'retinal imaging' section, including repeat measure of ffERG and RET*eval* score
- Patients with mild or worse NPDR with RET*eval* score ≥ 21 should be considered for repeat ffERG/clinical exam within 6-12 months to assess for worsening severity of structural or functional abnormalities

4. **MANAGE: Utilize multi-disciplinary resources to manage all diabetic retinopathy patients, regardless of disease severity.** The time between retinal examinations depends on risk assessment as described above. Referral for consideration of retinal treatment should be based on disease severity, presence of DME, and individual risk factors, and functional abnormalities including ERG findings. Note that, in some cases, objective functional loss alone may be sufficient reason to increase exam frequency or initiate referral to a retinologist. In all cases, the patient's primary care provider should be promptly advised of retinal findings or lack thereof with special emphasis on whether the patient was dilated, DR severity, your recommended surveillance interval, the presence or absence of DME and any referral to retina subspecialty.

   All patients should be encouraged to engage in regular physical activity to achieve metabolic targets. Specifically, patients with diabetes, including those with stable retinal and cardiovascular disease, can be advised to engage in 150 minutes of moderate physical activity per week unless contraindicated by their medical status, including acute vitreous hemorrhage or actively treated proliferative diabetic retinopathy or macular edema. Aerobic, interval and light resistance training have all been shown to improve insulin sensitivity and well-being and to assist with weight loss.

   Good nutrition is essential for overall health, including eye health. All patients should be encouraged to consume a predominantly plant-based diet that is low in added sugars and devoid of trans fatty acids (hydrogenated oils), with consumption of lean protein sources and healthy fats (e.g., nuts, avocados, marine-sourced omega-3 fatty acids). Given the poor dietary quality of most American diets, recommending a broad-spectrum

multi-vitamin and mineral formulation is sensible, including evidence-based supplements that may afford protection against diabetic retinopathy.

5. **<u>SUPPORT</u>: Provide comprehensive patient education and strategies to help prevent disease progression.** Emphasize the asymptomatic nature of DR at its earlier, most treatable levels of severity and encourage patients to achieve individually optimized metabolic control in concert with their diabetes physicians. Patients referred to retina specialty for evaluation or treatment should be scheduled for follow-up examination by the referring eye doctor to help mitigate high rates of lost-to-follow-up (LTFU) seen in patients with diabetes, DR/DME and other chronic retinal diseases.

   All patients with diabetes should be encouraged to achieve individually appropriate metabolic targets for diabetes control per established guidelines from the American Diabetes Association (ADA) and American Academy of Clinical Endocrinology (AACE), particularly blood glucose, pressure and lipid targets:
   - Generally, most adult patients should achieve HbA1c $\leq$ 7%, BP $\leq$ 140/90, and LDL-C <100.
   - Patients with shortened lifespan, cognitive impairment, established cardiovascular disease or multiple comorbidities typically have less strict targets for HbA1c ($\leq$ 8%).
   - Glucose control has been shown to be most effective against preventing DR/DME when instituted soon after diagnosis of diabetes and when there is either no DR or mild NPDR.
   - Patients with high-risk retinal disease should be referred to retinal specialty independently of their current level of glucose control, as studies show good contemporaneous glucose control if of little to no protective value once DR progresses past the moderate NPDR stage (PANORAMA and Protocol W).