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# Focus on diabetic retinopathy in adolescents

*Collin Asheim*[1], *Ahmed Kassem*[1,2]

[1]Department of Surgery, School of Medicine and Health Sciences, University of North Dakota, Grand Forks, North Dakota, USA; [2]Department of Ophthalmology, Sanford Health, Fargo, North Dakota, USA

**Abstract.** *Background and aim:* Diabetic retinopathy (DR) is a vision threatening and preventable complication of diabetes (DM) that was historically rare in the pediatric population but increasing incidence is noted in the adolescent age group. *Methods:* In this review, we present the etiology, magnitude of the problem, challenges to screening and new opportunities for early detection. *Results:* The incidence of diabetic retinopathy in children with type 2 DM (T2DM) is estimated to be 6.99% 5 years from diagnosis and the risk of DR in T2DM is twice as much as in T1DM and is significantly higher after puberty. Smart phone-based screening has reported sensitivity and specificity for any DR being 52-92.2% and 73.3-99% respectively. The use of Artificial Intelligence has high sensitivity and specificity for identifying DR of 90.5% and 91.6% respectively. *Conclusions*: Diabetic retinopathy is increasingly noted in children and adolescents necessitating reconsideration of current guidelines. Technologies such as Smartphone-compatible devices, telemedicine, and use artificial intelligence (AI) show promise in overcoming anticipated shortage in healthcare professionals available for screening. (www.actabiomedica.it)

**Key words:** diabetes, diabetic retinopathy, telemedicine, screening, fundus photography, artificial intelligence

## Introduction

Diabetic retinopathy (DR) is a well-recognized complication of diabetes which has traditionally been regarded as a disease process predominantly afflicting the adult population. While the incidence in the pediatric population is comparatively low, recent research has shown an increase in risk for development of DR and is more common than we may have believed (1). This shift in our understanding of DR in adolescents necessitates a reevaluation of the approach to screening and interventions in patients with diabetes. This review article aims to evaluate the evolving landscape of DR in adolescence, identify various methods of screening, examine the effectiveness of screening methods, and discuss the implications for both patients and pediatricians. Within the US, the pediatric prevalence of both Type 1 Diabetes (T1DM) and Type 2 Diabetes (T2DM) has been on an upward trend with recent reports showing 35 youths per 10,000 individuals under the age of 20 had diagnosed diabetes with approximately 30 of those being T1DM (2). This continues to increase with recent studies showing increased incidence of T1DM and T2DM in recent years surrounding the COVID pandemic (3,4). The obesity epidemic is thought to be a primary factor in the increase of both types of T1DM and T2DM (5,6). Along with the increases in the incidence of diabetes within the pediatric population, there is also discovery of an increase in ocular complications including DR showing a prevalence of 6.99% in individuals with T2DM (1,7). The coexistence of diabetes with ocular complications emphasizes the need for a proactive approach to adequately reduce the risk of sight threatening disease. Screening methods for diabetic retinopathy include a variety of methods which include screening with eye specialists, however new methods such as smartphone based retinal screening, and wide and ultrawide

field fundus photography in a community setting, are emerging which may increase the availability of screening and potentially provide a useful tool to identify at risk individuals and subsequently put them in contact with the proper healthcare professionals to address and mitigate.

## Methods

*Pathophysiology of diabetic retinopathy*

Diabetic retinopathy is the result of chronic hyperglycemia in diabetes causing end organ damage in areas with dense microvasculature commonly including the kidneys, peripheral nerves, and the retina (8). In the retina, formation of advanced glycation end products (AGEs) leads to microvascular damage with increased vascular permeability and microvascular occlusion causing retinal ischemia (9). This damage is known as diabetic retinopathy and first presents as non-proliferative (NPDR) and can later advance to a more severe form called proliferative (PDR). Advancement to PDR occurs when retinal ischemia is significant enough to induce the production of VEGF and other pro-angiogenic growth factors causing proliferation of new vessels, which gives the disease its namesake (8–10).

In NPDR clinical signs vary from dot and blot hemorrhages, hard exudates, cotton wool spots to venous beading (10). PDR is distinguished by the presence of retinal neovascularization in addition to the symptoms seen in NPDR (8–11). New, immature vessels can induce traction on the retina by pulling the vitreous away from the surface of the retina, increasing the potential for tractional retinal detachment (9). These fragile vessels are also more likely to break which introduces the potential to bleed into the vitreous which also severely impairs vision (9).

At any stage either form of DR can occur with or without diabetic macular edema (DME), which is caused by the upregulation of inflammatory cytokines as a result of the diabetic disease process (8–10). Chronic inflammation in addition to the microvascular endothelial damage mentioned above leads to increased permeability and the leakage of fluid into the retina. Sediment remains when the edema is cleared and leaves yellow lipid byproducts known as hard exudates. DME is more common in PDR because of increased vascular permeability.

## Results

*Epidemiology of DR*

Diabetic retinopathy is the leading cause of preventable blindness in working age adults and accounts for 14.4% of blindness within this demographic (11,12). DR affects approximately one third of patients with known diabetes with 4.4% having vision threatening retinopathy, and is estimated to affect 191 million people globally by 2030 with 56.3 million having vision threatening retinopathy by 2030 (13). As the obesity epidemic continues to worsen, the incidence of diabetic retinopathy is also increasing. Globally, the prevalence of DR in patients was 6.99% of patients diagnosed with T2DM diagnosed at 21 years or younger and that prevalence increased significantly at more than 5 years after diagnosis (6). There are several factors thought to be increasing the incidence of DR in adolescence. The likelihood of developing DR is directly proportional to the age of the patient and relates to the duration of diabetes and level of control of blood sugar as well as hypertension (7). Incidence of DR in patients with T1DM is as high as 98% in patients with the disease for 15 years or more, with 67% getting PDR after 35+ years. The age of onset is also related to the development of DR with the highest risk of developing DR occurring in groups who developed T1DM during ages 5-15, with the average time to DR after diagnosis being 20.1 years after diagnosis (14). Having a lower age of onset <5 years old may have a protective effect on the development of retinopathy (14). Pubertal release of hormones is thought to increase the risk of DR as previous studies have found significantly higher prevalence of DR in post pubertal patients when compared to pre-pubertal patients (7). This increased risk for DR in patients diagnosed in adolescence highlights the importance of increased screening in these individuals. A recent study showed that children with T2DM were nearly twice as likely

to develop retinopathy when compared to children with T1DM (26.6% & 52.7% respectively) (15). This is in contrast the adult patients where prevalence of DR is 77.3% in T1DM and 25.1% in T2DM patients (16). This suggests that children with T2DM especially may require earlier surveillance when compared to children with T2DM to prevent potential vision loss.

*Screening options & effectiveness*

In order to avoid visual loss as a result of DR, routine screening aimed at early detection and timely intervention are paramount. Current screening guidelines for the US were most recently updated in 2018 by the International Council of Ophthalmology (ICO) and the American Diabetes Association (ADA) (10). According to these guidelines, individuals with T1DM and T2DM should receive their first exam within 3-5 years or at the time of diagnosis respectively. It defines an adequate DR screening as involving a visual acuity exam and a retinal examination. The retinal examination includes at least one mode of imaging including 1. Direct or indirect ophthalmoscopy or slit lamp biomicroscopy or 2. Fundus photography including a. 30 degree to widefield, mono-photography, stereophotography, and dilated or non-dilated photography (10). Traditionally, diabetic patients have been recommended to visit an eye specialist, either an ophthalmologist or optometrist to receive annual comprehensive eye exams. While this approach remains highly effective, limited availability of eye specialists, particularly in rural or underserved areas poses a major challenge. This can ultimately lead to delays in diagnosis and treatment, leading to worse patient outcomes and greater potential for vision loss. Fundus photography is a highly valuable tool utilized for DR screening. These photos provide several advantages including the comparison of new photos to old photos to detect changes over time as well as ease of documentation of tracking disease progression. A variety of fundus imaging methods exist, with different forms capturing differing degrees of field of view, as well as monocular vs stereoscopic imaging in a dilated or non-dilated eye (17). A recent review of various photographic screening methods revealed that the sensitivity and specificity of DR screening has a positive association with the number of photographic fields with 7 standard field fundus photography acting as the gold standard (18,19). More basic photography (two field, non-dilated) can be sufficient for screening methods of DR but only to a point as single field, non-dilated photography was found to be inadequate to detect DR (20–22). New advancements using wide field and ultra-wide field fundus photography allow for more reliable image capture even in non-dilated eyes and result in gradable images in at least one eye 94% of the time, and 46% in both eyes (23). In cases where non-dilated photographs are ungradable, a gradable image can be obtained 98.2% of the time is dilation is utilized, highlighting the high usability of this tool for screening purposes (24). Screening programs have integrated fundus photography into primary care settings to help reduce the burden on specialized eye care providers and empower primary care providers to capture retinal images during routine diabetes exams (25). DR screening is a cost-effective method to reduce blindness, however many DM patients still do not receive screening from barriers including poor access, need for training, service delivery, lack of knowledge of the need for screening, expenses, poor patient coordination, and time commitment (26,27). One option seeking to resolve this involves telemedicine, in which photos taken at one site are transmitted to be interpreted at another. This provides a cost-effective option to screen for DR while remaining highly sensitive and specific with averages over 80% and 90% respectively (28). Despite the cost required to set up and maintain the telemedicine screening particularly in low access communities, these programs increase the availability to those who previously may have gone unchecked (29). Additionally, the use of remote analysis for photos acquired in the primary care setting have been shown to be comparable to a dilated fundus examination performed by an ophthalmologist with both sensitivity and specificity over 80%. (30). While the infrastructure may not always support the use of these devices in places without reliable internet access, and the initial cost can be prohibitive, the use of telemedicine allows for increased access and timely interventions which can help optimize resource allocation to prioritize care provided by eye care specialist to those who are in greatest need.

One potential solution in lower resource communities is the use of smartphone compatible devices to allow for screening in these communities. The quality of these images is not as good as standard fundus photography equipment; however, these devices have great potential to increase the cost effectiveness of DR screening (31). There is a fairly wide range of diagnostic accuracy between devices, with reported sensitivity and specificity for any DR being 52-92.2% and 73.3-99% respectively (31). A recent meta-analysis by Tan Et. Al. evaluating studies from 2000-2018 showed an overall pooled sensitivity and specificity to detect any DR with 87%, and 94% respectively (32). Overall, the use of smartphone compatible retinal imaging devices has limitations including a limited field of view, lower image quality, and require adequate training for effective use. However, the portability, cost effectiveness, and the capability for non-specialist operation make them particularly suitable for use in community settings and - provide an acceptable alternative particularly in low resource areas.

Artificial Intelligence (AI) is another tool that has great potential to increase availability of DR screening options in underserved communities. AI has been shown to have high sensitivity and specificity for identifying DR with studies showing >94% sensitivity and >86% specificity (33–35). Even in cases where poor image quality is present, accurate DR diagnosis is still obtained with 96.3% sensitivity and 90.0% specificity (36). Images captured by non-specialist operators found a sensitivity of 100% with no false negative results reported (34). These programs allow for accessible and efficient evaluation of high volumes of images and can accurately prioritize those needing further evaluation by an eye specialist. Additionally, AI could be used in real time to indicate when captured images are usable or not, and could prompt the imager to attempt a recapture, reducing the amount of patients going unevaluated due to poor image quality (35).

The American Diabetes Association (ADA) has determined that the use of these deep learning algorithms are cost effective and largely reliable methods that significantly reduce the screening burden of DR worldwide (37). As AI technology rapidly evolves, the accuracy and precision of these systems will likely increase even further, meaning that the option of a reliable cost-effective alternative to assist in addressing preventable blindness will only become more available as time moves on. While the International Council of Ophthalmology (ICO) and the American Diabetes Association (ADA) provide comprehensive guidelines, other organizations such as the American Academy of Pediatrics (AAP) and the International Diabetes Federation (IDF) offer varying recommendations. For instance, the AAP suggests more frequent screening for adolescents with rapid glycemic control changes, whereas the IDF emphasizes individualized screening intervals based on risk factors. Comparing these guidelines illustrates the lack of consensus and the potential benefits of integrating new diagnostic technologies to create more unified and effective screening protocols. There is some concern for legal liability if there is an incorrect AI analysis, and this will be an area for further development of systems to prevent mistakes such as these from happening. Additionally, there are high development costs associated with creating these models, and they often can inherit bias from their training datasets, which potentially affect accuracy across diverse populations. This raises regulatory and ethical issues as well as the use of AI raises the questions of who is accountable in cases of missed or incorrect diagnosis. Despite these setbacks associated with AI, it provides a different yet complementary strength when compared to humans. It provides a consistent read with minimal variability, high accuracy, and it is capable of analyzing large volumes of images rapidly (38). AI as a first line screening tool offers to enhance efficiency while reducing costs, removing the need for eye specialists to perform these exams, opening their availability to focus on more complex exams.

## Conclusions

The evolution of the understanding of DR in adolescents has revealed that DR is no longer confined to adulthood. With DM being diagnosed earlier and more frequently in the pediatric population, we are seeing an increase in DR in said population. This shift necessitates a reevaluation of our approach to screening and interventions within diabetic patients, with a growing emphasis on earlier detection and prevention.

The most recent screening guidelines recommend the first eye exam for patients with T2DM within 3-5 years and at the time of diagnosis, respectively. However, the increasing prevalence of diabetes and the rising risk of DR among adolescents challenge these guidelines. With the incidence of T1DM and T2DM on the rise, as well as the incidence of DR within these years, particularly among those diagnosed during adolescence, the need for earlier DR screening becomes apparent. Studies have shown that adolescents, particularly those with T2DM, are at greater risk of developing DR compared to their adult counterparts.

Screening has proven to be an effective method for the early detection of DR, and with the advent of new tools and technologies, it is becoming more efficient and accessible. Smartphone-compatible devices, telemedicine, and artificial intelligence (AI) are transforming the landscape of DR screening. These tools enhance the accessibility and cost-effectiveness of screening, particularly in underserved communities.

In comparing traditional screening workflows with enhanced methods using telemedicine and AI as shown in Figure 1 and further detailed in Table 1 we are able to see that each distinct approach has advantages

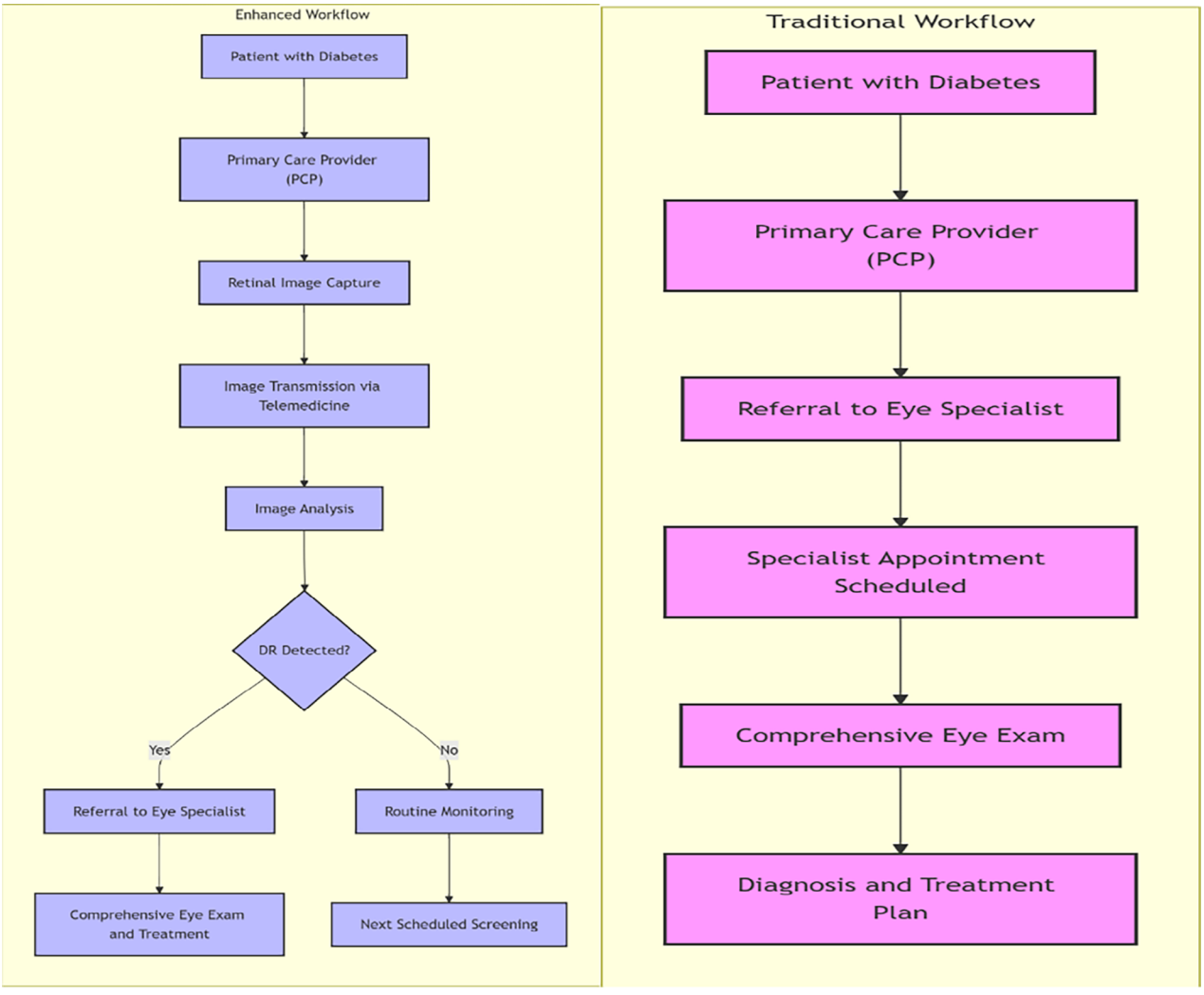


**Figure 1.** Comparison of Traditional Diabetic Retinopathy (DR) Screening Workflow vs. Enhanced Workflow with Telemedicine and AI Integration.

**Table 1.** Comparative Analysis of Current DR Screening Guidelines and Emerging Diagnostic Technologies. This table highlights key aspects such as initial screening timing, frequency, accessibility, cost, accuracy, and the respective pros and cons of each approach.

| Aspect | Current guidelines | Smartphone based screening | Telemedicine | AI driven screening |
|---|---|---|---|---|
| **Initial screening** | Within 3-5 years for T1DM. At diagnosis for T2DM | At diagnosis and periodically thereafter | At diagnosis and periodically thereafter | At diagnosis and periodically thereafter |
| **Frequency of screening** | Annual Comprehensive eye exams | Flexible- potentially more frequent based on access | Annual or as recommended based on initial findings | Automated reminders and adaptive scheduling based on risk |
| **Accessibility** | Limited by availability of eye care specialists | High in remote and underserved areas | High, especially in areas with appropriate infrastructure | High, particularly in areas with appropriate infrastructure |
| **Cost** | Higher due to specialist involvement | Lower initial costs, scalable | Moderate initial setup, cost-effective in long term | High initial development, low per screen cost |
| **Accuracy** | High with specialist evaluation | Variable, improving with technology advancements | High when combined with specialist review | Consistently high, comparable to specialists |
| **Pros** | Comprehensive and accurate | Portable and cost effective | Expands access and allows for timely evaluations | High accuracy, scalable, consistent |
| **Cons** | Limited access and higher costs | Lower image quality, training required | Requires access, data security concerns | High development cost, potential bias, ethical concerns |

and disadvantages. The traditional approach typically involves specialist referral from the PCP which can be time consuming and resource intensive.

This requires multiple appointments, higher reliance on patient compliance, and increased healthcare costs. The updated workflows reduce these burdens by allowing remote screening, faster evaluations, and earlier detection. However, they do come with their own challenges such as ensuring quality and accuracy of AI interpretations and overcoming technological barriers in underserved areas.

When looking at accessibility, telemedicine and AI allow for greater reach into rural and underserved populations, but its implementation rely on adequate training for healthcare providers, and reliable internet access which may not always be feasible. Additionally, while AI can speed up the process through its ability to review images in mass quantities, they are not foolproof and require strict oversight by trained specialists to confirm results which offers a potential chokepoint in providing final diagnosis. There needs to be an established balance between implementing these innovations, while also maintaining the need for human expertise and this article highlights the trade-offs each method presents.

While new workflows show great promise in addressing the growing need for earlier DR detection in adolescents the shifting landscape of DR incidence in adolescence underscores the importance of timely and earlier screening. New technology shows great promise in addressing this growing need, but careful consideration must be given to balance the thoroughness of traditional care with the efficiency and accessibility of modern technology. A collaborative effort between healthcare providers and researchers is needed to refine screening methods, improve accessibility, and ensure that diabetic patients, including adolescents, receive the care and intervention they need to preserve their vision.

**Ethic Approval:** not required due to non-involvement of human subjects.

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**Correspondence:**
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Ahmed Kassem, MD
Sanford Health, Sanford Eye Center, 1717 S University Dr E, Fargo, ND 58103
E-mail: kassema86@gmail.com
ORCID: 0000-0001-8099-0208