Retinal Telescreening for Diabetic Retinopathy

Policy Number: 9.03.13
Origination: 7/2008
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Next Review: 7/2019

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for digital imaging systems for the detection and evaluation of diabetic retinopathy when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Retinal telescreening with digital imaging and manual grading of images may be considered medically necessary as a screening technique for the detection of diabetic retinopathy.

When Policy Topic is not covered
Retinal telescreening is considered investigational for all other indications, including the monitoring and management of disease in individuals diagnosed with diabetic retinopathy.

Considerations
The 2016 diabetic retinopathy screening recommendations of the American Diabetes Association (see Table PG1) include the following (American Diabetes Association, 2016):

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>First Retinal Examination</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults with type 1 diabetes</td>
<td>Initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 5 y after the onset of diabetes</td>
<td>Every 2 years if no evidence of retinopathy for 1 or more annual eye exams; dilated retinal examinations at least annually if any level of retinopathy is present.¹</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>Initial dilated and comprehensive eye examination by an ophthalmologist or optometrist</td>
<td>Every 2 years if no evidence of retinopathy for 1 or more annual eye exams; dilated retinal examinations at least annually if</td>
</tr>
</tbody>
</table>
at the time of diagnosis of diabetes any level of retinopathy is present. a
Before pregnancy in preexisting diabetes
Before pregnancy or early in the first trimester of pregnancy
Every trimester throughout pregnancy and for 1 y postpartum
a More frequent retinal examinations may be required if retinopathy is progressing or threatens sight.

### Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Individuals: With diabetes without known diabetic retinopathy | Interventions of interest are:
  - Digital retinal photography with optometrist or ophthalmologist image interpretation | Comparators of interest are:
  - Dilated retinal fundus evaluation via ophthalmoscopy
  - 7-field fundus photography | Relevant outcomes include:
  - Test accuracy
  - Test validity
  - Change in disease status
  - Functional outcomes |
| Individuals: With diabetes without known diabetic retinopathy | Interventions of interest are:
  - Digital retinal photography with automated image interpretation | Comparators of interest are:
  - Dilated retinal fundus evaluation via ophthalmoscopy
  - 7-field fundus photography | Relevant outcomes include:
  - Test accuracy
  - Test validity
  - Change in disease status
  - Functional outcomes |

### Summary

Retinopathy telescreening and risk assessment with digital imaging systems are proposed as an alternative to conventional dilated fundus examination in diabetic individuals. Digital imaging systems use a digital fundus camera to acquire a series of standard field color images and/or monochromatic images of the retina of each eye. Captured digital images may be transmitted via the Internet to a remote center for interpretation by trained readers, storage, and subsequent comparison.

For individuals who have diabetes without known diabetic retinopathy who receive digital retinal imaging with optometrist or ophthalmologist image interpretation, the evidence includes retrospective studies comparing the accuracy of digital screening with standard methods, systematic reviews of these studies, and a randomized controlled trial. Relevant outcomes include test accuracy and validity, change in disease status, and functional outcomes. A number of studies have reported on the agreement between direct ophthalmoscopy and photography and between standard film and digital imaging regarding the presence and stage of retinopathy. The studies have generally found high levels of agreement between retinal examination and imaging. There is limited direct evidence related to visual outcomes for patients evaluated with a strategy of retinal telescreening. However, given evidence from the large Early Treatment Diabetic Retinopathy Study that early retinopathy treatment improves outcomes, coupled with studies showing high concordance between the screening methods used in Early Treatment Diabetic Retinopathy Study and a randomized controlled trial demonstrating higher uptake of screening with a telescreening strategy, a strong chain of evidence can
be made that telescreening is associated with improved health outcomes. Digital imaging systems have the additional advantages of short examination time and the ability to perform the test in the primary care physician setting. For individuals who cannot or would not be able to access an eye care professional at the recommended screening intervals, the use of telescreening has low risk and is very likely to increase the likelihood of retinopathy detection. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have diabetes without known diabetic retinopathy who receive digital retinal imaging with automated image interpretation, the evidence includes retrospective studies and a prospective study comparing the accuracy of automated scoring of digital images with standard methods. Relevant outcomes include test accuracy and validity, change in disease status, and functional outcomes. The available studies have tended to report high sensitivity with moderate specificity, although there is variability across studies. Also, available studies have reported on different automated interpretation systems. These scoring systems have potential to improve screening in the primary care setting. However, given the variability in test characteristics across different systems, there is uncertainty about the accuracy of automated scoring systems in practice. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical input obtained in 2011 addressed the need for pupil dilation in retinal telescreening and the use of retinal telescreening for individuals with diagnosed diabetic retinopathy. Although evidence has shown that digital imaging without mydriasis leads to an increase in the proportion of ungradable photographs, practice guidelines, and clinical input have supported the use of both dilated and undilated retinal telescreening.

**Background**

**Diabetic Retinopathy**

Diabetic retinopathy is the leading cause of blindness among adults aged 20 to 74 years in the United States. The major risk factors for developing diabetic retinopathy are duration of diabetes and severity of hyperglycemia. After 20 years of disease, almost all patients with type 1 and more than 60% of patients with type 2 diabetes will have some degree of retinopathy. Other factors that contribute to the risk of retinopathy include hypertension and elevated serum lipid levels.

Diabetic retinopathy progresses, at varying rates, from asymptomatic, mild nonproliferative abnormalities to proliferative diabetic retinopathy (PDR), with new blood vessel growth on the retina and posterior surface of the vitreous. The 2 most serious complications for vision are diabetic macular edema (DME) and PDR. At its earliest stage (nonproliferative retinopathy), the retina develops microaneurysms, intraretinal hemorrhages, and focal areas of retinal ischemia. With disruption of the blood-retinal barrier, macular retinal vessels become permeable, leading to exudation of serous fluid and lipids into the macula (macular edema). As the
disease progresses, retinal blood vessels are blocked, triggering the growth of new and fragile blood vessels (proliferative retinopathy). The new blood vessels that occur in PDR may fibrose and contract, resulting in tractional retinal detachments with significant vision loss. Severe vision loss with proliferative retinopathy arises from vitreous hemorrhage. Moderate vision loss can also arise from macular edema (fluid accumulating in the center of the macula) during the proliferative or nonproliferative stages of the disease. Although proliferative disease is the main cause of blinding in diabetic retinopathy, macular edema is more frequent and is the leading cause of moderate vision loss in people with diabetes.

**Screening**
There is potential value in screening for diabetic retinopathy because diabetic retinopathy has few visual or ocular symptoms until vision loss develops. Because treatments are primarily aimed at preventing vision loss, and retinopathy can be asymptomatic, it is important to detect disease and begin treatment early in the process. Annual dilated, indirect ophthalmoscopy, coupled with biomicroscopy or 7-standard field stereoscopic 30° fundus photography, has been considered the screening technique of choice. Because these techniques require a dedicated visit to a competent eye care professional, typically an ophthalmologist, retinopathy screening is underutilized. This underuse has resulted in the exploration of remote retinal imaging, using film or digital photography, as an alternative to direct ophthalmic examination of the retina.

**Treatment**
With early detection, diabetic retinopathy can be treated with modalities that can decrease the risk of severe vision loss. Tight glycemic and blood pressure control is the first line of treatment to control diabetic retinopathy, followed by laser photocoagulation for patients whose retinopathy is approaching the high-risk stage. Although laser photocoagulation is effective at slowing the progression of retinopathy and reducing visual loss, it causes collateral damage to the retina and does not restore lost vision. Focal macular edema (characterized by leakage from discrete microaneurysms on fluorescein angiography) may be treated with focal laser photocoagulation, while diffuse macular edema (characterized by generalized macular edema on fluorescein angiography) may be treated with grid laser photocoagulation. Corticosteroids may reduce vascular permeability and inhibit vascular endothelial growth factor (VEGF) production, but are associated with serious adverse events including cataracts and glaucoma, with damage to the optic nerve. Corticosteroids also can worsen diabetes control. VEGF inhibitors (eg, ranibizumab, bevacizumab, pegaptanib), which reduce permeability and block the pathway leading to new blood vessel formation (angiogenesis), are being evaluated for the treatment of DME and PDR.

**Digital Photography and Transmission Systems for Retinal Imaging**
A number of photographic methods have been evaluated that capture images of the retina to be interpreted by expert readers, who may or may not be located proximately to the patient. Retinal imaging can be performed using digital retinal photographs with (mydriatic) or without (nonmydriatic) dilating of the pupil. One approach is mydriatic standard field 35-mm stereoscopic color fundus.
photography. Digital fundus photography has also been evaluated as an alternative to conventional film photography. Digital imaging has the advantage of easier acquisition, transmission, and storage. Digital images of the retina can also be acquired in a primary care setting and evaluated by trained readers in a remote location, in consultation with retinal specialists.

**Regulatory Status**

Several digital camera and transmission systems (see Table 1 for examples) have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process and are currently available (product codes: HKI and NFJ).

**Table 1. Digital Camera and Transmission Systems Cleared by FDA for Retinal Telescreening**

<table>
<thead>
<tr>
<th>Camera and Transmission Systems</th>
<th>Manufacturer</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRIS Intelligent Retinal Imaging System™</td>
<td>Ora Inc.</td>
<td>2015</td>
</tr>
<tr>
<td>DigiScope®</td>
<td>Eye Tel Imaging with Johns Hopkins Medicine</td>
<td>1999</td>
</tr>
<tr>
<td>The Fundus AutoImager™</td>
<td>Visual Pathways</td>
<td>2002</td>
</tr>
<tr>
<td>ImageNet™ Digital Imaging System</td>
<td>Topcon Medical Systems</td>
<td>2008</td>
</tr>
<tr>
<td>Zeiss FF450 Fundus Camera and the VISUPAC® Digital Imaging System</td>
<td>Carl Zeiss Meditec</td>
<td>2001</td>
</tr>
</tbody>
</table>

**Rationale**

This evidence review was created in November 2004 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through January 8, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances,
nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

**Optometrist or Ophthalmologist Image Interpretation**

**Seven-Field Fundus Photography**
The benefit of early treatment of diabetic retinopathy was established in the early 1990s in the large Early Treatment Diabetic Retinopathy Study (ETDRS), which was supported by the National Eye Institute. Local acquisition/remote interpretation technique, with interpretation by skilled readers, was used to consistently detect and evaluate the retinal changes of participants in the study. ETDRS used mydriatic 30° stereoscopic color fundus 35-mm photographs of 7 standard fields evaluated by a single reading center.

Seven-field fundus photography is considered the criterion standard for the detection of diabetic retinopathy and has sensitivity and specificity superior to direct and indirect ophthalmoscopy by ophthalmologists. Studies from the 1970s established the accuracy of 7-field fundus photography in the detection of diabetic retinopathy. Moss et al (1985) reported on an overall agreement of 85.7% when comparing retinopathy detection by ophthalmoscopy performed by skilled examiners with 7-standard-field stereoscopic 30° fundus photography evaluated by trained readers. Kinyoun et al (1992) found fair-to-good agreement between ophthalmoscopy and evaluation of 7-standard-field stereoscopic 30° fundus photography by the examining ophthalmologist, as well as by trained readers. Analysis of the discordance suggested that conventional ophthalmoscopy could miss up to 50% of microaneurysms, which are some of the earliest manifestations of diabetic retinopathy.

**Digital Imaging**
While 7-field fundus photography with evaluation by a skilled examiner has high sensitivity for diabetic retinopathy detection, its time-consuming nature limits its value as a screening tool. As a result, the use of digital image acquisition, with evaluation of images by an ophthalmologist who may or may not be co-located with the patient, has been evaluated for screening.

The efficacy of diabetic retinopathy detection with digital image acquisition, compared with the film-based acquisition, has been reported by several investigators.

Shi et al (2015) reported on a systematic review and meta-analysis of studies that compared telemedicine (digital image acquisition) with 7-field fundus photography for the detection of diabetic retinopathy or diabetic macular edema (DME). Twenty studies (total N=1960 patients) were included in the qualitative analysis; however, because 4 studies had the same primary author and reported on the same patient population, only one was included, leaving 17 studies for inclusion in the meta-analysis. Studies varied in the specific digital photography techniques
used, the number of fields evaluated, the use of stereoscopic vs monoscopic imaging, and the use of mydriatic vs nonmydriatic techniques. In pooled analysis, the sensitivity of digital imaging with telemedicine ophthalmologic evaluation for various diabetic retinopathy states (presence/absence of diabetic retinopathy, mild, moderate, or severe nonproliferative diabetic retinopathy, high- and low-risk proliferative diabetic retinopathy, DME, and clinically significant macular edema) was greater than 70%, except for the detection of severe nonproliferative diabetic retinopathy (sensitivity, 53%; 95% confidence interval [CI], 45% to 62%). In the pooled analysis, the specificity of digital imaging for various diabetic retinopathy states was greater than 90%, except for the detection of mild nonproliferative diabetic retinopathy (specificity, 89%; 95% CI, 88% to 91%). Summary receiver operating characteristic curves showed an area under the curve of greater than 0.9 for the detection of diabetic retinopathy and DME, across a range of severity.

One 2015 RCT was identified; it compared the effectiveness of a telemedicine screening program for diabetic retinopathy with traditional surveillance with an eye care professional. The trial randomized 567 adults with diabetes to a telemedicine program (n=296) or traditional surveillance (n=271). After 2 years of enrollment, those randomized to the traditional surveillance program were offered the opportunity to cross over to telemedicine screening. The telemedicine photography protocol involved the capture of 6 undilated 45° fundus photographs of each eye, with grading of the retinal images by 2 investigators into 5 categories of retinopathy and for the presence of DME. At 0- to 6-month follow-ups, those randomized to the telemedicine program were more likely to undergo retinopathy screening (94.6%) compared with those randomized to traditional surveillance (43.9%; risk difference, 50.7%; 95% CI, 46.6% to 54.8%; p<0.001). There was also a significant difference in screening rates at 6- to 18-month follow-ups—53.0% in the telemedicine group and 33.2% in the traditional screening group (risk difference, 19.8%; 95% CI, 16.5% to 23.1%; p<0.001). Beyond 18 months, when telemedicine was offered to all participants, there were no significant differences in screening rates between groups. Throughout follow-up, most subjects (>90%) had a diabetic retinopathy stage within ±1 unit of their baseline stage.

Examples of individual studies that have reported on the diagnostic accuracy of digital image acquisition include those by Liesenfeld et al (2000) and Tennant et al (2001), both of which collectively found high correlations between diabetic retinopathy diagnoses made by slit-lamp biomicroscopy performed by an ophthalmologist and by 7-field, 35-mm photography. Fransen et al (2002) published comparative results of standard evaluations using film and the same fields captured and transmitted as digital images. In their study of 290 adults with diabetes, the sensitivity of digital imaging compared with film was 98.2% and the specificity was 98.7%. Statistical analysis identified that the evaluation of film and digital images provided substantially equivalent results. When comparing high-resolution stereoscopic digital fundus photography with contact lens biomicroscopy, Rudnisky et al (2002) found a high level of agreement in the detection of clinically significant DME in diabetic patients.
Pupil Dilation
The 7-field fundus photography technique used in ETDRS, and in some of the studies of digital photography referenced above, used dilated pupils. However, screening using undilated pupils has advantages regarding time, cost, and patient compliance. Thus, in addition to the examination technique and the comparison of different photographic techniques, the results of dilated (mydriatic) vs undilated (nonmydriatic) fundus photography have been studied. Scanlon et al (2003) compared mydriatic and nonmydriatic photo screening programs using dilated slit-lamp biomicroscopy as the reference standard. In their study of 3611 patients, the sensitivity of mydriatic digital photography was 87.8%, the specificity was 86.1%, and the technical failure rate was 3.7%. Photography through an undilated pupil was found to provide a sensitivity of 86.0%, a specificity of 76.6%, and a technical failure rate of 19.7%.

Bragge et al (2011) conducted a meta-analysis to evaluate variations in qualifications of photographers and mydriatic status. Twenty studies were included that assessed the accuracy of a diabetic retinopathy screening method that used photography- or examination-based retinopathy screening compared with a standard of either 7-field mydriatic photography or dilated fundal examination. Studies with film or digital cameras were also selected. Studies of automated analysis techniques and technologies were excluded because they were not considered current standard practice. For meta-analysis, 40 assessments of screening methods were grouped into 6 categories: nonmydriatic camera, nonspecialist photographer (n=5); mydriatic camera, nonspecialist photographer (n=8); nonmydriatic camera, specialist photographer (n=4); mydriatic camera, specialist photographer (n=3); direct examination (n=8); method mixed or not reported (n=12). Sensitivity and specificity were assessed for the presence or absence of diabetic retinopathy as compared with the reference standard. Across all selected studies, in pooled analysis, the sensitivity and specificity rates for diabetic retinopathy detection were 82.5% (95% CI, 75.6% to 87.9%) and 88.4% (95% CI, 84.5% to 91.4%), respectively. In a multivariable logistic regression, variations in mydriatic status alone did not significantly influence sensitivity (odds ratio [OR], 0.89; 95% CI, 0.56 to 1.41) or specificity (OR=0.94; 95% CI, 0.57 to 1.54). The variations in medical qualifications of photographers did not significantly influence sensitivity (OR=1.25; 95% CI, 0.31 to 5.12), but the specificity of detection of any diabetic retinopathy was significantly higher for screening methods that used a photographer with specialist medical or eye qualifications. When photographs were taken by a specialist, the odds of a negative screening test when diabetic retinopathy was not evident with the reference standard were 3.86 (95% CI, 1.78 to 8.37) times that when photographs were taken by nonspecialists. This was largely due to the effect of specialists or nonspecialists in photographs taken without mydriasis (OR=5.65). The lower specificity seen with nonspecialist photographers could lead to increased referrals to an eye care specialist for further examination in some patients without diabetic retinopathy. This finding might have been biased because 6 of 7 assessments in the specialist category were derived from a single study. Interpretation is further limited by the inclusion of both standard film and digital imaging in the meta-analysis.
Since the publication of the Bragge systematic review, Rasmussen et al (2015) compared the concordance of diabetic retinopathy screening results obtained with ETDRS 7-field fundus photography with those obtained from single-image mydriatic wide field photography, nonmydriatic wide field photography, and mydriatic steered photography among 95 diabetic patients. Agreement within 1 level of retinopathy occurred in 99% of cases ($\kappa=0.98$; 95% CI, 0.97 to 0.99). Exact agreement between the nonmydriatic wide field photography and the 7-field fundus photography occurred in 76.3% of cases ($\kappa=0.71$; 95% CI, 0.63 to 0.78).

There is some evidence that retinal images from nonmydriatic cameras are more likely to be ungradable. Included in the Bragge review (2011) was a study by Murgatroyd et al (2004) that evaluated digital image screening with a nonmydriatic camera in 398 patients (794 eyes). Mydriasis was found to reduce the proportion of ungradable photographs from 26% to 5% ($p<0.001$). Sensitivity and specificity, based on gradable photographs only, were similar for the undilated single field (77% and 95%, respectively) and dilated images (81% and 92%, respectively). Because 64% of patients had gradable images, the authors suggested the possibility of targeted mydriasis or dilating only those patients who fail initial undilated photography. Mizrachi et al (2014) reported on a retrospective study of 6962 consecutive patients who underwent nonmydriatic digital imaging at community health centers. Although the photographer had viewed each image immediately and retook the photograph if the original image was considered of insufficient quality, a final 85.6% of the photographs were of adequate quality for diagnosis of diabetic retinopathy. Patients younger than 70 years of age had a greater chance of having good-quality images (93.7%) than patients older than 70 years (73.1%; $p<0.001$). In a random sample of 362 patients from the larger cohort of 6962 patients, comparison of nonmydriatic digital photographs with the reference standard (mydriatic retinal exams by an ophthalmologist) showed a sensitivity of 99.3%, specificity of 88.3%, and positive predictive value of 85.3%.

**Section Summary: Optometrist or Ophthalmologist Image Interpretation**

Data from multiple observational studies and an RCT have demonstrated that there is high concordance between direct ophthalmoscopy and grading by telescreening. Given findings from ETDRS that early retinopathy treatment improves outcomes, a strong chain of evidence can be made that telescreening with manual image interpretation is associated with improved health outcomes.

**Automated Image Interpretation**

The telemedicine screening programs using digital images (described above) rely on image interpretation by a trained ophthalmologist. A number of automated scoring systems are being evaluated for diabetic retinopathy screening. Many of the relevant studies have involved retrospective analyses of established datasets. The studies are described briefly below, and their diagnostic characteristics summarized in Table 1.

Sanchez et al (2011) examined the accuracy of a computer-aided system to diagnose diabetic retinopathy using a publicly available dataset of 1200 digital images.
color fundus photographs. The reference standard was based on 2 diagnoses provided with the dataset. At a specificity of 50%, the automated system had a sensitivity of 92.2% to detect diabetic retinopathy, which was similar to the results of 2 expert reviewers (sensitivity, 94.5% and 91.2%; specificity, 50%). Fifty-one abnormal images were wrongly classified as normal.

Oliveira et al (2011) assessed the accuracy of another automated screening system (RetmarkerSR) in a study of nonmydriatic images from 5386 patients in a diabetic retinopathy screening program. Automated analysis classified 47.5% as having no disease and 52.5% as having the disease (CIs not reported). A 2-step approach, in which patients marked as diseased on the first screen had a second screening visit, improved specificity to 63.2% (95% CI, 60.8% to 65.7%) with no loss of sensitivity. The sample in this study was biased because it did not include another 9.5% of images that a grader had identified as being of poor quality. The omission of these cases could have led to an erroneously high estimate of accuracy.

The Iowa Detection Program, an automated screening system, uses standardized algorithms to detect various retinal findings. This system was evaluated with a publicly available sample of digital color photographs from 1748 eyes (874 patients with diabetes) who were at risk for diabetic retinopathy. The photographs were taken in primary care diabetic retinopathy clinics from 3 hospitals in France and then graded by 3 masked retinal specialists. The prevalence of referable diabetic retinopathy (more than mild nonproliferative retinopathy and/or macular edema) was 21.7% (95% CI, 19.0% to 24.5%). The diagnostic characteristics of the Iowa Detection Program, compared with expert consensus standard, are summarized in Table 1. The area under the receiver operating curve was 0.937.

In 2016, the same study group reported on a deep learning algorithm add-on to the Iowa Detection Program algorithm, using the same dataset as in their 2013 study. The updated diagnostic characteristics for referable diabetic retinopathy of the deep learning algorithm are summarized in Table 1.

Also, Tufail et al (2016, 2017) reported on the screening performance of 4 automated retinal image analysis systems in a retrospective, observational study, which included 20,258 patients seen for diabetes eye screening, run by the National Health Service from 2012 to 2013. The manual images were graded by a team of 18 optometrists and nonoptometrists who had undergone prestudy training and evaluation. The automated scoring systems identified included EyeArt (Eyenuk), Retmarker (Retmarker), iGradingM (Medalytix Group, now EMIS UK), and IDx-DR (IDx). However, the iGradingM was determined to be unable to process disc-centered images, and IDx withdrew from the study, so details on their test performance are not discussed here further. The overall prevalence of referable diabetic retinopathy (defined as ungradable images, maculopathy, and preproliferative and proliferative retinopathy) was 2767 (13.7%) of 20,212. Compared with manual grading, referable diabetic retinopathy using the EyeArt and Retmarker systems was associated with likelihood ratios of 1.38 (95% CI,
1.35 to 1.4) and 1.63 (95% CI, 1.59 to 1.66), respectively. The sensitivity rates of automated test scoring for referable diabetic retinopathy, compared with manual image review, are summarized in Table 2.

### Table 2. Detection of Referable Diabetic Retinopathy With Automated Screening

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Reference Standard</th>
<th>Sens (95% CI), %</th>
<th>Spec (95% CI), %</th>
<th>PPV (95% CI), %</th>
<th>NPV (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanchez et al (2011)³⁶</td>
<td>1200 patients</td>
<td>2 expert reviewers</td>
<td>92.2</td>
<td>Set at 50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oliveira et al (2011)³⁷</td>
<td>5386 patients</td>
<td>Experienced ophthalmologist</td>
<td>96.1 (94.4 to 97.8)</td>
<td>51.7 (50.3 to 53.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abramoff et al (2013)³⁸</td>
<td>1748 eyes</td>
<td>3 retina specialists</td>
<td>96.8 (94.4 to 99.3)</td>
<td>59.4 (55.7 to 63.0)</td>
<td>39.8 (35.2 to 44.3)</td>
<td>98.5 (97.4 to 99.7)</td>
</tr>
<tr>
<td>Abramoff et al (2016)³⁹</td>
<td>1748 eyes</td>
<td>3 retina specialists</td>
<td>96.8 (93.3 to 98.8)</td>
<td>87.0 (84.2 to 89.4)</td>
<td>67.4 (61.5 to 72.9)</td>
<td>99.0 (97.8 to 99.6)</td>
</tr>
<tr>
<td>Tufail et al (2016)⁰⁰</td>
<td>20,258 patients</td>
<td>Trained optometrist and nonoptometrist graders</td>
<td>99.6 (97 to 99.9)</td>
<td></td>
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<tr>
<td>EyeArt</td>
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<tr>
<td>Retmarker</td>
<td></td>
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<td></td>
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<tr>
<td>Bawankar et al (2017)⁰¹</td>
<td>560 patients</td>
<td>3 ophthalmologists</td>
<td>91.2 (86.4 to 94.7)</td>
<td>96.9 (94.5 to 98.5)</td>
<td>94.4 (90.4 to 96.8)</td>
<td>95.0 (92.5 to 96.8)</td>
</tr>
</tbody>
</table>

CI: confidence interval; NPV: negative predictive value; PPV: positive predictive value; Sens: sensitivity; Spec: specificity.

Walton et al (2015) compared manual interpretation of nonmydriatic fundus images with the Intelligent Retinal Imaging System, an automated computer algorithm–based interpretation system, in a large retrospective study of 15,015 individuals with diabetes who were a subset of 18,025 patients with fundus photographs obtained as part of a county screening program, an automated computer algorithm–based interpretation system, in the detection of sight-threatening diabetic eye disease (severe nonproliferative diabetic retinopathy or proliferative diabetic retinopathy).²⁶ Compared with centralized manual interpretation, in the screening population, the Intelligent Retinal Imaging System algorithm had the following sensitivity, specificity, and positive and negative predictive values for sight-threatening diabetic eye disease: 66.4% (95% CI, 62.8% to 69.9%), 72.8% (95% CI, 72.0% to 72.5%), 10.8% (95% CI, 9.6% to 11.9%), and 97.8% (95% CI, 96.8% to 98.6%), all respectively.

### Section Summary: Automated Image Interpretation

The available studies on automated image interpretation have generally reported high sensitivity with moderate specificity, but with variability across studies,
leading to uncertainty about the accuracy of automated scoring systems in practice.

**Summary of Evidence**
For individuals who have diabetes without known diabetic retinopathy who receive digital retinal imaging with optometrist or ophthalmologist image interpretation, the evidence includes retrospective studies comparing the accuracy of digital screening with standard methods, systematic reviews of these studies, and a randomized controlled trial. Relevant outcomes include test accuracy and validity, change in disease status, and functional outcomes. A number of studies have reported on the agreement between direct ophthalmoscopy and photography and between standard film and digital imaging regarding the presence and stage of retinopathy. The studies have generally found high levels of agreement between retinal examination and imaging. There is limited direct evidence related to visual outcomes for patients evaluated with a strategy of retinal telescreening. However, given evidence from the large Early Treatment Diabetic Retinopathy Study that early retinopathy treatment improves outcomes, coupled with studies showing high concordance between the screening methods used in Early Treatment Diabetic Retinopathy Study and a randomized controlled trial demonstrating higher uptake of screening with a telescreening strategy, a strong chain of evidence can be made that telescreening is associated with improved health outcomes. Digital imaging systems have the additional advantages of short examination time and the ability to perform the test in the primary care physician setting. For individuals who cannot or would not be able to access an eye care professional at the recommended screening intervals, the use of telescreening has low risk and is very likely to increase the likelihood of retinopathy detection. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have diabetes without known diabetic retinopathy who receive digital retinal imaging with automated image interpretation, the evidence includes retrospective studies and a prospective study comparing the accuracy of automated scoring of digital images with standard methods. Relevant outcomes include test accuracy and validity, change in disease status, and functional outcomes. The available studies have tended to report high sensitivity with moderate specificity, although there is variability across studies. Also, available studies have reported on different automated interpretation systems. These scoring systems have potential to improve screening in the primary care setting. However, given the variability in test characteristics across different systems, there is uncertainty about the accuracy of automated scoring systems in practice. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Supplemental Information**
Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 2 academic medical centers and 1 physician specialty society while this policy was under review in 2011. Input supported the medical necessity of retinal telescreening when performed with or without dilation. Input was mixed on the use of retinal telescreening for monitoring and managing disease in individuals diagnosed with diabetic retinopathy. One reviewer commented that retinal telescreening could be useful for monitoring patients with stable disease, particularly in outlying areas where access to this technology exceeds access to ophthalmologists.

Practice Guidelines and Position Statements

American Diabetes Association

In 2016, the American Diabetes Association (ADA) updated its position statements on standards of medical care for diabetes (previous updates in 2010 and 2004).27-29 Included in the guidelines were specific recommendations for initial and subsequent screening examinations for retinopathy:

“Retinal photography, with remote reading by experts, has great potential to provide screening services in areas where qualified eye care professionals are not readily available. High-quality fundus photographs can detect most clinically significant diabetic retinopathy. Interpretation of the images should be performed by a trained eye care provider.... In-person exams are still necessary when the retinal photos are unacceptable and for follow-up if abnormalities are detected. Retinal photos are not a substitute for a comprehensive eye exam, which should be performed at least initially and at intervals thereafter as recommended by an eye care professional. Results of eye examinations should be documented and transmitted to the referring health care professional.”

American Association of Clinical Endocrinologists

The American Association of Clinical Endocrinologists published guidelines on comprehensive diabetes care in 2011.30 Guidelines for the first retinal screening exam, and a subsequent annual dilated eye examination by an ophthalmologist is consistent with the ADA’s 2016 position statement.27 The American Association of Clinical Endocrinologists guidelines stated, based on level 3 evidence (observational studies), that:

“the use of nonmydriatic fundus cameras, equipped with digital transmission technology, enables large-scale, point-of-care screening for retinopathy. Patients with abnormal retinal photographs are then triaged to full
examination by an ophthalmologist. This 2-step approach can be an efficient strategy for retinopathy screening at the population level, particularly in remote areas. However, the system is still under development and does not replace the current recommendation for annual dilated eye examination.”

American Academy of Ophthalmology
A 2017 preferred practice pattern from the American Academy of Ophthalmology (AAO), which updated AAO’s guidelines from 2003 and 2008, has provided the following on screening for diabetic retinopathy: “The purpose of an effective screening program for diabetic retinopathy is to determine who needs to be referred to an ophthalmologist for close follow-up and possible treatment and who may simply be screened annually. Some studies have shown that screening programs using digital retinal images taken with or without dilation may enable early detection of diabetic retinopathy along with an appropriate referral.”

AAO also published clinical statements on screening for diabetic retinopathy in 2014, which stated:

“Several forms of retinal screening with standard fundus photography or digital imaging, with and without dilation, are under investigation as a means of detecting retinopathy. Appropriately validated digital imaging technology can be a sensitive and effective screening tool to identify patients with diabetic retinopathy for referral for ophthalmic evaluation and management. Some studies have found that photography is more sensitive in identifying sight-threatening retinopathy than clinical examination with ophthalmoscopy.”

For pediatric patients with type 1 diabetes, AAO found that appropriate screening strategies are not adequately implemented. AAO indicated that the usefulness of digital photography in detecting retinopathy has been demonstrated but is unlikely to become widely used until it can be performed rapidly, simply, and at a reasonable cost.

American Telemedicine Association
In 2011, the American Telemedicine Association published guidelines on the clinical, technical, and operational performance standards for diabetic retinopathy screening. Recommendations were based on reviews of current evidence, medical literature, and clinical practice. The Association stated that Early Treatment Diabetic Retinopathy Study 30°, stereo 7-standard field, color 35-mm slides are an accepted standard for evaluating diabetic retinopathy. Although no standard criteria have been widely accepted as performance measurements of digital imagery used for diabetic retinopathy evaluation, clinical trials sponsored by the National Eye Institute have transitioned to digital images for diabetic retinopathy assessment. Telehealth programs for diabetic retinopathy should demonstrate an ability to compare favorably with Early Treatment Diabetic
Retinopathy Study film or digital photography as reflected in $k$ values for agreement of diagnosis, false-positive and false-negative readings, positive predictive value, negative predictive value, sensitivity and specificity of diagnosing levels of retinopathy, and macular edema. Inability to obtain or read images should be considered a positive finding, and patients with unobtainable or unreadable images should be promptly reimagined or referred for evaluation by an eye care specialist.

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Medicare National Coverage**

There is no national coverage determination specific to retinal telescreening. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

There is a national coverage determination on intraocular photography, originally developed in 1979, which states\(^\text{35}\):  

“Intraocular photography is covered when used for the diagnosis of such conditions as macular degeneration, retinal neoplasms, choroid disturbances and diabetic retinopathy, or to identify glaucoma, multiple sclerosis and other central nervous system abnormalities. Make Medicare payment for the use of this procedure by an ophthalmologist [sic] in these situations when it is reasonable and necessary for the individual patient to receive these services.”

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 3.

**Table 3. Summary of Key Trials**

<table>
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<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
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<tr>
<td>NCT02579837</td>
<td>CLEAR SIGHT: A Randomized Trial of Non-Mydriatic Ultra-Widefield Retinal Imaging to Screen for Diabetic Eye Disease</td>
<td>740</td>
<td>Mar 2019</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

**References**

23. Tufail A, Kapetanakis VV, Salas-Vega S, et al. An observational study to assess if automated diabetic retinopathy image assessment software can replace one or more steps of manual


**Billing Coding/Physician Documentation Information**

**92227** Remote imaging for detection of retinal diseases (e.g., retinopathy in a patient with diabetes) with analysis and report under physician supervision, unilateral or bilateral

**92228** Remote imaging for monitoring and management of active retinal disease (e.g., diabetic retinopathy) with physician review, interpretation and report, unilateral or bilateral

**92250** Fundus photography with interpretation and report

**0380T** Computer-aided animation and analysis of time series retinal images for the monitoring of disease progression, unilateral or bilateral, with interpretation and report

**ICD-10 Codes**

**E08.00** Diabetes mellitus; code range

**E13.9**

**Z13.5** Encounter for screening for eye and ear disorders
**Additional Policy Key Words**

N/A

**Policy Implementation/Update Information**

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<td>1/1/11</td>
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<td>Investigational policy statement added for all other indications.</td>
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