Retinal Telescreening for Diabetic Retinopathy

Policy Number: 9.03.13
Origination: 7/2008
Last Review: 7/2019
Next Review: 7/2020

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.

Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals: With diabetes without known diabetic retinopathy</td>
<td>Interventions of interest are: Digital retinal photography with optometrist or ophthalmologist image interpretation</td>
<td>Comparators of interest are: Dilated retinal fundus evaluation via ophthalmoscopy 7-field fundus photography</td>
<td>Relevant outcomes include: Test validity Change in disease status Functional outcomes</td>
</tr>
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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 systematic reviews and a randomized controlled trial. The relevant outcomes include test validity, change in disease status, and functional outcomes. Data from systematic reviews have demonstrated there is concordance between direct ophthalmoscopy and grading by mydriatic or non-mydriatic photography and remote evaluation. A randomized controlled trial that compared a telemedicine screening program with traditional surveillance found that patients who were randomized to the telemedicine arm were more likely to undergo screening (95% vs 44%). There is limited direct evidence related to visual outcomes for patients evaluated with a strategy of retinal telescreening. However, given evidence from the 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 a 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 a prospective study comparing the validity of automated scoring of digital images to remote interpretation. The relevant outcomes include test validity, change in disease status, and functional outcomes. One automated artificial intelligence system for evaluating diabetic retinopathy in primary care has received De Novo marketing clearance from the U.S. Food and Drug Administration. The pivotal study for this system met its non-inferiority margin compared to expert photography and image evaluation from a centralized site with sensitivity of 87.2% and specificity of 90.7%. The positive predictive value, which would be an important determinant of the value of a screening method to refer to an ophthalmologist, was not included in the published report, but could be calculated at 74.9%. Further development of this algorithm is needed to increase the clinical validity. 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 proximally 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>FDA Clearance</th>
<th>Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Welch Allyn RetinaVue 100 Imager (RV100)</td>
<td>Welch Allyn</td>
<td>Exempt</td>
<td></td>
</tr>
<tr>
<td>IRIS Intelligent Retinal Imaging System™</td>
<td>Ora Inc.</td>
<td></td>
<td>2015</td>
</tr>
<tr>
<td>CenterVue Digital Retinography System (DRS)</td>
<td>Welch Allyn</td>
<td>K101935</td>
<td>2010</td>
</tr>
<tr>
<td>ImageNet™ Digital Imaging System</td>
<td>Topcon Medical Systems</td>
<td></td>
<td>2008</td>
</tr>
<tr>
<td>The Fundus AutoImagerâ</td>
<td>Visual Pathways</td>
<td></td>
<td>2002</td>
</tr>
<tr>
<td>Zeiss FF450 Fundus Camera and the VISUPACâ Digital</td>
<td>Carl Zeiss Meditec</td>
<td></td>
<td>2001</td>
</tr>
</tbody>
</table>
Table 2. Automated Analysis Systems

<table>
<thead>
<tr>
<th>Automated Analysis Systems</th>
<th>Manufacturer</th>
<th>Clearance</th>
<th>Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDx-DR Artificial Intelligence Analyzer for the Topcon NW400</td>
<td>IDx, LLC</td>
<td>FDA De Novo</td>
<td>2018</td>
</tr>
<tr>
<td>EyeArt(TM)</td>
<td>Eyenuk(TM)</td>
<td>CE</td>
<td></td>
</tr>
<tr>
<td>Retmarker</td>
<td>Retmarker</td>
<td>CE</td>
<td></td>
</tr>
<tr>
<td>iGradingM</td>
<td>EMIS Health</td>
<td>CE</td>
<td></td>
</tr>
</tbody>
</table>

CE: Conformite Europeenne; FDA: Food and Drug Administration.

**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 February 6, 2019.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function—who include benefits and harms. Every clinical condition has specific outcomes that are important to patients and 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 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**

**Clinical Context and Test Purpose**

The purpose of retinal telescreening with manual grading of images in patients who have diabetes is to inform a decision whether to refer to an ophthalmologist.
The benefit of early treatment of diabetic retinopathy was established in the early 1990's 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. 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 question addressed in this evidence review is: Does digital retinal imaging with manual grading of images improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest are patients with diabetes who are undergoing screening for diabetic retinopathy.

**Interventions**
The test being considered is digital retinal imaging with manual image interpretation.

The diabetic retinopathy screening recommendations of the American Diabetes Association (2017) are provided in Table 3.

<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 beginning5 y after onset of diabetes</td>
<td>Yearly</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>Initial dilated and comprehensive eye examination by an ophthalmologist or optometrist at the time of diagnosis of diabetes</td>
<td>Yearly</td>
</tr>
<tr>
<td>Pregnancy in preexisting diabetes</td>
<td>Soon after conception and early in the first trimester</td>
<td>Every 1 to 3 months for severe NPRD or every 3 to 12 months if no to moderate NPRD</td>
</tr>
</tbody>
</table>

NPRD: non proliferative diabetic retinopathy
Adapted from American Diabetes Association (2017).

**Comparators**
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 1970's 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.

Outcomes
The general outcomes of interest are sensitivity and specificity to detect retinopathy in order to facilitate early treatment and prevent a loss of visual function.

The beneficial outcome of a true-positive test is the early detection of diabetic retinopathy with treatment and preservation of vision. The beneficial outcome of a true-negative test is continued assurance with follow-up scheduled after one year.

A harmful outcome of a false-positive test is unnecessary referral to an ophthalmologist. A harmful outcome of a false-negative test is delay in treatment potentially resulting in vision loss.

Timing
Comparison with 7-field fundus photography would be immediate. A change in retinopathy can be observed over the period of a year, while a change in vision may occur over several years.

Setting
The setting is outpatient care by a primary care physician or specialist in diabetes or in a community screening program.

Study Selection Criteria
For the evaluation of clinical validity of the test, studies that meet the following eligibility criteria were considered:
- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard

Review of Evidence
The efficacy of diabetic retinopathy detection with digital image acquisition, compared with 7-field fundus photography, has been evaluated in over 20 studies (total n=1960 patients) and summarized in a systematic review by Shi et al (2015). In pooled analysis, the sensitivity of digital imaging with telemedicine ophthalmologic evaluation for various diabetic retinopathy states was greater than 70%. The pooled specificity of digital imaging for various diabetic retinopathy
states was greater than 90%, except for the detection of mild non-proliferative diabetic retinopathy (specificity, 89%; 95% confidence interval [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 diabetic macular edema, across a range of severity.

The 7-field fundus photography technique used in ETDRS, and in some of the studies of digital photography, 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. 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. In a multivariable logistic regression, variations in mydriatic status alone did not significantly influence sensitivity (odds ratio, 0.89; 95%, CI, 0.56 to 1.41) or specificity (odds ratio=0.94; 95% CI, 0.57 to 1.54).

One 2015 RCT 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 two years of enrollment, those randomized to the traditional surveillance program were offered the opportunity to cross over to telemedicine screening. At 0- to 6-month follow-up, 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).

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

Data from systematic reviews have demonstrated there is concordance between direct ophthalmoscopy and grading by mydriatic or nonmydriatic photography and remote evaluation. An RCT that compared a telemedicine screening program with traditional surveillance found that patients who were randomized to the telemedicine arm were more likely to undergo screening (95% vs 44%). There is limited direct evidence related to visual outcomes for patients evaluated with a strategy of retinal telescreening. However, given evidence from the EDTRS that early retinopathy treatment improves outcomes, coupled with studies showing high concordance between the screening methods used in ETDRS, 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 a low risk and is very likely to increase the likelihood of retinopathy detection.

Automated Image Interpretation

Clinical Context and Test Purpose
The purpose of digital retinal imaging with automated image interpretation in patients who have diabetes is to inform a decision whether to refer to an ophthalmologist. The telemedicine screening programs (described above) rely on image interpretation by a trained ophthalmologist. A number of automated scoring systems are being evaluated for diabetic retinopathy screening.

The question addressed in this evidence review is: Does digital retinal imaging with automated image interpretation improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest are patients with diabetes who are undergoing screening for diabetic retinopathy.

Interventions
The test being considered is digital retinal imaging with automated image interpretation. Algorithms for retinal imaging analysis are undergoing rapid evolution. In 2018, the U.S. Food and Drug Administration gave the first marketing clearance for an automated analysis system with artificial intelligence (AI)(IDx-DR)through the De Novo classification process. The IDx-DR was previously known as the Iowa Detection Program for Referable Diabetic Retinopathy.

Comparators
Seven-field fundus photography with expert evaluation of images is considered the criterion standard for the detection of diabetic retinopathy.

Outcomes
The general outcomes of interest are the sensitivity, specificity, positive predictive value (PPV) and negative predictive value to detect retinopathy in order to facilitate early treatment and prevent a loss of visual function.

The beneficial outcome of a true-positive test is the early detection of diabetic retinopathy with treatment and preservation of vision. The beneficial outcome of a true-negative test is assurance with scheduling follow-up for one year.

The harmful outcome of a false-positive test is unnecessary referral to an ophthalmologist. The harmful outcome of a false-negative test is delay in treatment potentially resulting in vision loss.
**Timing**
Comparison with 7-field fundus photography would be immediate. A change in retinopathy can be observed over the period of a year, while a change in vision would occur over several years.

**Setting**
The setting is outpatient care by a primary care physician or specialist in diabetes.

**Study Selection Criteria**
For the evaluation of clinical validity of the test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard

**Review of Evidence**
The pivotal study of the IDx-DRAI image analysis system was published by Abramoff et al (2018). This was a non-inferiority trial that compared the AI analysis system with expert mydriatic photography and centralized reading of images (see Table 4). Nine hundred patients with diabetes and no history of diabetic retinopathy were enrolled at primary care centers. The primary care staff received four hours of training in image capture and use of the system. The system includes an image quality algorithm, which recommended pupil dilation in 23.6% of patients when 3 attempts at nonmydriatic image capture had failed. Compared to expert mydriatic photography and centralized image assessment, the AI system had sensitivity of 87.2%, specificity of 90.7%, PPV of 74.9% and negative predictive value of 95.7% (see Table 5).

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population</th>
<th>Design</th>
<th>Reference Standard</th>
<th>Threshold for Positive Index Test</th>
<th>Timing of Reference and Index Tests</th>
<th>Blinding of Assessors</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abramoff et al (2018)</td>
<td>900 Patients with diabetes and no history of DR seen at primary care sites</td>
<td>Multicenter prospective non-inferiority design with intent-to-screen</td>
<td>Expert mydriatic photography and centralized image assessment</td>
<td>Diagnostic algorithm based on multiple detectors</td>
<td>Not specifically stated but images appear to be taken at the same time</td>
<td>Yes</td>
<td>23.6% required pupil dilation for adequate image quality</td>
</tr>
</tbody>
</table>

DR: diabetic retinopathy; NR: not reported

**Table 5. Clinical Validity**

<table>
<thead>
<tr>
<th>Study</th>
<th>Initial N</th>
<th>Final N</th>
<th>Excluded Samples</th>
<th>Prevalence of Condition</th>
<th>Clinical Validity (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sensitivity</td>
</tr>
<tr>
<td>Abramoff et al</td>
<td>900</td>
<td>819</td>
<td>33 not</td>
<td>24.2%</td>
<td>87.2%</td>
</tr>
</tbody>
</table>
Table 6. Study Design and Conduct Gaps

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection(^a)</th>
<th>Blinding(^b)</th>
<th>Delivery of Test(^c)</th>
<th>Selective Reporting(^d)</th>
<th>Data Completeness(^e)</th>
<th>Statistical(^f)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abramoff et al (2018)(^10)</td>
<td>1. not described</td>
<td>1. not blinded to results of reference or other comparator tests</td>
<td>1. Timing of delivery of index or reference test not described</td>
<td>1. Not registered</td>
<td>1. Inadequate description of indeterminate and missing samples</td>
<td>1. Confidence intervals for PPV and NPV not reported</td>
</tr>
</tbody>
</table>

PPV: positive predictive value; NPV: negative predictive value.

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

\(^a\)Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).

\(^b\)Blinding key: 1. Not blinded to results of reference or other comparator tests.

\(^c\)Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.


\(^e\)Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

\(^f\)Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Section Summary: Automated Image Interpretation

One automated AI system for evaluating diabetic retinopathy in primary care has received De Novo marketing clearance from the U.S. Food and Drug Administration. The pivotal study for this system met its non-inferiority margin compared to expert photography and image evaluation from a centralized site with sensitivity of 87.2% and specificity of 90.7%. The PPV, which would be an important determinant of the value of a screening method to refer to an ophthalmologist, was not included in the published report, but could be calculated at 74.9%. Further study as the AI system evolves is needed to determine whether the PPV can approach that of an expert evaluator.

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 systematic reviews and an RCT. The relevant outcomes include test validity, change in disease status, and functional outcomes. Data from systematic reviews have demonstrated there is concordance between direct ophthalmoscopy and grading by mydriatic or nonmydriatic photography and remote evaluation. An RCT that compared a telemedicine screening program with traditional surveillance found that patients who were randomized to the telemedicine arm were more likely to undergo screening (95% vs 44%). There is limited direct evidence related to visual outcomes for patients evaluated with a strategy of retinal telescreening. However, given evidence from the ETDRS that early retinopathy treatment improves outcomes, coupled with studies showing
high concordance between the screening methods used in ETDRS, and an RCT 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 a 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 a prospective study comparing the validity of automated scoring of digital images to remote interpretation. The relevant outcomes include test validity, change in disease status, and functional outcomes. One automated AI system for evaluating diabetic retinopathy in primary care has received De Novo marketing clearance from the U.S. Food and Drug Administration. The pivotal study for this system met its non-inferiority margin compared to expert photography and image evaluation from a centralized site with sensitivity of 87.2% and specificity of 90.7%. The PPV, which would be an important determinant of the value of a screening method to refer to an ophthalmologist, was not included in the published report, but could be calculated at 74.9%. Further development of this algorithm is needed to increase the clinical validity. 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
The American Diabetes Association (2017) updated its position statements on standards of medical care for diabetes. Included in the guidelines were specific recommendations for initial and subsequent screening examinations for retinopathy:

- "Adults with type 1 diabetes should have an initial eye examination by an ophthalmologist or optometrist within 5 years after the onset of diabetes. (B)"
- "Patients with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist at the time of the diabetes diagnosis. (B)"
- "Eye examinations should occur before pregnancy or in the first trimester in patients with preexisting type 1 or type 2 diabetes, and then these patients should be monitored every trimester and for 1 year postpartum as indicated by the degree of retinopathy. (B)"
- "While retinal photography may serve as a screening tool for retinopathy, it is 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. (E)"

The American Diabetes Association noted that "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."

American Academy of Ophthalmology
A preferred practice pattern from the American Academy of Ophthalmology (2017) 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."

American Telemedicine Association
The American Telemedicine Association (2011) 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 reimaged 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:\[13:\]

“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 7.

<table>
<thead>
<tr>
<th>Table 7. Summary of Key Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NCT No.</strong></td>
</tr>
<tr>
<td>NCT02579837</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

REFERENCES


### Billing Coding/Physician Documentation Information

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>92227</td>
<td>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</td>
</tr>
<tr>
<td>92228</td>
<td>Remote imaging for monitoring and management of active retinal disease (e.g., diabetic retinopathy) with physician review, interpretation and report, unilateral or bilateral</td>
</tr>
<tr>
<td>92250</td>
<td>Fundus photography with interpretation and report</td>
</tr>
</tbody>
</table>

### 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

- **7/1/08** - New policy; considered medically necessary.
- **7/1/09** - No policy statement changes.
- **7/1/10** - No policy statement changes.
- **1/1/11** - Coding updated.
- **7/1/11** - No policy statement changes.
- **7/1/12** - Investigational policy statement added for all other indications.
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