Regence

Medical Policy Manual Medicine, Policy No. 175.04

Digital Therapeutic Products for Amblyopia

Effective: January 1, 2025

Next Review: September 2025
Last Review: November 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Digital health products are technologies, platforms, and systems that engage consumers for lifestyle, wellness, and health-related purposes. A digital therapeutic product is a specific type of digital health product that is practitioner-prescribed software that delivers evidence-based therapeutic intervention directly to a patient to prevent, manage, or treat a medical disorder or disease. Digital therapeutic products have been proposed to supplement or replace established treatments for amblyopia.

MEDICAL POLICY CRITERIA

Notes:

- Member contracts for covered services vary. Member contract language takes precedence over medical policy.
- This policy addresses the use of practitioner-prescribed software applications for therapeutic intervention.
- This policy does not address:
  - Software that is used for the function or control of an FDA-cleared or approved stand-alone medical device (e.g., external insulin pump or pacemaker).

- Applications operated by a health care practitioner for remote health monitoring.
- Products not meeting the definition of a digital therapeutic (see Policy Guidelines in Digital Therapeutic Products, Medicine, Policy No. 175).

The use of a digital therapeutic product for the treatment of amblyopia either as a stand-alone treatment or as an adjunct to standard treatment, is considered **investigational** including but not limited to CureSight™, Luminopia One™, and RevitalVision.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Digital Therapeutic Products, Medicine, Policy No. 175

BACKGROUND

AMBLYOPIA

Amblyopia is reduced vision without a cause detected by physical eye examination. Amblyopia is also known as lazy eye and occurs in one, or less often, both eyes and is caused by abnormal visual system development in infancy and childhood.[1] In early childhood, the brain's visual system learns to interpret images from both eyes. The brain relies more heavily on the non-amblyopic eye and suppresses poor images from the amblyopic eye, which worsens vision in the amblyopic eye. Amblyopia can also cause loss of stereopsis and depth perception, reduced reading speed, impaired motor skills, and lower self-confidence in children.

Amblyopia is the leading cause of preventable monocular vision loss and is prevalent among children. Amblyopia can be caused by multiple factors including myopia, hyperopia, astigmatism, strabismus, or cloudiness in the crystalline lens. Amblyopia and its associated risk factors are more common in children who are premature, small for their gestational age, have a developmental delay, or have a first-degree relative with amblyopia. If untreated or inadequately treated, amblyopia can cause lifelong vision loss, and the risk of bilateral vision impairment is doubled for individuals with amblyopia.

Treatment

Timely amblyopia treatment decreases the likelihood of vision loss later in life, usually improves visual acuity, and sometimes improves binocularity.[1] Success rates of amblyopia treatment decline as age increases. Many strategies are used to improve visual acuity in amblyopia, and the goal of treatment is to achieve equal visual acuity between both eyes although this is not always possible. Treatment steps include correction of any cause of visual deprivation, correction of refractive errors likely to cause blur, and promotion of amblyopic eye use by occluding, fogging, or reducing contrast of images detected by the stronger eye.

According to the American Academy of Ophthalmology's (AAO) evidence-based Preferred Practice Pattern, recommended treatment is based on age, visual acuity, and adherence and response to previous treatment as well as the child's physical, social, and psychological status. Recommended treatments for amblyopia in children include[1]:

- ***"Refractive correction with eyeglasses is recommended as the initial step in care of children 0-17 years of age."*** Occlusion of the non-amblyopic eye with eye patching or pharmacological treatment with blurring atropine eye drops are each recommended *as "an appropriate choice for amblyopia treatment in children who do not improve with refractive correction alone or who have incomplete resolution of their visual acuity deficit."*

- Surgery is indicated when amblyopia is caused by opacity issues in the ocular media, e.g., cataract, nonclearing vitreous opacity, cornmeal opacities, that are severe enough to prevent successful amblyopia therapy without surgical correction.

Success of current treatments varies due to severity of amblyopia and issues with therapy adherence.[2] Vision improvement is typically greatest for the first four months and beyond with eyeglasses. Success with patching and atropine eye drops is similar; both result in statistically and clinically significant improvements in visual acuity and stereopsis. Issues with patching and blurring eye drops include poor adherence to treatment and suboptimal treatment outcomes. Lack of adherence to patching is common with adherence ranging from 41% to 57%. With current treatments, approximately 25% of eyes with severe amblyopia and 58% of eyes with moderate amblyopia improve to a level of 0.20 Logarithm of the Minimum Angle of Resolution (logMAR), an improvement of two lines of letters on the LogMAR visual acuity chart. Common goals of digital therapeutics for amblyopia are to promote use of both eyes with binocular visual stimulation and to increase adherence to therapy using appealing visuals such as movies, television shows, or video games.

REGULATORY STATUS

The RevitalVision system (Talshir Guy Medical Technologies) received U.S. Food and Drug Administration (FDA) 510(k) approval in August 2001, then known as the AA-1 System (K012530).[3] RevitalVision is software for at-home use on the patient's personal computer and is customized to match the patient's visual acuity. The technology is designed to improve visual acuity by facilitating neural connections in the visual cortex through a visual training regime using interactive visual tasks and Gabor patches, grate-like images that stimulate neurons in the visual cortex. RevitalVision is indicated for the treatment of amblyopia in patients nine years or older when prescribed by a vision care provider. Use of RevitalVision does not require simultaneous use of eyeglasses. A minimum of 12 training sessions per month are recommended, three to four times per week for approximately 30 minutes. Total training sessions vary by condition and eye care provider.

In October 2021, Luminopia One™ (Luminopia, Inc.) received marketing clearance by the U.S. FDA through the De Novo premarket review process (DEN210005).[4] Luminopia One™ is a prescription software-only digital therapeutic indicated for the improvement of visual acuity in patients 4 to 7 years old who have amblyopia associated with anisometropia and/or with mild strabismus. The application incorporates dichoptic presentations into displays of digital content, e.g., movies and television shows, via therapeutic algorithms designed to strengthen visual processing and increase use of the amblyopic eye. Luminopia One™ is to be used with commercially available head-mounted displays which are compatible with the software application in an at-home environment. Luminopia One™ is intended for previously treated and untreated patients, but patients with greater than 12 months prior treatment, other than refractive correction, have not been studied. Luminopia One™ is indicated as an adjunct to full-time refractive correction with glasses, which should also be warn under the head-mounted

display during therapy. One hour viewing sessions, six days per week for at least three months are recommended.

In September 2022, the CureSight-CS100™ (Nova-Sight) device received U.S. FDA 510(k) approval, listing Luminopia One™ as the predicate device.[5] CureSight-CS100™ is a prescription device and software indicated for the improvement of visual and stereo acuity in amblyopia patients 4 to 9 years old, with anisometropia and/or with mild strabismus. The system uses digital content, real-time eye tracking, and separation of visual stimuli presented on a monitor into two separate digital channels for each eye. Refractive correction glasses are to be warn underneath the CureSight-CS100 device, a dichoptic anaglyph (red-blue glasses). During treatment, patients wear anaglyph glasses and interact with the interface touchscreen by selecting digital content. Gaze and eye position are tracked, and the software blurs images for the non-amblyopic eye and sharpens images for the amblyopic eye. This system is designed to force the patient's visual system to use information from the central vision area of the amblyopic eye. CureSight-CS100™ is intended for both previously treated and untreated patients as an adjunct to full-time refractive correction. CureSight-CS100™ is intended for at-home use under remote supervision of an eye-care provider and NovaSight's Monitoring Center. Treatment requires a minimum of 90 minutes per day, five days per week. Duration of treatment is determined by an eye care provider.

EVIDENCE SUMMARY

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 including 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 a 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.

DIGITAL THERAPIES FOR AMBLYOPIA

Clinical Context and Therapy Purpose

The purpose of digital visual therapeutic products is to provide a treatment option that is an alternative to, or an improvement on, existing therapies for patients with amblyopia. Issues with established amblyopia therapies include discomfort, low adherence, stigmatization among peers, and failure to restore normal visual function in some children.[6] Digital visual therapeutics for amblyopia use dichoptically presented images such that each eye receives an

altered version of the same image in order to balance input from each eye to the brain. This technique is referred to as balanced binocular viewing, or binocular therapy. Binocular therapies present a range of visual stimuli (e.g., Gabor patches, movies, television shows, or video games) and exist in a range of platforms such as computer or tablet screens, specialized glasses, or virtual reality systems. These digital therapeutics have been designed to be child-friendly with the goal of increasing adherence to therapy. In contrast to conventional patching or pharmacological treatments, binocular therapies are designed to promote the two eyes working together instead of occluding the non-amblyopic eye.

REVIEW OF EVIDENCE

Systematic Reviews

Tsani (2024) conducted a systematic review of digital binocular treatment for amblyopia across 20 RCTs published between 2014 and 2024.[7] Included studies compared digital binocular therapy to standard amblyopia treatment or placebo. The reviewers concluded that binocular amblyopia treatment has shown promising results in improving visual acuity in patients with unilateral amblyopia. However, the reviewers also concluded that additional RCTs are needed to establish the optimal dosage, type, and duration of binocular therapy as a standard component of amblyopia care. The review also found that binocular therapy did not have a significant advantage in enhancing stereoscopic vision compared to established approaches and did not identify any safety concerns or evidence of induced reverse amblyopia. The reviewers noted that the evidence is limited by lack of long-term outcomes, which makes it difficult to determine the incidence of recurrent amblyopia.

A 2022 Cochrane Systematic Review compared binocular treatment to conventional patching or pharmacological blurring treatment to determine whether binocular treatments result in better visual outcomes.[2] The inclusion criteria were RCTs that enrolled children between the ages of 3 and 8 years old with unilateral amblyopia and any type of binocular viewing intervention on any device (e.g. computer monitors viewed with liquid-crystal glasses, hand-held screens, or virtual reality displays). The review excluded children who had received any previous treatment other than optical correction and studies with a follow-up time of less than eight weeks. The authors identified one eligible RCT by Holmes 2016, discussed below, that compared conventional patching to binocular treatment and analyzed a subset of 68 children from the study who met the age criterion of this review. The review authors concluded with moderate certainty that 16 weeks of binocular treatment is likely comparable to conventional patching treatment. The authors noted that due to the limited sample size and absence of long-term (e.g. 52 week) follow-up data, it is not yet possible to draw robust conclusions on the overall effectiveness and safety of binocular treatment for amblyopia.

Roda (2021) performed a systematic review and meta-analysis of five RCTs to compare efficacy of binocular treatment for amblyopia, including digital dichoptic training methods, to patching in children with unilateral amblyopia.[8] Primary outcome measures were visual acuity and stereopsis. No significant difference in visual acuity between patients treated with patching or binocular treatment was observed (standardized difference in means [SDM] = -0.07; 95% confidence interval [CI]: -0.45-0.20; p=0.464). Similarly, no significant difference in stereopsis was demonstrated between patients treated with patching or binocular treatment. The authors concluded that this meta-analysis did not reveal substantial evidence to support binocular treatment as an alternative treatment to traditional patching therapy but that it may be considered as a complementary therapy in unusual cases. The authors note that future studies

are required to draw conclusions as to whether more engaging digital therapies are more effective than standard treatments.

Chen (2021) conducted a systematic review and meta-analysis to evaluate the efficacy of binocular therapy versus patching and to determine whether binocular therapy could be an affective supplementary treatment for children with amblyopia.[9] The review included six RCTs in which a total of 304 participants received binocular therapy and 332 received conventional patching therapy. Mean best corrected visual acuity improvement in the binocular group was determined to be 0.13±0.14 logMAR and 0.16±0.14 logMAR in patching group. The combined effect analysis result was Z=3.01 (p=0.003). The authors reported severe heterogeneity among studies (I^2=56.8%, p=0.04) which they attribute to small sample size and diversity of binocular therapies. The authors concluded that binocular therapy may be an effective treatment for amblyopia but that a more statistically significant improvement was obtained with patching. The authors note that limitations of this study include the small sample size of six trials, lack of statistical analysis of masked data, inadequate randomization in one trial, and multiple trials demonstrated low adherence in binocular therapy groups which could influence treatment outcomes. Overall, the authors concluded that additional RCTs with larger sample sizes and longer treatment durations are necessary to assess the efficacy of binocular therapy for amblyopia.

In 2020, the AAO conducted a technology assessment of the efficacy of binocular therapy for the treatment of amblyopia compared to standard treatments.[10] The review also assessed whether binocular treatment confers sensory benefits, such as improved stereoacuity or reduced suppression to dichoptic treatment of amblyopia compared to conventional treatments which occlude the non-amblyopic eye. 20 studies were included in the review and were assigned a level of evidence rating: level I was assigned to well-designed and well-conducted RCTs (n=6); level II was assigned to well-designed case-control and cohort studies and lower-quality randomized studies (n=1); and level III was assigned to case series, case reports, and lower-quality cohort and case-control studies (n=13). Two level I and II studies reported a significant improvement in visual acuity in the binocular-treated group versus standard patching treatment (n=147 participants). Five studies failed to show a visual improvement from binocular therapy compared to standard treatments, and these studies were larger and more rigorously designed (n=813 patients). Level I and II studies did not show significant improvement over baseline in sensory status, including depth of suppression and stereopsis in participants treated with binocular therapy. 13 small, level III case series (n=163 participants) reported more improvements with binocular therapy than the level I and II studies. The review authors note that multiple level III studies included therapies deemed to be more engaging and therefore associated with better therapy adherence. The authors concluded that there is no level I evidence to support the use of binocular treatment as a substitute for standard treatments for amblyopia. Additionally, two large RCTs yielded inferior performance of binocular therapy compared to standard treatments. The authors suggest that more research is necessary to determine the potential benefits of binocular treatments for amblyopia.

Randomized Controlled Trials

Wygnanski-Jaffe (2024) published an evaluator-masked, multi-center RCT that compared the efficacy of CureSight-CS100™ (n=75) to eye patching (n=74) in children with anisometropic, small-angle strabismic, or mixed-mechanism amblyopia (ages four to nine years).[11] CureSight-CS100™ treatment occurred for 90 minutes per day, five days per week, for 16 weeks, and eye patching occurred for two hours per day, five days per week, for 16 weeks.

The primary outcome was the mean improvement from baseline in amblyopic eye visual acuity to week 16 in both groups, with a non-inferiority margin of less than or equal to 0.10 logMAR. Mean improvement from baseline at week 16 in the binocular treatment group was non-inferior to the patching group in the modified intent-to-treat dataset, with a least squares mean difference between groups of 0.034 logMAR (95% CI -0.009 to 0.076). Both groups showed significant median improvement in stereoacuity at week 16, with no significant between-group difference in the magnitude of improvement. Binocular visual acuity improved in both groups ($p<0.0001$). Notably, median adherence in the CureSight-CS100™ group was significantly higher than in the patching group (94.0% vs 83.9%, $p=0.0038$). Limitations of this study include that most participants had anisometropic amblyopia (82%) and lack of long-term follow-up.

Wygnanski-Jaffe (2023) published a multi-center RCT that compared visual outcomes of digital CureSight-CS100™ treatment to conventional patching treatment.[12] 103 participants ages 4 to 8 years with amblyopia received either digital (n=51) or eye patch (n=52) therapy. CureSight™ participants used the treatment for 90 minutes per day, 5 days per week for 16 weeks. Eye patch participants wore their patch for two hours per day, seven days per week. The primary outcome was mean improvement of visual acuity from baseline at 16 weeks (a non-inferiority of no more than 0.10 logMAR). Participants were assessed at 4, 8, 12, and 16 weeks. The baseline mean amblyopic eye visual acuity in the digital treatment group was 0.37±0.15 logMAR and 0.37±0.14 logMAR in the eye patch group. At 16 weeks, the mean change from baseline was 0.26 logMAR in the CureSight-CS100™ group and 0.23 logMAR in the eye patch group (standard error 0.02). Overall, the percentage of patients with a 2-line or more improvement in the binocular treatment group was 79% (34/43 patients) versus 61% (30/49 patients) in the patching group. A significantly greater median adherence was observed for the CureSight™ group (91%) compared to the patching group (83%). No serious adverse events were reported, and headaches occurred at a lower incidence in the CureSight™ group (4%) than the patching group (8%). Study limitations include the use of subjective self-logging compliance diaries for the patching group and that most patients had anisometropic amblyopia (90% of the patients in this study versus 50% to 60% in comparable RCTs). The authors note that a more conservative noninferiority limit, more similar to other studies, should have been used and that future studies are necessary to explore longer treatment durations, dosing, and effectiveness compared to other types of amblyopia treatments.

Xiao (2022) conducted a phase 3 RCT to evaluate the safety and efficacy of the Luminopia One™ (Luminopia, Inc.) dichoptic digital therapeutic for amblyopia.[13] 105 children 4 to 7 years old with amblyopia were randomized to receive either Luminopia One™ therapy or conventional optical correction with glasses. Participants in the treatment group (n=51) used Luminopia One™ at home for one hour per day, six days per week, and wore glasses full-time. Participants in the control group continued to wear glasses full-time (n=54). The primary outcome was change in visual acuity from baseline at 12 weeks, measured by masked examiners. 12 weeks after treatment, visual acuity improved by 1.8 lines (95% CI 1.4–2.3 lines; n=45) in the treatment group and by 0.8 lines (95% CI 0.4–1.3 lines; n=45) in the control group. Upon 12-week interim analysis, the difference between the treatment and control groups was significant (1.0 lines; $p=0.0011$; 96.14% CI 0.33-1.63 lines), and the authors stopped the study for early success, according to the study protocol. No serious adverse events were reported. Limitations of this study include lack of comparison to standard treatments, such as eye patching or blurring drops, and lack of long-term follow-up. Future studies are needed to assess the treatment's long-term effects and to compare to current standard treatments.

Manny (2022) published a multi-center RCT that compared treatment of children ages 4 to 6 years with the dichoptic iPad game, Dig Rush (Ubisoft, not yet commercially available), in addition to glasses (n=92) versus continued treatment with glasses only (n=90).[14] Participants in the video game group were prescribed to play one hour per day, five days per week. Participants in the glasses group were prescribed to wear glasses during all waking hours. At the four-week visit, there were 85 participants (92%) in the video game group and 84 participants (93%) in the glasses group available for analysis. Parents reported adherence of greater than 75% for 74 glasses group participants (95%) and 66 (78%) video game participants. At eight weeks, 75% adherence was reported for 78 (95%) in the glasses-wearing group and 69 participants (78%) in the video game group. At four weeks, mean visual acuity improved by 1.1 lines in the video game group and 0.6 lines in the group who wore glasses. At eight weeks, the mean visual acuity improvement for the video game group was 1.3 lines and 1.0 lines in the glasses group. Additional studies are necessary to compare this treatment to eye patching and to assess the long-term effectiveness of this treatment.

Elhusseiny (2021) published a double-masked, single-center RCT that assessed best-corrected visual acuity and stereoacuity gains in 20 children greater than 7 years old and adults with unilateral anisometropic and/or strabismic amblyopia treated with a prototype virtual reality-based binocular amblyopia therapy.[15] Participants had a history of prior amblyopia treatment failure and were randomized to either a full-treatment group (eight weeks of binocular treatment using therapeutic software on a virtual reality headset) or a sham-crossover group (four weeks of sham treatment followed by four weeks of binocular treatment). The full treatment group included 11 participants, and the sham group included 9 participants. Amblyopic eye visual acuity and stereoacuity were evaluated at 4, 8, and 16 weeks. In the full-treatment group, the mean amblyopic eye logMAR visual acuity at 16 weeks was 0.49 ± 0.26, compared with 0.47 ± 0.20 at baseline. In the sham-crossover group, it was 0.51 ± 0.18 at 16 weeks, compared with 0.53 ± 0.21 at baseline. The improvement in visual acuity was not significantly different between treatment groups. Stereoacuity (log arcsec) was significantly improved, from 7.3 ± 2 at baseline to 6.6 ± 2.3 at 8 weeks (< 0.001) and 6.7 ± 2.6 at 16 weeks ($p<0.001$). No significant adverse events (diplopia, asthenopia, or worsening strabismus) were noted in either group. The authors noted that larger studies are necessary to confirm these results.

In a double-masked RCT, Gao (2018) evaluated efficacy of a home-based digital therapy video game compared to a placebo video game to improve visual function.[16] The study included children 7 years old and older and adults. Participants were prescribed video game play for a minimum of one hour per day for six weeks. The primary outcome was the change in visual acuity from baseline to six weeks. Treatment compliance was recorded by the video game software as well as a written diary completed by study participants. 56 participants were randomized to the active group and 59 participants to the placebo video game. At the six-week follow-up, there were 50 participants available for analysis in the active group and 57 participants in the placebo group. In the active group, there were 36 participants (64%) who met the study definition of compliance compared to 49 (83%) in the placebo group. At six weeks, the mean improvement of visual acuity from baseline was 0.06 lines (3 letters on a vision chart) in the active group and 0.07 lines (3.5 letters) in the placebo group. No significant differences were found between the two groups.

An RCT by Manh (2018) compared improvement of visual acuity in participants with amblyopia by following either treatment with a binocular video game or eye patching.[17] Participants were 13 to 16 years old and were followed for 16 weeks after treatment. Those in the binocular

video game group (n=40) were prescribed one hour of game play each day for seven days per week. Those in the eye patch group (n=60) were prescribed to wear the patch two hours per day. Parents or participants recorded the number of hours of treatment each day, and the video game device recorded the duration of game play. There were 39 participants (98%) in the video game group and 58 participants (97%) in the eye patch group who completed the 16 weeks of treatment. Adherence after 16 weeks was assessed to be adequate in 24 video game participants (62%) and 42 eye patch participants (75%). However, in the video game group, the game device recorded only 13% of participants who completed 75% of their prescribed treatments. At 16 weeks, mean visual acuity in the amblyopic eye improved by 3.5 letters (2-sided 95% CI 1.3 to 5.7 letters) in the binocular group and by 6.3 letters (2-sided 95% CI 4.4 to 8.5 letters) in the eye patch group. While a major limitation of this study is poor treatment adherence, the authors reported more improvement in VA in the eye patch group compared to the binocular vision treatment group.

Holmes (2016) conducted a multi-center RCT to compare visual acuity improvement in children with amblyopia treated with a binocular iPad game versus part-time patching.[18] Visual acuity was measured at baseline and after 16 weeks of treatment. 195 participants wore an eye patch for two hours per day, seven days per week. 190 participants played the binocular video game for one hour per day, seven days per week. Parents reported compliance by recording the number of hours spent using either treatment. 172 participants (92.5%) in the eye patch group completed over 75% of the prescribed treatments. 176 participants (66.7%) in the video game group were available for evaluation at the 16-week follow-up. Only 39 video game participants (22.2%) completed more than 75% of their prescribed treatments, as measured by the video game log file data. Mean visual acuity improved from 1.08 lines from baseline in the video game group and by 1.32 lines in the eye patch group. There were no significant between-group differences found for changes in amblyopic eye visual acuity. Limitations include lack of occlusion dose monitors, adherence data reliance on parental report (particularly for eye patch wearing), low adherence among the video game participants, and no monitoring of wearing the red-green glasses required to play the video game.

Nonrandomized Studies

Wygnanski-Jaffe (2024) published a prospective, non-randomized, one-year follow-up study that evaluated the efficacy of CureSight-CS100™ in 27 children (ages four to nine years) with anisometropic, small-angle strabismic, or mixed-mechanism amblyopia.[19] At one-year, there was a partial reduction in visual acuity gain in the amblyopic eye, but a significant residual gain of 0.20 logMAR remained compared to baseline. Additionally, gains in stereoacuity and binocular visual acuity were maintained at both 12 weeks and one year post-treatment, with no significant change compared to end of treatment. However, amblyopia recurrence, defined as a worsening of ≥2 logMAR levels, occurred in 5.3% of patients at 12 weeks and 20.4% at one year post-treatment. Limitations of this study include small sample size and lack of comparison with eye patching for long-term follow-up.

Zhu (2023) conducted a prospective study of CureSight-CS100™ that included 34 participants ages 4 to 9 years with unilateral anisometropic amblyopia who had not received prior treatment.[20] The study included a full treatment group in which participants used CureSight-CS100™ for 90 minutes per day, five days per week (n=12); a part-time treatment group who used CureSight-CS100™ for 90 minutes per day, three days per week (n=8); and a control group who received standard patching treatment for two hours per day, seven days per week (n=14). Participants were evaluated at 4, 8, and 12 weeks. At 12 weeks, mean amblyopic eye

distance visual acuity improved by 1.8 lines (95% CI 1.1 to 2.5) in the full treatment group, 1.5 lines (95% CI, 0.4-2.7) in the part-time treatment group, and 3.0 lines in the patching group. Stereoacuity improved 0.38 log-arcseconds (95% CI, 0.24-0.53) in the full-time treatment group, 0.59 log-arcseconds (95% CI, 0.36-0.82) in the part-time treatment group, and 0.40 log-arcseconds (95% CI, 0.13-0.67) in the patching group. Limitations of this study are small sample size and lack of long-term outcomes assessment.

Wygnanski-Jaffe (2023) published the results of the first-in-human prospective study of 23 amblyopic children 4 to 15 years of age, 20 of whom completed 6 months of treatment with the CureSight-CS100™ system.[21] Three participants left the study before the four-week follow-up. 13 participants had been previously treated with patching. At the primary endpoint of 24 weeks, amblyopic eye visual acuity (VA) significantly improved by 0.19 ± 0.11 logMAR for distance crowded VA, 0.27 ± 0.13 logMAR for near crowded VA, and by 0.22 ± 0.15 logMAR for distance single letter VA ($p<0.001$ for each). Stereoacuity improved by 198 ± 218 arcsec ($p=0.001$). Binocular VA improved 0.09 ± 0.13 logMAR for distance crowded VA ($p=0.007$), 0.12 ± 0.11 logMAR for near crowded VA ($p<0.001$) and 0.07 ± 0.12 logMAR for distance single letter VA ($p=0.018$). At 52 weeks, distance crowded visual acuity, distance single letter visual acuity, and stereoacuity were not significantly different from the 24-week measurements.

Abdal (2022) conducted a retrospective study of 161 children, 4 to 13 years old, with unilateral or bilateral amblyopia, who received dichoptic digital treatment with the Bynocs® platform (Kanohi Eye Pvt. Ltd.), an artificial intelligence-based video game that is used in-office or at-home via an online eye care appointment.[22] Participants used the therapy 30 minutes per day, 5 times per week, for 6 weeks. Best corrected mean visual acuity in the amblyopic eye improved by 0.39 logMAR ($p<0.001$), and binocular function score improved by a mean change of 1.55 ($p<0.001$). Study limitations include lack of control or comparison group and a short, six-week, treatment period.

Magdalene (2022) published the results of a prospective, observational study that measured visual outcomes in 45 patients with unilateral or bilateral amblyopia.[23] Participants received RevitalVision therapy after at least six months of no improvement with part-time occlusion therapy (e.g., with eye patching or atropine eye drops). Participants completed 40 training sessions within 3 months. Mean best-corrected visual acuity improved by approximately 2 logMAR lines ($p<0.001$) in 3 months. Issues with this study include lack of a comparison group, small sample size, and a large age range among participants (8 to 48 years of age).

Murali (2022) performed a prospective study of 29 adults ages 18 to 40 years with anisometropic amblyopia who were treated with the binocular video game, VisuoPrime (Visuoprime Neurapy, Ltd.) for 30 minutes per day, 7 days per week, for 6 weeks.[24] Participants had the option of completing game training in an eye care office (n=5) or at home (n=24). The video game included a tracking mechanism to determine therapy compliance. 14 subjects were compliant with therapy, and 15 subjects were noncompliant, playing less than 80% of prescribed therapy. Best corrected visual acuity and binocularity were assessed at one and three months. Best corrected visual acuity of the amblyopic eye improved from 0.60 ± 0.40 logMAR to 0.45 ± 0.29 logMAR and 0.38 ± 0.23 logMAR at one and three months, respectively ($p=0.0001$). Near acuity improved from 0.21 ± 0.14 to 0.14 ± 0.08 logMAR and 0.1 ± 0.04 logMAR at one and three months respectively ($p<0.0001$). The authors reported that stereopsis improved in 24% of subjects at one month, and this change persisted at three months. Study limitations included lack of a control or comparison group, small sample size, and lack of long-term follow-up.

Xiao (2021) published the results of a single-arm, multicenter prospective pilot study that evaluated the efficacy of Luminopia One™ in 90 children 4 to 12 years old with anisometropic, strabismic, or mixed amblyopia.[25] Digital therapy was prescribed for 1 hour per day, 6 days per week, for 12 weeks of at-home use. Of the 90 participants, 73 (81%) had prior treatment beyond refractive correction with glasses. Adherence to therapy was 86%. 74 participants (82%) completed the 12-week follow-up. Mean amblyopic eye best corrected visual acuity improved from 0.50 logMAR to 0.35 logMAR (1.5 logMAR lines; 95% CI, 1.2-1.8 lines; p<0.0001). Mean stereoacuity improved by 0.28 log arcsec (95% CI, 0.14-0.42 log arcsec; p<0.0001). Median adherence was 86% (interquartile range, 70%-97%). This study is limited by lack of a comparison group. The authors noted that visual improvement in this study was less than the improvement observed in their previous study, Xiao (2020), discussed below, possibly due to the larger sample size in this study.

Xiao (2020) assessed visual acuity improvement and therapy adherence to the Luminopia One™ technology in 10 amblyopia patients ages 4 to 7.[26] Researchers monitored participants for adverse effects, such as double vision, new or worsening eye misalignment, worsening visual acuity, or other unanticipated adverse events. Therapy was prescribed for at-home use 1 hour per day, 7 days per week for 12 weeks. Follow-up visits occurred at 2, 4, 8, and 12 weeks. Adherence to therapy was recorded automatically by Luminopia One™. Amblyopic eye best-corrected visual acuity improved by 0.29 logMAR (2.9 logMAR lines, p<0.01) from baseline to 12 weeks. Six patients experienced resolution of amblyopia, defined by a difference in visual acuity between the two eyes of less than 0.3 logMAR. Therapy adherence over the 12-week study was 78% ± 27%. No serious adverse events were reported. This study is limited by small sample size, lack of a comparison group, and lack of long-term outcomes.

A prospective study by Yalcin (2014) evaluated the efficacy of the RevitalVision neural vision therapy in improving best corrected visual acuity and contrast sensitivity in patients with amblyopia, aged 9 to 50 years.[27] 53 participants received RevitalVision therapy, and 46 participants were in the control group. The active treatment group completed 45 training sessions with perceptual vision therapy of approximately 30 minutes during which the participant responded to visual perception tasks on a computer screen. Initial sessions were supervised in the clinic, and additional sessions were performed at home. The control group received 30 minutes of eye patching three times per week and played a placebo computer games at home. All participants were followed for up to four months. At follow-ups within four to eight months, a mean improvement of 2.6 logMAR lines in visual acuity was observed in the treatment group. Contrast sensitivity function improved at 1.5, 3, 6, 12, and 18 cycles per degree spatial frequencies. The control group did not experience a significant change in visual acuity or contrast sensitivity function. Study limitations include lack of a control group that received standard eye patch treatment only.

Section Summary

The evidence for digital visual therapy for the treatment of amblyopia includes four systematic reviews, seven RCTs, and several uncontrolled cohort studies and case series. Relevant outcomes are visual acuity, stereoacuity, and adherence to therapy. Several questions remain regarding the efficacy of, and adherence to, this treatment based on the limitations of the included studies. Additional high-quality randomized trials with comparison to standard treatments and long-term follow-up and are needed to establish the effectiveness and durability of digital visual therapeutics. Currently, the evidence is insufficient to determine that

digital visual therapeutics improve health outcomes as much as or more than established treatments for amblyopia.

PRACTICE GUIDELINE SUMMARY

American Academy of Ophthalmology (AAO)

In 2024, the AAO published a limited update to the Amblyopia Preferred Practice Pattern based on a literature review by the Pediatric Ophthalmology/Strabismus Preferred Practice Pattern Panel. Selected studies used to form a recommendation for care were graded for strength of evidence individually, and grades were listed with the study citation.

The recommendation section of these guidelines includes evidence ratings for each treatment. Regarding binocular (dichoptic) digital therapy, the guidelines state:

"Research with this technology is ongoing, which will be used to delineate use of binocular therapy for treatment of amblyopia."

- This recommendation was rated as *I+, Good, Discretionary*: "the evidence for this recommendation includes well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias; further research is unlikely to change our confidence in the estimate of effect; and trade-offs of therapy are less certain—either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced."

SUMMARY

There is not enough research to show that digital therapeutic products for the treatment of amblyopia improve net health outcomes as much as or more than established treatments. No clinical guidelines based on research recommend digital visual therapeutic products for the treatment of amblyopia. Therefore, digital visual therapeutics for the treatment of amblyopia are considered investigational.

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CODES

NOTE: Not all digital health products will have a specific code. These are examples of codes that may be relevant.

Codes	Number	Description
CPT	0687T	Treatment of amblyopia using an online digital program; device supply, educational set-up, and initial session
	0688T	Treatment of amblyopia using an online digital program; device supply, educational set-up, and assessment of patient performance and program data by physician or other qualified health care professional, with report, per calendar month
	0704T	Remote treatment of amblyopia using an eye tracking device; device supply with initial set-up and patient education on use of equipment
	0705T	Remote treatment of amblyopia using an eye tracking device; surveillance center technical support including data transmission with analysis, with a minimum of 18 training hours, each 30 days
	0706T	Remote treatment of amblyopia using an eye tracking device; interpretation and report by physician or other qualified health care professional, per calendar month
HCPCS	A9292	Prescription digital visual therapy, software-only, fda cleared, per course of treatment

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