9.03.20	Intraocular Radiotherapy for Age-Related Macular Degeneration		
Original Policy Date:	April 1, 2011	**Effective Date:**	May 1, 2024
Section:	9.0 Other	**Page:**	Page 1 of 13

Policy Statement

I. Intraocular placement of a radiation source (brachytherapy) for the treatment of choroidal neovascularization is considered **investigational**.

II. Proton beam therapy for the treatment of choroidal neovascularization is considered **investigational**.

III. Stereotactic radiotherapy for the treatment of choroidal neovascularization is considered **investigational**.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Coding
See the Codes table for details.

Description

Intraocular radiation, including brachytherapy, proton beam therapy, and stereotactic radiotherapy, are being evaluated to treat choroidal neovascularization associated with age-related macular degeneration.

Related Policies

- Stereotactic Radiosurgery and Stereotactic Body Radiotherapy
- Photodynamic Therapy for Choroidal Neovascularization

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

No devices are specifically approved by the U.S. Food and Drug Administration (FDA) for intraocular radiation. An investigational device exemption was granted by the FDA for a phase 3 multicenter trial of the EPI-RAD90™ (now known as Vidion Anti-Neovascular Epimacular Brachytherapy [EMBT] System; NeoVista) to provide data for a device application to the FDA. This is a category B procedure.

Rationale

Background

Age-Related Macular Degeneration

Age-related macular degeneration is the leading cause of legal blindness in individuals older than age 60 in developed nations. Age-related macular degeneration is characterized in its earliest stages by minimal visual impairment and the presence of large drusen and other pigmentary abnormalities on ophthalmoscopic examination. Two distinctive forms of degeneration may be observed. The first, called the atrophic or areolar or dry form, evolves slowly. Atrophic age-related macular degeneration is the most common form of degeneration and may be a precursor of the more visually impairing exudative neovascular form, also referred to as disciform or wet age-related macular degeneration. The wet form is distinguished from the atrophic form by the development of choroidal neovascularization and serous or hemorrhagic detachment of the retinal pigment epithelium. Risk of developing severe irreversible loss of vision is greatly increased by the presence of choroidal neovascularization.

Standard Clinical Management

Usual care for neovascular age-related macular degeneration includes intravitreal agents that target vascular endothelial growth factor, including pegaptanib, ranibizumab, bevacizumab, and aflibercept. Photodynamic therapy is an older method that has been largely replaced by anti-vascular endothelial growth factor therapies. The intravitreal therapies may necessitate repeated intravitreal injections. Hence, alternative treatments, such as intraocular radiation, including brachytherapy, proton beam therapy, and stereotactic radiotherapy, are being investigated.

Intraocular Radiotherapy

The NeoVista Epi-Rad90 Ophthalmic System, a brachytherapy device, treats choroidal neovascularization by delivering focal radiation to a subfoveal choroidal neovascular lesion. Using a standard vitrectomy procedure, the cannula tip of a handheld (pipette-like) surgical device is inserted into the vitreous cavity and positioned under visual guidance over the target lesion. The radiation source (strontium 90) is advanced down the cannula until it reaches the tip, which is then held in place over the lesion for a "prescribed" time to deliver focused radiation. The system is designed to deliver a 1-time peak dose of beta particle energy (24 Gray) for a target area 3 mm in depth and up to 5.4 mm in diameter. This dose is believed to be below that toxic to the retina and optic nerve. Radiation exposure outside of the target area is expected to be minimal.

Proton beam therapy is a type of external radiotherapy that uses charged atomic particles (protons or helium ions) to target a given area. Proton beam therapy differs from conventional electromagnetic (photon) radiotherapy in that, with proton beam therapy, there is less scatter as the particle beams pass through tissue to deposit ionizing energy at precise depths (Bragg peak). The theoretical advantage of proton beam therapy over photon therapy is the ability to deliver higher radiation doses to the target without harm to adjacent normal tissue.

Stereotactic radiotherapy is a nonsurgical procedure performed in an office setting. It uses a robotically controlled device to deliver radiation beams through the inferior sclera to overlap at the macula.

Other Treatments

Other available therapeutic options for age-related macular degeneration not addressed in this evidence review include photodynamic therapy (evidence review/reference Blue Shield of California Medical Policy: Photodynamic Therapy for Choroidal Neovascularization) and vascular endothelial growth factor antagonists or angiostatics.
For those whose visual loss impairs their ability to perform daily tasks, low-vision rehabilitative services offer resources to compensate for deficits.

Literature Review

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 individuals 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 a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 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. Randomized controlled trials 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Brachytherapy

Clinical Context and Therapy Purpose

The purpose of brachytherapy for individuals who have choroidal neovascularization associated with age-related macular degeneration is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with choroidal neovascularization associated with age-related macular degeneration.

Interventions

The treatment being considered is brachytherapy. Brachytherapy treats choroidal neovascularization by delivering focal radiation to a subfoveal choroidal neovascular lesion.

Brachytherapy is performed in a surgical setting. After surgery, individuals are hospitalized for 2 to 4 days during the brachytherapy. Once the brachytherapy is complete, the individual undergoes another operation to remove the protective gold plaque that was placed on the eye during the first operation. At this point the individual may go home.

Comparators

The following practices are currently being used to treat choroidal neovascularization associated with age-related macular degeneration: intravitreal vascular endothelial growth factor and photodynamic therapy.

Outcomes
The general outcomes of interest are change in disease status, morbid events, functional outcomes, quality of life, medication use, and treatment-related morbidity.

Follow-up of 1 to 2 years is desirable to assess outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Systematic Review
Evans et al (2020) evaluated the efficacy of radiotherapy on neovascular age-related macular degeneration in a Cochrane review.[1,] The review included 18 RCTs in which radiotherapy (dosage range: 7.5 to 24 Gy) was compared to another treatment, sham treatment, low dosage irradiation, or no treatment. Of the 18 studies, 3 involved brachytherapy (plaque and epimacular). Two of these 3 studies (discussed below) evaluated epimacular brachytherapy combined with intravitreal vascular endothelial growth factor injections versus intravitreal vascular endothelial growth factor alone.

Overall, individuals receiving combination radiotherapy/intravitreal vascular endothelial growth factor injections were more likely to lose 3 or more lines of best-corrected visual acuity at 12 months compared with injections alone across the 3 trials (risk ratio, 2.11; 95% confidence interval [CI], 1.40 to 3.17; moderate certainty). The authors also concluded that visual outcomes with epimacular brachytherapy are likely to be worse, with an increased risk of adverse events, probably related to vitrectomy.

Randomized Controlled Studies
Jackson et al. (2016) reported on the results of a phase 3 RCT, Macular Epiretinal Brachytherapy versus Ranibizumab (Lucentis) Only Treatment (MERLOT), comparing epimacular brachytherapy plus as-needed ranibizumab (n=224) with as-needed ranibizumab alone (n=119) in individuals with neovascular age-related macular degeneration, already receiving ranibizumab.[2,] It was not feasible to mask individuals to their surgical group (epimacular brachytherapy), but visual acuity testing and macular imaging results were evaluated by masked assessors. The trial was powered to test the hypothesis that epimacular brachytherapy would reduce the number of antivascular endothelial growth factor treatments, with a noninferior visual outcome (a margin of 5 letters of visual acuity).

Over 12 months of follow-up, the mean number of as-needed ranibizumab injections did not differ significantly between the epimacular brachytherapy arm (4.8 treatments) and the ranibizumab monotherapy arm (4.1 treatments; p=.068). From baseline to month 12, the mean change in best-corrected visual acuity was -4.8 letters in the epimacular brachytherapy arm compared with -0.9 letters in the ranibizumab monotherapy arm (between-group difference 95% CI, -6.6 to -1.8, which did not demonstrate inferiority at the prespecified 5-letter margin). In contrast to the null hypothesis, ranibizumab monotherapy individuals had superior outcomes for visual acuity. Adverse events were more common in the epimacular brachytherapy arm. Overall, these results did not support the use of epimacular brachytherapy over ranibizumab monotherapy for neovascular age-related macular degeneration.

In 2020, Jackson et al published 24 month efficacy and safety data from the MERLOT trial as epimacular brachytherapy typically takes several months to have an effect, and radiation damage is thought to be more likely in the second year after treatment.[3,] Results at 24 months of follow-up revealed that the mean number of ranibizumab injections was 9.3 in the brachytherapy group versus 8.3 in the ranibizumab group (p=.13) and the mean change in best-corrected visual acuity was -11.2 letters in the brachytherapy group versus -1.4 in the ranibizumab group (difference: 9.8; 95% CI: -6.7 to -12.9). Microvascular abnormalities were seen in 20 (9.7%) of 207 eyes in the brachytherapy group versus 1 (1%) of 97 eyes in the ranibizumab group. Overall, the results continued to show that epimacular brachytherapy did not reduce the number of ranibizumab injections and was associated with worse visual acuity than ranibizumab alone.

In 2022, Jackson et al published 36 month results from the MERLOT trial.[4,] These results were primarily intended to monitor safety. After 24 months, participants reverted to standard care, receiving either ranibizumab or aflibercept, and returned for month 36 study visit. Results at 36 months revealed that the mean number of ranibizumab injections was 12.1 in the brachytherapy group versus 11.4 in the ranibizumab group (p=.41) between months 1 and 36, and 3.6 versus 3.9 (p=.43) between months 25 and 36 (standard care). Over 36 months, the mean change in best-corrected visual acuity was -19.7 letters in the brachytherapy group versus -4.8 in the ranibizumab group (difference: -14.9; 95% CI: -18.5 to -11.2). The most frequent ocular serious adverse events (SAEs) in the study eye during the study period were retinal detachment occurring in 5 participants (2.0%) in the brachytherapy group and retinal hemorrhage occurring in 4 participants (1.6%) in the brachytherapy group and 1 participant (0.8%) in the ranibizumab group. Overall, the long-term follow-up results continued to show that epimacular brachytherapy did not reduce the number of ranibizumab injections that individuals require within or outside a trial setting, and was associated with worse visual acuity than ranibizumab alone.

A phase 3 multicenter RCT, A Study of Strontium90 Beta Radiation with Lucentis to Treat Age-Related Macular Degeneration (CABERNET; NCT00454389), enrolled 494 subjects with age-related macular degeneration related wet choroidal neovascularization from 42 sites.[5,6,] The safety and efficacy of epimacular brachytherapy combined with 2 loading injections of ranibizumab (Lucentis) were compared with ranibizumab monotherapy (2 loading doses and then quarterly). Individuals in both arms of the trial could receive monthly treatment with ranibizumab as needed. At 24 months, 77% of the individuals in the epimacular brachytherapy group lost fewer than 15 letters compared with 90% in the control group. This result did not meet the prespecified noninferiority margin. Epimacular brachytherapy treatment also did not meet the superiority end point, which was the proportion of participants gaining more than 15 letters (16% vs. 26% for the ranibizumab group). The most common serious adverse event was cataract surgery (known to be associated with vitrectomy), which occurred in 40% of the epimacular brachytherapy group compared with 11% of the ranibizumab monotherapy group. Mild radiation retinopathy occurred in 3% of the individuals who received epimacular brachytherapy treatment. This trial did not support the use of epiretinal radiotherapy.

Nonrandomized Studies

Twelve- and 24-month results from the multi-center study, Macular EpiRetinal brachytherapy in Treated AGE-related macular degeneration (MERITAGE; NCT00809419), were reported between 2012 and 2014.[7,8,9,] MERITAGE was a phase 1/2 study of epimacular brachytherapy for the treatment of subfoveal choroidal neovascularization associated with wet age-related macular degeneration in individuals requiring continued antivascular endothelial growth factor therapy to maintain an adequate response. Following a single 24-gray dose, the 53 individuals in the study received retreatment with ranibizumab administered monthly (as needed). In the 12 months before the study, participants received 0.45 injections per month. At the 12-month follow-up, 81% (43/53) of individuals maintained stable vision (loss of <15 letters), with a mean of 3.49 antivascular endothelial growth factor injections (0.29 per month). Over 24 months, the durability of the application diminished, with

68% (32/47) of individuals maintaining stable vision at a mean of 8.7 antivascular endothelial growth factor injections (0.72 per month).

Three publications from 2 studies have been reported by Avila et al on epimacular brachytherapy using the EPI-RAD90 System.[10,11,12,] One report (2009) described 12-month safety and visual acuity results of a feasibility study in 34 treatment-naive individuals from Turkey, Mexico, and Brazil who were recruited between 2005 and 2006.[10,] The second report (2009) described 12-month safety and visual acuity results for 24-gray (Gy) epimacular brachytherapy combined with bevacizumab in 34 treatment-naive individuals enrolled between 2006 and 2007.[11,] Adverse events related to the device or procedure included subretinal hemorrhage (n=1), retinal tear (n=1), subretinal fibrosis (n=2), epiretinal membrane (n=1), and cataract (n=6/24; 24 individuals were phakic at baseline). All occurrences of cataracts were deemed to be related to the vitrectomy procedure. Two- and 3-year results from this trial were published in 2012.[12,] All 34 subjects were followed for 24 months; 1 site that enrolled 19 individuals agreed to re-consent and follow individuals for 3 years. On average, the cohort followed for 36 months received 3.0 bevacizumab injections. Twelve (50%) of the 24 phakic individuals developed cataracts, and 4 had phacoemulsification with intraocular lens implantation. Mean change in visual acuity at 36 months was +3.9 letters. Seven (54%) of 13 phakic individuals developed cataracts, and 4 had phacoemulsification with intraocular lens implantation. One case of nonproliferative radiation retinopathy was observed at 36 months.

Section Summary: Brachytherapy

At least 2 RCTs, which have been supported by additional non-randomized studies and a Cochrane review, have found that epimacular brachytherapy is inferior to local treatment with ranibizumab for the treatment of wet age-related macular degeneration.

Proton Beam Therapy

Clinical Context and Therapy Purpose

The purpose of proton beam therapy for individuals who have choroidal neovascularization associated with age-related macular degeneration is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with choroidal neovascularization associated with age-related macular degeneration.

Interventions

The treatment being considered is proton beam therapy. Proton beam therapy is external therapy that uses charged atomic particles to target a given area with less scatter of particle beams than conventional electromagnetic (photon) radiotherapy. Multiple treatments are required.

Comparators

The following practices are currently being used to treat choroidal neovascularization associated with age-related macular degeneration: intravitreal vascular endothelial growth factor and photodynamic therapy. These treatments are generally administered by an ophthalmologist or other eye specialist in an outpatient clinical setting.

Outcomes

The general outcomes of interest are change in disease status, morbid events, functional outcomes, quality of life, medication use, and treatment-related morbidity.

Follow-up of 1 to 3 years is desirable to assess outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Pilot Study

Park et al. (2012) reported on 12- to 36-month follow-up for a pilot study of ranibizumab combined with proton beam therapy for age-related macular degeneration.[13,] Six eyes (6 individuals) were treated with 4 monthly ranibizumab plus 24-Gy proton beam treatments, followed by ranibizumab if needed. No radiation retinopathy was observed at follow-up.

Randomized Controlled Trial

Ciulla et al. (2002) reported on results from a randomized, prospective, sham-controlled, double-masked treatment trial that examined the effect of proton beam therapy on subfoveal choroidal neovascular membranes associated with age-related macular degeneration.[14,] Thirty-seven subjects were randomized to 16-Gy proton irradiation delivered in 2 fractions 24 hours apart or to sham control treatment. Recruitment was halted at 37 subjects for ethical reasons related to randomization to sham treatment when Food and Drug Administration approval of verteporfin (Visudyne; a light-activated drug used with photodynamic therapy) was anticipated. Proton beam therapy was associated with a trend toward stabilization of visual acuity, but this association was not statistically significant.

Section Summary: Proton Beam Therapy

There is currently no available clinical trial evidence suggesting that proton beam therapy is noninferior to available treatment alternatives for age-related macular degeneration.

Stereotactic Radiotherapy

Clinical Context and Therapy Purpose

The purpose of stereotactic radiotherapy for individuals who have choroidal neovascularization associated with age-related macular degeneration is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with choroidal neovascularization associated with age-related macular degeneration.

Interventions

The treatment being considered is stereotactic radiotherapy. Stereotactic radiotherapy is a nonsurgical procedure using a robotically controlled device to deliver radiation beams through the inferior sclera to overlap at the macula.

Comparators

The following practices are currently being used to treat choroidal neovascularization associated with age-related macular degeneration: intravitreal vascular endothelial growth factor and photodynamic therapy.

Outcomes
The general outcomes of interest are change in disease status, morbid events, functional outcomes, quality of life, medication use, and treatment-related morbidity.

Follow-up of 1 to 2 years is desirable to assess outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Randomized Controlled Trials
A study reported by Jackson et al (2013), IRay in Conjunction with Anti-VEGF [antivascular endothelial growth factor] Treatment for Patients with Wet Age-related Macular Degeneration (INTREPID), was a randomized, sham-controlled, double-masked trial with 230 individuals that assessed the efficacy and safety of stereotactic radiotherapy to treat neovascular age-related macular degeneration.[15,] The primary outcome measure was the number of ranibizumab injections needed over 52 weeks. Both stereotactic radiotherapy and sham control individuals received ranibizumab as needed. After 1 year, treatment with 16- or 24-Gy stereotactic radiotherapy reduced the number of ranibizumab treatments (median, 2 vs. 3.5 for sham controls) with no significant differences in changes in visual acuity over the 1-year follow-up. No safety concerns were identified in the first 12 months.

In 2015, year 2 safety and efficacy results from the INTREPID trial were published.[16,] Participants received 16- or 24-Gy stereotactic radiotherapy plus ranibizumab or sham stereotactic radiotherapy plus ranibizumab for 12 months, with bevacizumab or ranibizumab thereafter as needed. At year 2, the 16- and 24-Gy arms received fewer as-needed bevacizumab (mean, 4.5; p=.008) or ranibizumab (mean, 5.4; p=.09) treatments compared with sham (mean, 6.6). Changes in mean best-corrected visual acuity were -10.0, -7.5, and -6.7 letters, respectively, with 68%, 75%, and 79% losing fewer than 15 letters, respectively. Differences for visual acuity were not statistically significant. Microvascular abnormalities were detected in 6 control eyes and 29 stereotactic radiotherapy eyes, of which 18 were attributed to radiotherapy, with only 2 possibly affecting vision. The authors concluded that a single dose of stereotactic radiotherapy significantly reduced intravitreal injections over 2 years and that, although radiotherapy can induce microvascular changes, only in 1% of eyes did this seem to affect vision.

Observational Study
Ranjbar et al. (2016) reported on results from an observational study of 32 individuals (32 eyes) with neovascular age-related macular degeneration who met criteria for best responders in the INTREPID trial and were treated with stereotactic radiotherapy (16 Gy) along with aflibercept or ranibizumab.[17,] For the study's primary outcome (the number of antivascular endothelial growth factor treatments in the 12 months after stereotactic radiotherapy), significantly fewer intravitreal injections were given (3.47) compared with the year preceding stereotactic radiotherapy (6.81; p<.001). No ocular or systemic adverse events occurred.

Section Summary: Stereotactic Radiotherapy
Evidence from a double-blind, randomized trial comparing stereotactic radiotherapy with ranibizumab for neovascular age-related macular degeneration has suggested that stereotactic radiotherapy can reduce the number of ranibizumab injections, but was associated with radiation retinopathy leading to microvascular changes.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Ophthalmology

In 2015, the American Academy of Ophthalmology updated its evidence-based preferred practice pattern on age-related macular degeneration.[18,] For extrafoveal choroidal neovascularization, radiotherapy was not recommended (SIGN grade: III; GRADE assessment: moderate level of evidence, strong recommendation).

In their 2019 Preferred Practice Pattern (updated as of November 2021) for age-related macular degeneration, the Academy states that current data is insufficient "to demonstrate clinical efficacy" of radiation therapy for extrafoveal choroidal neovascularization.[19,]

National Institute for Health and Care Excellence

The 2011 guidance from the National Institute for Health and Care Excellence stated that current evidence on the efficacy of epiretinal brachytherapy for wet age-related macular degeneration is "inadequate and limited to small numbers of patients."[20,] For safety, "vitrectomy has well-recognised complications and there is a possibility of subsequent radiation retinopathy." The Institute concluded that wet age-related macular degeneration should only be used for "research."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

Ongoing and Unpublished Clinical Trials

Some currently ongoing trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02988895	A Prospective Study of Episcleral Brachytherapy for the Treatment of Neovascular Age-related Macular Degeneration (NEAMES)	12	May 2025
NCT04268836	Vision Improvement for Patients with Age-Related Macular Degeneration	200	May 2025
NCT02243878	StereoTactic Radiotherapy for Wet Age-Related Macular Degeneration (STAR): A Randomised, Double-masked, Sham-controlled, Clinical Trial Comparing Low-voltage Irradiation With as Needed Ranibizumab, to as Needed Ranibizumab Monotherapy	411	Jun 2024

NCT: national clinical trial.

References

1. Evans JR, Igwe C, Jackson TL, et al. Radiotherapy for neovascular age-related macular degeneration. Cochrane Database Syst Rev. Aug 26 2020; 8(8): CD004004. PMID 32844399
2. Jackson TL, Desai R, Simpson A, et al. Epimacular Brachytherapy for Previously Treated Neovascular Age-Related Macular Degeneration (MERLOT): A Phase 3 Randomized Controlled Trial. Ophthalmology. Jun 2016; 123(6): 1287-96. PMID 27086023
3. Jackson TL, Soare C, Petrarca C, et al. Evaluation of Month-24 Efficacy and Safety of Epimacular Brachytherapy for Previously Treated Neovascular Age-Related Macular Degeneration: The MERLOT Randomized Clinical Trial. JAMA Ophthalmol. Aug 01 2020; 138(8): 835-842. PMID 32644148
4. Jackson TL, Soare C, Petrarca C, et al. Epimacular brachytherapy for previously treated neovascular age-related macular degeneration: month 36 results of the MERLOT randomised controlled trial. Br J Ophthalmol. Jul 2023; 107(7): 987-992. PMID 35217515
5. Dugel PU, Bebchuk JD, Nau J, et al. Epimacular brachytherapy for neovascular age-related macular degeneration: a randomized, controlled trial (CABERNET). Ophthalmology. Feb 2013; 120(2): 317-27. PMID 23174399
6. Jackson TL, Dugel PU, Bebchuk JD, et al. Epimacular brachytherapy for neovascular age-related macular degeneration (CABERNET): fluorescein angiography and optical coherence tomography. Ophthalmology. Aug 2013; 120(8): 1597-603. PMID 23490325
7. Dugel PU, Petrarca R, Bennett M, et al. Macular epiretinal brachytherapy in treated age-related macular degeneration: MERITAGE study: twelve-month safety and efficacy results. Ophthalmology. Jul 2012; 119(7): 1425-31. PMID 22465819
8. Petrarca R, Dugel PU, Nau J, et al. Macular epiretinal brachytherapy in treated age-related macular degeneration (MERITAGE): month 12 optical coherence tomography and fluorescein angiography. Ophthalmology. Feb 2013; 120(2): 328-33. PMID 23178157
9. Petrarca R, Dugel PU, Bennett M, et al. Macular epiretinal brachytherapy in treated age-related macular degeneration (MERITAGE): month 24 safety and efficacy results. Retina. May 2014; 34(5): 874-9. PMID 24169101
10. Avila MP, Farah ME, Santos A, et al. Twelve-month safety and visual acuity results from a feasibility study of intraocular, epiretinal radiation therapy for the treatment of subfoveal CNV secondary to AMD. Retina. Feb 2009; 29(2): 157-69. PMID 19202425
11. Avila MP, Farah ME, Santos A, et al. Twelve-month short-term safety and visual-acuity results from a multicentre prospective study of epiretinal strontium-90 brachytherapy with bevacizumab for the treatment of subfoveal choroidal neovascularisation secondary to age-related macular degeneration. Br J Ophthalmol. Mar 2009; 93(3): 305-9. PMID 19019935
12. Avila MP, Farah ME, Santos A, et al. Three-year safety and visual acuity results of epimacular 90 strontium/90 yttrium brachytherapy with bevacizumab for the treatment of subfoveal choroidal neovascularization secondary to age-related macular degeneration. Retina. Jan 2012; 32(1): 10-8. PMID 21817963
13. Park SS, Daftari I, Phillips T, et al. Three-year follow-up of a pilot study of ranibizumab combined with proton beam irradiation as treatment for exudative age-related macular degeneration. Retina. May 2012; 32(5): 956-66. PMID 22183743
14. Ciulla TA, Danis RP, Klein SB, et al. Proton therapy for exudative age-related macular degeneration: a randomized, sham-controlled clinical trial. Am J Ophthalmol. Dec 2002; 134(6): 905-6. PMID 12470761
15. Jackson TL, Chakravarthy U, Kaiser PK, et al. Stereotactic radiotherapy for neovascular age-related macular degeneration: 52-week safety and efficacy results of the INTREPID study. Ophthalmology. Sep 2013; 120(9): 1893-900. PMID 23490327
16. Jackson TL, Chakravarthy U, Slakter JS, et al. Stereotactic radiotherapy for neovascular age-related macular degeneration: year 2 results of the INTREPID study. Ophthalmology. Jan 2015; 122(1): 138-45. PMID 25208859

17. Ranjbar M, Kurz M, Holzhey A, et al. Stereotactic radiotherapy in neovascular age-related macular degeneration: Real-life efficacy and morphological evaluation of the outer retina-choroid complex. Medicine (Baltimore). Dec 2016; 95(52): e5729. PMID 28033280
18. American Academy of Ophthalmology Retina/Vitreous Panel. Preferred Practice Pattern: Age-Related Macular Degeneration. San Francisco, CA: American Academy of Ophthalmology; 2015.
19. American Academy of Ophthalmology. Age-related macular degeneration. Preferred practice pattern. October 2019.https://www.aao.org/preferred-practice-pattern/age-related-macular-degeneration-ppp. Accessed February 16, 2024.
20. National Institute for Health and Care Excellence. Epiretinal brachytherapy for wet age-related macular degeneration [IPG415]. 2011; https://www.nice.org.uk/guidance/IPG415. Accessed February 15, 2024.

Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	67036	Vitrectomy, mechanical, pars plana approach;
	67299	Unlisted procedure, posterior segment
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
04/01/2011	BCBSA Medical Policy adoption
06/30/2015	Coding Update Policy revision without position change
06/01/2016	Policy revision without position change
04/01/2017	Policy revision without position change
05/01/2018	Policy revision without position change
01/01/2019	Coding update
05/01/2019	Policy revision without position change
06/01/2023	Policy reactivated. Previously archived from 05/01/2020 to 05/31/2023.
05/01/2024	Annual review. No change to policy statement. Policy guidelines and literature updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Intraocular Radiotherapy for Age-Related Macular Degeneration 9.03.20 **Policy Statement:** I. Intraocular placement of a radiation source (brachytherapy) for the treatment of choroidal neovascularization is considered **investigational**. II. Proton beam therapy for the treatment of choroidal neovascularization is considered **investigational**. III. Stereotactic radiotherapy for the treatment of choroidal neovascularization is considered **investigational**.	**Intraocular Radiotherapy for Age-Related Macular Degeneration 9.03.20** **Policy Statement:** I. Intraocular placement of a radiation source (brachytherapy) for the treatment of choroidal neovascularization is considered **investigational**. II. Proton beam therapy for the treatment of choroidal neovascularization is considered **investigational**. III. Stereotactic radiotherapy for the treatment of choroidal neovascularization is considered **investigational**.