Policy Statement

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

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

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

Policy Guidelines

- N/A

Description

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

Related Policies

- Charged-Particle (Proton or Helium Ion) Radiotherapy for Neoplastic Conditions
- Photodynamic Therapy for Choroidal Neovascularization
- Stereotactic Radiosurgery and Stereotactic Body Radiotherapy

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 for intraocular radiation. An investigational device exemption was granted by the Food and Drug Administration 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 Food and Drug Administration. This is a category B procedure.
Rationale

Background
Age-Related Macular Degeneration
Age-related macular degeneration (AMD) is the leading cause of legal blindness in individuals older than age 60 in developed nations. AMD 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 AMD 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 AMD. The wet form is distinguished from the atrophic form by the development of choroidal neovascularization (CNV) 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 CNV.

Standard Clinical Management
Usual care for neovascular AMD 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 (PBT), and stereotactic radiotherapy, are being investigated.

The NeoVista Epi-Rad90 Ophthalmic System, a brachytherapy device, treats CNV 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.

PBT is a type of external radiotherapy that uses charged atomic particles (protons or helium ions) to target a given area. PBT differs from conventional electromagnetic (photon) radiotherapy in that, with PBT, there is less scatter as the particle beams pass through tissue to deposit ionizing energy at precise depths (Bragg peak). The theoretical advantage of PBT 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 AMD not addressed in this policy review include Blue Shield of California Medical Policy: Photodynamic Therapy for Choroidal Neovascularization.

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 patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice. The following is a summary of the key literature to date.

**Intraocular Radiotherapy**

**Brachytherapy**

Jackson et al (2016) reported on the results of a phase 3 RCT (MERLOT) comparing epimacular brachytherapy (EMB) plus as needed ranibizumab (n=224) with as needed ranibizumab alone (n=119) in patients with neovascular age-related macular degeneration (AMD), already receiving ranibizumab.1 It was not feasible to mask patients to their surgical group (EMB), but visual acuity testing and macular imaging were evaluated by masked assessors. The trial was powered to test the hypothesis that EMB would reduce the number of anti-vascular endothelial growth factor (anti-VEGF) treatments, with a noninferior visual outcome (with 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 EMB arm (4.8 treatments) and the ranibizumab monotherapy arm (4.1 treatments; p=0.068). From baseline to month 12, the mean change in best-corrected visual acuity was -4.8 letters in the EMB arm compared with -0.9 letters in the ranibizumab monotherapy arm (between-group difference 95% confidence interval [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 patients had superior outcomes for visual acuity. Adverse events were more common in the EMB arm. Overall, these results did not support the use of EMB over ranibizumab monotherapy for neovascular AMD.

A phase 3 multicenter RCT (CABERNET; NCT00454389) enrolled 494 subjects with AMD-related wet CNV from 42 sites.2,3 The safety and efficacy of EMB combined with 2 loading injections of ranibizumab (Lucentis) were compared with ranibizumab monotherapy (2 loading doses and then quarterly). Patients in both arms of the trial could receive monthly treatment with ranibizumab as needed. At 24 months, 77% of the patients in the EMB group lost fewer than 15 letters compared with 90% in the control group. This result did not meet the prespecified noninferiority margin. EMB 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 EMB group compared with 11% of the ranibizumab monotherapy group. Mild radiation retinopathy occurred in 3% of the patients who received EMB treatment. This trial did not support the use of epiotretinal radiotherapy.

Twelve- and 24-month results from the multicenter MERITAGE study (NCT00809419) were reported between 2012 and 2014.4,6 MERITAGE was a phase 1/2 study of EMB for the treatment of subfoveal choroidal neovascularization (CNV) associated with wet AMD in patients requiring continued anti-VEGF therapy to maintain an adequate response. Following a single 24-gray (Gy) dose, the 53 patients 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 patients maintained stable vision (loss of <15 letters), with a mean of 3.49 anti-VEGF injections (0.29 per month). Over 24 months, the durability of the application diminished, with 68% (32/47) of patients maintaining stable vision at a mean of 8.7 anti-VEGF injections (0.72 per month).

Three publications from 2 studies have been reported by Avila et al on EMB using the EPI-RAD90 System.7-9 One report (2009) described 12-month safety and visual acuity results of a feasibility study in 34 treatment-naive patients from Turkey, Mexico, and Brazil, recruited between 2005 and 2006.7 The second report (2009) described 12-month safety and visual acuity results for 24-Gy EMB combined with bevacizumab in 34 treatment-naive patients enrolled between 2006 and 2007.8 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 patients 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 2012.9 All 34 subjects were followed for 24 months; 1 site that enrolled 19 patients agreed to re-consent and follow patients for 3 years. On average, the cohort followed for 36 months received 3.0 bevacizumab injections. Twelve (50%) of the 24 phakic patients 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 patients 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 nonrandomized studies, have found that EMB is inferior to local treatment with ranibizumab for the treatment of wet AMB.

Proton Beam Therapy
Park et al (2012) reported on 12- to 36-month follow-up for a pilot study of ranibizumab combined with proton beam therapy (PBT) for AMD.10 Six eyes (6 patients) 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.

Ciulla et al (2002) reported on results from a randomized, prospective, sham-controlled, double-masked treatment trial that examined the effect of PBT on subfoveal choroidal neovascular membranes associated with AMD.11 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 U.S. Food and Drug Administration approval of verteporfin (Visudyne; a light-activated drug used with photodynamic therapy) was anticipated. PBT 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 PBT is noninferior to available treatment alternatives for AMD.

Stereotactic Radiotherapy
INTREPID was a randomized, sham-controlled, double-masked trial (2013) with 230 patients that assessed the efficacy and safety of stereotactic radiotherapy (SRT) to treat neovascular AMD.12 The primary outcome measure was the number of ranibizumab injections needed over 52 weeks. Both SRT and sham control patients received ranibizumab as needed. After 1 year, treatment with 16- or 24-Gy SRT reduced the number of ranibizumab treatments (median, 2 vs 3.5 for sham controls) with no significant differences from controls 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.13 Participants received 16- or 24-Gy SRT plus ranibizumab or sham SRT 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=0.008) or ranibizumab (mean, 5.4; p=0.09) 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 SRT eyes, of which 18 were attributed to radiotherapy, with only 2 possibly affecting vision. The authors concluded that a single dose of SRT 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.

Ranjbar et al (2016) reported on results from an observational study of 32 patients (32 eyes) with neovascular AMD who met criteria for best responders in the INTREPID trial and were treated with SRT (16 Gy) along with aflibercept or ranibizumab.\textsuperscript{14} For the study’s primary outcome (the number of anti-VEGF treatments in the 12 months after SRT), significantly fewer intravitreal injections were given (3.47) compared with the year preceding SRT (6.81; p<0.001). No ocular or systemic adverse events occurred.

**Section Summary: Stereotactic Radiotherapy**

Evidence from a double-blind, randomized trial comparing SRT with ranibizumab for neovascular AMD has suggested that SRT can reduce the number of ranibizumab injections, but was associated with radiation retinopathy leading to microvascular changes.

**Summary of Evidence**

For individuals who have CNV due to AMD who receive brachytherapy, the evidence includes 2 RCTs comparing brachytherapy plus vascular endothelial growth factor with vascular endothelial growth factor monotherapy as well as phase 1/2 trials and case series on the use of brachytherapy. Relevant outcomes are change in disease status, morbid events, functional outcomes, quality of life, medication use, and treatment-related morbidity. Both RCTs showed that brachytherapy did not attain noninferiority for visual acuity outcomes and was associated with a higher proportion of adverse events. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have CNV due to AMD who receive PBT, the evidence includes a randomized, prospective, sham-controlled trial and a pilot study. Relevant outcomes are change in disease status, morbid events, functional outcomes, quality of life, medication use, and treatment-related morbidity. Recruitment into the RCT was halted for ethical concerns, and available results did not show statistically significant stabilization of visual acuity. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have CNV due to AMD who receive stereotactic radiotherapy, the evidence includes an RCT with sham control. Relevant outcomes are change in disease status, morbid events, functional outcomes, quality of life, medication use, and treatment-related morbidity. The RCT showed a reduction in the number of vascular endothelial growth factor treatments at 12- and 24-month intervals, but no significant differences vs controls for changes in visual acuity. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Supplemental Information**

**Practice Guidelines and Position Statements**

**American Academy of Ophthalmology**

In 2015, the American Academy of Ophthalmology updated its evidenced-based preferred practice pattern on age-related macular degeneration.\textsuperscript{15} For extrafoveal choroidal neovascularization, radiotherapy was not recommended (SIGN grade: III; GRADE assessment: moderate level of evidence, strong recommendation).
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.” For safety, “vitrectomy has well-recognized 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
A search of ClinicalTrials.gov in February 2018 did not identify any ongoing or unpublished trials that would likely influence this review.

References


**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. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**IE**

The following services may be considered investigational.

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<th>Code</th>
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<td>Placement of intraocular radiation source applicator (List separately in addition to primary procedure)</td>
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<td>Destruction of localized lesion of retina (e.g., macular edema, tumors), 1 or more sessions; radiation by implantation of source (includes removal of source)</td>
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Policy History

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

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<td>01/01/2019</td>
<td>Coding update</td>
<td>Administrative Review</td>
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Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**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 (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. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

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.