Age-Related Macular Degeneration

Number: 0765

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

Aetna considers home monitoring with preferential hyperacuity perimetry (ForeseeHome device) experimental and investigational for detection of age-related macular degeneration-associated choroidal neovascularization and for all other indications.

Aetna considers the following therapies medically necessary for the treatment of neovascular (wet) age-related macular degeneration (ARMD):

- Aflibercept (Eylea) injection (CPB 0701 - Vascular Endothelial Growth Factor Inhibitors for Ocular Indications (/../700_799/0701.html))
- Bevacizumab (Avastin) injection (CPB 0685 - Bevacizumab (Avastin) for Non-Ocular Indications (/../600_699/0685.html))
- Pegaptanib sodium (Macugen) injection (CPB 0701 - Vascular Endothelial Growth Factor Inhibitors for Ocular Indications (0701.html))

Policy History

Last Review 09/08/2016
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Review History

Definitions

Additional Information

Clinical Policy Bulletin Notes
- Photodynamic therapy (PDT) with light-activated verteporfin ([CPB 0594 - Visudyne (Verteporfin) Photodynamic Therapy](../500_599/0594.html))
- Ranibizumab (Lucentis) injection ([CPB 0701 - Vascular Endothelial Growth Factor Inhibitors for Ocular Indications](0701.html))

Aetna considers the implantable miniature telescope (IMT) medically necessary for monocular implantation in members aged 65 years and older with stable, untreated, severe-to-profound central vision impairment caused by blind spots (bilateral central scotoma) associated with end-stage ARMD as determined by fluorescein angiography when all of the following are met:

- Achieve at least a 5-letter improvement on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart in the eye scheduled for surgery using an external telescope; and
- Adequate peripheral vision in the eye not scheduled for surgery, to allow for orientation and mobility; and
- Agree to undergo 2 to 4 pre-surgical training sessions with low vision specialist (optometrist or occupational therapist); and
- Evidence of a visually significant cataract (grade 2 or higher); and
- No active wet ARMD (no sign of active choroidal neovascularization in either eye); and
- No sign of eye disease other than well-controlled glaucoma; and
- Not been treated for wet ARMD in the previous 6 months; and
- Visual acuity poorer than 20/160, but not worse than 20/800 in both eyes; and
- Willingness to participate in a post-operative visual rehabilitation program.

Aetna considers the following interventions/therapies experimental and investigational for the
management/treatment of ARMD because their effectiveness for this indication has not been established:

- Anecortave acetate (CPB 0706 - Anecortave acetate (Retaane) (0706.html))
- Ciliary neurotrophic factor
- Epiretinal radiation therapy (also known as epimacular brachytherapy) (CPB 0756 - Epiretinal Radiation Therapy (0756.html))
- Gene therapy
- Injection of bevacizumab, pegaptanib, or ranibizumab for dry/non-neovascular ARMD
- Interferon alpha (CPB 0404 - Interferons (../400_499/0404.html))
- Intra-ocular electrically stimulated devices (e.g., optic nerve, cortical, epiretinal and subretinal)
- Intra-vitreal bevasiranib
- Intra-vitreal triamcinolone
- Laser photocoagulation of macular drusen (CPB 0609 - Laser Photocoagulation of Drusen (../600_699/0609.html))
- Macular/foveal translocation (CPB 0409 - Macular/Foveal Translocation (../400_499/0409.html))
- Polymorphism testing as markers of ARMD (e.g., ABCA1 rs1883025, CX3CR1, and TLR3 rs3775291)
- Polymorphism testing as a predictor of therapeutic response to anti-VEGF therapy (e.g., Y402H)
- Proton beam radiotherapy (CPB 0270 - Proton Beam and Neutron Beam Radiotherapy (../200_299/0270.html))
- Simultaneous use of Visudyne PDT in combination with anti-angiogenic agents (for choroidal neovascularization due to ARMD)
- Single-nucleotide polymorphism (SNP)-based genotype testing (e.g., Macula Risk PGx, RetnaGene AMD, RetnaGene LR) (see CPB 0140 - Genetic Testing).
- Stem cell transplantation (CPB 0606 - Hematopoietic Cell Transplantation for Autoimmune Diseases and Miscellaneous Indications (../600_699/0606.html))
- Submacular surgery
- Subretinal injection of tissue plasminogen activator
combined with intra-vitreal air injection (for subretinal hemorrhage in ARMD)
- Surgical implantation of optic nerve
- Transpupillary thermotherapy (CPB 0490 - Transpupillary Thermal Therapy (../400_499/0490.html)).

**Background**
Age-related macular degeneration (ARMD), a progressive degenerative disease of the macula, is the leading cause of blindness in developed countries afflicting about 15 million people in the United States. The risk of ARMD increases with age, and usually affects people 60 years of age and older. Heavy alcohol consumption (more than 3 standard drinks per day) is associated with an increased risk of early ARMD (Chong et al, 2008). Early ARMD is characterized by the presence of a few (less than 20) medium-size drusen or retinal pigmentary abnormalities. Intermediate ARMD is characterized by at least one large druse, numerous medium-size drusen, or geographic atrophy that does not extend to the center of the macula. Late or advanced ARMD can be either neovascular (wet or exudative) or non-neovascular (dry, atrophic, or non-exudative). The neovascular form includes serous or hemorrhagic detachment of retinal pigment epithelium and choroidal neovascularization (CNV), which lead to leakage and scarring. It is responsible for the majority of cases of severe vision loss and is due to proliferation of abnormal blood vessels behind the retina. These blood vessels leak blood and fluid into the retina, resulting in visual abnormalities. The development of these abnormal blood vessels is due in part to the activity of vascular endothelial growth factor (VEGF), which induces angiogenesis, and increases vascular permeability and inflammation, all of which are thought to contribute to the progression of the neovascular form of ARMD. The non-neovascular form leads to a slow deterioration of the macula with a gradual loss of vision over a period of years. It does not involve leakage of blood or serum, and is characterized by drusen and geographic atrophy extending to the center of the macula. Patients with non-exudative ARMD can progress to the exudative form of ARMD, in which
pathologic CNV membranes develop under the retina, leak fluid and blood, and ultimately cause a blinding disciform scar in a relatively short time. Approximately 10 to 20 % of patients with non-exudative ARMD eventually progress to the exudative form, which is responsible for most of the cases of advanced ARMD in the United States (AAO, 2006; Comer, 2006; Jager et al, 2008).

Various therapeutic approaches have been employed in the treatment of patients with ARMD. High-dose antioxidants are thought to be able to limit the damage caused by oxidative stress in the macula. However, this treatment only slows progression in some patients and does not reverse damage already present. After ARMD becomes exudative, laser photocoagulation, photodynamic therapy (PDT) with verteporfin (Visudyne), and intra-vitreal injections of pegaptanib sodium (Macugen), bevacizumab (Avastin) and ranibizumab (Lucentis) have been used to control CNV. Because of the limitations in current treatment, researchers are presently developing alternative therapies for wet ARMD including alternative types of PDT, irradiation, intra-ocular devices, intra-vitreal administration of bevasiranib (a small interfering RNA agent that inhibits intra-cellular transcription of VEGF), transpupillary thermotherapy, treatment with a variety of growth-factor modulators, and vitreo-retinal surgery (AAO, 2006; Comer, 2006; Jager et al, 2008).

Argon laser photocoagulation therapy was once the most common therapy for wet ARMD. It is now used only occasionally to treat CNV that extends by more than 200 µm from the center of the macula, since this treatment itself can create a large retinal scar associated with permanent visual loss (Jaeger, 2008). In a Cochrane review, Virgili and Bini (2007) examined the effects of laser photocoagulation for wet ARMD. A total of 15 trials were included in the review (2,064 subjects). Three types of photocoagulation were used in the trials: (i) direct photocoagulation of the entire CNV (11 trials), (ii) perifoveal photocoagulation (1 trial) and (iii) grid photocoagulation (3 trials). In 12 trials the control group was
observation only. One trial compared photocoagulation to submacular surgery and 2 trials compared different lasers. Data on the progression of visual loss could be extracted from 5 of the 8 trials of direct photocoagulation of the CNV versus observation. The treatment effect was in the direction of harm in all studies at 3 months follow-up (RR 1.41, 95% confidence intervals [CI]: 1.08 to 1.82). After 2 years the treatment effect was in the direction of benefit (RR 0.67, 95% CI: 0.53 to 0.83). These studies were clinically heterogeneous with participants having CNV lesions in different locations and different baseline visual acuity (VA). There was little evidence of statistical heterogeneity at 3 months but substantial statistical heterogeneity at 2 years. However, all treatment effects in the individual trials were in the direction of benefit. One study comparing perifoveal photocoagulation or observation of subfoveal CNV found benefits that were statistically significant only at 2 years (RR 0.36, 95% CI: 0.18 to 0.72). Other comparisons did not demonstrate differences. The authors concluded that in the medium to long-term, laser photocoagulation of CNV slows the progression of visual loss in people with wet ARMD. However, it is associated with an increased risk of visual loss immediately after treatment and this period may be longer in people with subfoveal ARMD. With the advent of pharmacotherapies, and concern for the impact of iatrogenic scotoma in subfoveal CNV, laser photocoagulation of subfoveal CNV is not recommended. No studies have compared photocoagulation with modern pharmacological agents for ARMD for non-subfoveal CNV.

In a Cochrane review on laser treatment of drusen to prevent progression to advanced ARMD, Parodi and colleagues (2009) stated that the trials included in this review confirm the clinical observation that laser photocoagulation of drusen leads to their disappearance. However, there is no evidence that this subsequently results in a reduction in the risk of developing CNV, geographic atrophy or visual acuity loss.

In a Cochrane review, Giansanti et al (2009) evaluated the effectiveness of submacular surgery for preserving or improving
vision in patients with ARMD. These investigators searched CENTRAL, MEDLINE, EMBASE and LILACS. There were no language or date restrictions in the search for trials. The electronic databases were last searched on 11 February 2009. They included randomized or quasi-randomized controlled trials comparing submacular surgery with any other treatment or observation. Two authors independently extracted the data. The risk ratio of visual loss and visual gain was estimated at 1 year. Two multi-center studies with a similar design were conducted between 1997 and 2003 and compared submacular surgery with observation in people affected by subfoveal neovascular ARMD with (n = 336) or without (n = 454) extensive blood in the macula. At 1 year, there was high quality evidence of no benefit for preventing visual loss (risk ratio: 0.96; 95 % CI: 0.84 to 1.09). No difference could be demonstrated regarding the chance of visual gain (risk ratio: 1.06; 95 % CI: 0.75 to 1.51), although this evidence was of low quality because of imprecision. The risk difference was -2 % (95 % CI: -10 % to 5 %) and 1 % (95 % CI: -4 % to 6 %) for visual loss and visual gain, respectively, thus excluding a large benefit with surgery in terms of absolute risk in this sample. There was high quality evidence that cataract needing surgery (risk ratio: 8.69; 95 % CI: 4.06 to 18.61) and retinal detachment (risk ratio: 6.13; 95 % CI: 2.81 to 13.38) were more common among operated patients, and detachment occurred in 5 % of patients with no extensive blood and in 18 % of those with extensive blood beneath the macula. A pilot study compared submacular surgery with laser photocoagulation in 70 patients. No difference between the 2 treatments could be demonstrated for any outcome measure, but estimates were very imprecise because of small sample size. The authors concluded that there is no benefit with submacular surgery in most people with subfoveal CNV due to ARMD in terms of prevention of visual loss. Furthermore, the risk of developing cataract and retinal detachment increases after surgery.

A systematic evidence review published in BMJ Clinical Evidence (Arnold and Heriot, 2006) also concluded that submacular surgery for ARMD "is likely to be ineffective or harmful."

Ocular PDT entails the use of an intravenously administered, light-sensitive dye, verteporfin, which preferentially concentrates in new blood vessels. Visudyne is activated with the use of a 689-nm laser beam focused over the macula, causing localized choroidal neovascular thrombosis through a non-thermal chemotoxic reaction. Although it generally does not improve vision and its use as monotherapy appears to be less effective than other treatments, PDT does limit visual loss in wet ARMD, and its repeated use over a 5-year period appears to be safe, with minimal, infrequent side effects including dye extravasation at the injection site, back pain, and photosensitivity (Jager et al, 2008).

Kaiser (2007) discussed the rationale for combining anti-angiogenic treatment with Visudyne PDT in the management of CNV due to ARMD and evaluated available evidence for the therapeutic benefits of such approaches. Treatments for CNV due to ARMD can be directed at either the vascular component of CNV or the angiogenic component that leads to the development of the condition. Verteporfin targets the vascular component, whereas anti-angiogenic agents (such as pegaptanib and ranibizumab) target key mediators of the angiogenic cascade. The different mechanisms of action of these approaches offer the potential for additive or synergistic effects with combination therapy. In addition, anti-angiogenic agents might counteract up-regulation of angiogenic factors (including VEGF) that occur after verteporfin PDT. Results from pre-clinical and clinical studies of the combination of ranibizumab or pegaptanib with verteporfin warrant continued investigation. The author concluded that the use of anti-angiogenic agents in combination with verteporfin may have the potential to improve visual outcomes and reduce the number of treatments in eyes with CNV due to ARMD, and requires further evaluation in randomized, controlled clinical trials.

The first intra-vitreal agent approved by the Food and Drug Administration (FDA) for wet ARMD was pegaptanib, a messenger RNA aptamer and VEGF antagonist. Pegaptanib
binds to VEGF and inhibits its binding to cellular receptors; its anti-VEGF activity is expected to inhibit abnormal blood vessel proliferation and thus decrease the vision loss associated with the proliferation of abnormal blood vessels. However, the number of patients whose VA improved with pegaptanib was limited, so the agent is no longer widely used (Jager et al, 2008).

Currently, the most common treatments for wet ARMD are intra-vitreal bevacizumab and ranibizumab. Bevacizumab, a monoclonal antibody to VEGF is being used off-label for wet ARMD. Although data from long-term studies are not yet available, several short-term studies of intra-vitreal bevacizumab have shown improvement in VA that is similar to the improvement with ranibizumab. Intra-vitreal bevacizumab appears to have systemic adverse events similar to those of ranibizumab, which is designed to block new blood vessel growth and leakiness, and is the first treatment which, when given monthly, can maintain the vision of more than 90 % of patients with wet ARMD. In contrast to pegaptanib, ranibizumab is a recombinant humanized monoclonal antibody fragment with specificity for all isoforms of human VEGF. Ranibizumab exhibits high affinity for human VEGF and exerts its neutralizing effects by inhibiting the VEGF-receptor interaction. Unlike the larger whole antibody, ranibizumab can penetrate the internal limiting membrane and reach the subretinal space following intra-vitreal injection (van Wijngaarden et al, 2005).

In an editorial on the use of intra-vitreal bevacizumab as the low cost alternative to ranibizumab published in the American Journal of Ophthalmology, Rosenfeld (2006) stated that "[c]urrently, there appears to be a global consensus that the treatment strategy using intra-vitreal Avastin is logical, the potential risks to our patients are minimal, and the cost-effectiveness is so obvious that the treatment should not be withheld". On March 20, 2006, a survey by the American Society of Retinal Specialists of its membership was completed. It found that 92 % of 289 respondents felt intra-vitreal
bevacizumab was "somewhat better" or "much better" than other FDA-approved or covered therapies. Only 4% of respondents had seen any thromboembolic complications thought to be related to the intra-vitreal bevacizumab, and 96% thought intra-vitreal bevacizumab was the same or better in terms of overall safety compared to other FDA-approved or covered therapies.

On April 20, 2006, the American Academy of Ophthalmology (AAO) wrote to the Centers for Medicare and Medicaid Services supporting the reimbursement for treating ARMD with intra-vitreal injections of bevacizumab to meet the medical needs of patients who have not responded to Visudyne PDT or intra-vitreal pegaptanib. The AAO's support for reimbursement is limited to "such patients who are deemed by their treating physician to have failed FDA-approved therapies, or in the judgment of their treating physician, based on his/her experience, are likely to have greater benefit from the use of intra-vitreal bevacizumab". On October 5, 2006, the National Institutes of Health's National Eye Institute said it will fund a multi-center clinical trial to compare ranibizumab with bevacizumab in the treatment of ARMD (NIH, 2006).

In a Cochrane review, Vedula and Krzytlolik (2008) examined the effects of anti-VEGF modalities for treating neovascular ARMD. These investigators concluded that pegaptanib and ranibizumab reduce the risk of VA loss in patients with neovascular ARMD. Ranibizumab causes gains in VA in many eyes. Other agents blocking VEGF are being tested in ongoing trials.

In a multi-center, randomized controlled trial (RCT), the Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group (2012) described (i) the effects of ranibizumab and bevacizumab when administered monthly or as needed for 2 years, and (ii) the impact of switching to as-needed treatment after 1 year of monthly treatment. Subjects (n = 1,107) were those who were followed-up during year-2 among 1,185 patients with
neovascular ARMD who were enrolled in the clinical trial. At enrollment, patients were assigned to 4 treatment groups defined by drug (ranibizumab or bevacizumab) and dosing regimen (monthly or as needed). At 1 year, patients initially assigned to monthly treatment were re-assigned randomly to monthly or as-needed treatment, without changing the drug assignment. Main outcome measure was mean change in VA. Among patients following the same regimen for 2 years, mean gain in VA was similar for both drugs (bevacizumab-ranibizumab difference, -1.4 letters; 95 % CI: -3.7 to 0.8; p = 0.21). Mean gain was greater for monthly than for as-needed treatment (difference, -2.4 letters; 95 % CI: -4.8 to -0.1; p = 0.046). The proportion without fluid ranged from 13.9 % in the bevacizumab-as-needed group to 45.5 % in the ranibizumab monthly group (drug, p = 0.0003; regimen, p < 0.0001).

Switching from monthly to as-needed treatment resulted in greater mean decrease in vision during year 2 (-2.2 letters; p = 0.03) and a lower proportion without fluid (-19 %; p < 0.0001). Rates of death and arterio-thrombotic events were similar for both drugs (p > 0.60). The proportion of patients with 1 or more systemic serious adverse events was higher with bevacizumab than ranibizumab (39.9 % versus 31.7 %; adjusted risk ratio, 1.30; 95 % CI: 1.07 to 1.57; p = 0.009). Most of the excess events have not been associated previously with systemic therapy targeting VEGF. The authors concluded that ranibizumab and bevacizumab had similar effects on VA over a 2-year period. Treatment as needed resulted in less gain in VA, whether instituted at enrollment or after 1 year of monthly treatment. There were no differences between drugs in rates of death or arterio-thrombotic events. The interpretation of the persistence of higher rates of serious adverse events with bevacizumab is uncertain because of the lack of specificity to conditions associated with inhibition of VEGF.

In a prospective, double-masked, placebo-controlled, randomized clinical study, Lee and colleagues (2007) examined the effect of intra-vitreal injection of high-dose triamcinolone acetonide on minimally classic or occult CNV secondary to ARMD. The treatment group (21 eyes) received
intra-vitreal injection (20 to 25 mg) of triamcinolone acetonide and the control group (18 eyes) received intra-vitreal injection (500 mug) of dexamethasone at 6-month intervals. Best-corrected Early Treatment Diabetic Retinopathy Study (ETDRS) score, contrast sensitivity score, and central macular volume were measured at 1 month, 3 months, 6 months, and 12 months. Mean baseline best-corrected VA (BCVA [logarithm of the minimal angle of resolution]) was 0.64 (Snellen equivalent, 20/80) in each group. At 1 month, 3 months, and 6 months after the injection, neither group had a significant change in BCVA. At 12 months, mean BCVA +/- SD significantly decreased to 1.06 +/- 0.34 (Snellen equivalent, 20/200) in the treatment group (paired t-test, p < 0.001), whereas it was 0.78 +/- 0.52 (Snellen equivalent, 20/125) in the control group (p = 0.23). The difference was marginally significant (p = 0.06, Student’s t-test). All phakic eyes in the treatment group developed marked cataract progression. The authors concluded that intra-vitreal injection of high-dose triamcinolone had no beneficial effect on eyes with minimally classic or occult CNV secondary to ARMD and was associated with outcomes similar to those associated with intra-vitreal injection of dexamethasone, which was used as placebo.

On November 18, 2011, the FDA approved aflibercept ophthalmic solution (Eylea, Regeneron Pharmaceuticals Inc.) for the treatment of neovascular (wet) ARMD. The FDA’s approval of Eylea was based on positive results from the 2 phase III VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW) trials. Both found the drug non-inferior to ranibizumab, which is currently the most potent FDA-approved treatment option for wet ARMD. The most commonly reported adverse events in patients receiving aflibercept included eye pain, conjunctival hemorrhage, vitreous floaters, cataract, and an increase in eye pressure. Aflibercept should not be used in those who have an active eye infection or active ocular inflammation. It has not been studied in pregnant women, so the treatment should be used only in pregnant women if the potential benefits of the treatment outweigh any potential risks. Age-related macular degeneration does not occur in
children and aflibercept has not been studied in children. The recommended dose is 2 mg every 4 weeks (monthly) for the first 12 weeks, followed by 2 mg every 8 weeks (2 months).

In a review, Jager and colleagues (2008) discussed several evolving methods in the treatment of neovascular ARMD. Intra-vitreal administration of bevasiranib, a small interfering RNA agent, inhibits intra-cellular transcription of VEGF. This agent appears to inhibit CNV; phase III clinical trials are underway to ascertain its effectiveness in treating ARMD (Chappelow and Kaiser, 2008). The implantation of artificial intra-ocular devices might benefit patients who are refractory to pharmacotherapies. Implantable miniature telescopes might improve the quality of life of patients with severe visual loss from end-stage ARMD. Surgical implantation of optic nerve, cortical (visual cortex), subretinal, and epiretinal electrically stimulated devices have all led to the perception of phosphenes (discrete, reproducible perceptions of light) in humans. These devices may help restore functional vision in the future but are primitive at present.

Artificial lens systems usually consist of a single miniature telescope prosthesis or a combination of individual lenses implanted separately. Implantation is performed under local anesthesia. The natural lens is removed through a small incision at the limbus and the new lens system is inserted. An iridectomy is performed to prevent pupillary block. The exact technique for implantation may vary according to the system being used.

On July 6, 2010, the FDA approved the implantable miniature telescope (IMT) (VisionCare Ophthalmic Technologies, Saratoga, CA) for patients aged 75 years and older with stable, untreatable, severe-to-profound vision impairment (when vision impairment has not changed over time) caused by blind spots (bilateral central scotoma) associated with end-stage ARMD with evidence of a visually significant cataract.

In October 2014, the FDA expanded approval of IMT to patients
65 years of age or older. FDA approval to expand access to those age 65 and older was based on clinical data provided by the pivotal safety and efficacy study, IMT-002, and long-term studies IMT-002-LTM and IMT-002-LTME, which followed patients to 5 and 8 years, respectively.

The IMT device is a compound telescope system that consists of a glass cylinder (4.4 mm in length and 3.6 mm in diameter) housing wide-angle micro-optics. The height of the glass cylinder approximately equals that of 13 stacked intraocular lenses (IOLs). The device is heavier (115 mg in air and 60 mg in aqueous) and the carrier haptics are less flexible than those found on 1-piece polymethylmethacrylate IOLs. The IMT device is surgically implanted in the posterior chamber of the eye after removal of the eye’s lens and is designed to be implanted in 1 eye only; the implanted eye provides central vision, while the non-implanted eye is used for peripheral vision. The IMT protrudes 0.1 to 0.5 mm through the papillary plane, leaving a minimum of 2.0 mm of corneal clearance. When properly implanted in eyes with anterior chamber depths of 2.5 mm or more, the face of the optic should not touch the corneal endothelium. The device provides higher resolution images to the central retina and its telephoto effect also allows more to be seen in the central visual field. The device is used for both near and distance activities, with objects being brought into focus by standard spectacles. Prior to implantation, patients must agree to undergo training with an external telescope with a low vision specialist to determine whether adequate improvement in vision with the external telescope can be obtained and to verify if the patient has adequate peripheral vision in the eye that would not be implanted. Patients must also agree to participate in a post-operative visual training program. The device is available in 2 models: one provides 2.2 x magnification and the other provides 2.7 x magnification.

The IMT-002 clinical trial (Hudson et al, 2006) evaluated the safety and efficacy of VisionCare’s IMT in patients with bilateral, end-stage ARMD in a prospective, open-label, multi-center clinical trial with fellow eye controls. A total of 217 patients
(mean age of 76 years) with ARMD and moderate to profound bilateral central VA loss (20/80 to 20/800) resulting from bilateral untreatable geographic atrophy, disciform scars, or both were enrolled; however, 11 eyes did not receive the device because of an aborted procedure. The IMT was implanted monocularly in the capsular bag after lens extraction. Fellow eyes were not implanted to provide peripheral vision and served as controls. Study patients participated in 6 visual rehabilitation visits after surgery. The majority of patients (90%) met or exceeded the VA end-point defined as an improvement in 2 lines or more in either near or distance BCVA at the 1-year follow-up. Change in VA was not related to lesion type. Mean quality-of-life scores from the National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) and the Activities of Daily Life scale, a secondary outcome measure, improved by more than 7 points from baseline on 7 of 8 relevant subscales (e.g., social functioning, mental health, role difficulties, and dependency); at 12 months, 51.8% (100/193) of patients gained at least 5 points, 25.9% (50/193) of patients reported no change (i.e., change within +/-5 points), and 22.3% of patients (43/193) lost at least 5 points in VFQ-25 composite score from baseline. Mean endothelial cell density (ECD) loss at 3 months was 20% and 25% at 12 months. The decrease in ECD was correlated with post-surgical edema, and there was no evidence that endothelial cell loss accelerated by ongoing endothelial trauma after implantation. The authors concluded that the IMT can improve VA and quality of life in patients with moderate-to-profound visual impairment caused by bilateral, end-stage ARMD.

Because the IMT is large and non-foldable, it requires a much larger incision (12 mm) than phacoemulsification with foldable IOL. The risk of corneal endothelial cell loss during implantation is higher than conventional anterior segment procedures, but is comparable with that seen after large-incision cataract extraction (Colby et al, 2007). Significant losses in ECD may lead to corneal edema, corneal decompensation, and the need for corneal transplant. In the IMT-002 trial, 10 eyes had unresolved corneal edema, with 5
resulting in corneal transplants. The device was removed from 8 eyes post-operatively (4 subjects requested removal because they were dissatisfied with the device, 2 were removed due to condensation of the telescope portion, and 2 eyes underwent corneal transplantation as a result of corneal decompensation). The calculated 5-year risk for unresolved corneal edema, corneal decompensation, and corneal transplant are 9.2 %, 6.8 % and 4.1 %, respectively (FDA, 2010). Four device failures were reported during the IMT-002 trial.

According to the manufacturer’s website, the IMT is intended for monocular implantation in patients aged 65 years and older with stable, untreated, severe-to-profound vision impairment caused by blind spots (bilateral central scotoma) associated with end-stage ARMD as determined by fluorescein angiography when all of the following are met:

- Achieve at least a 5-letter improvement on the Early Treatment Diabetic Retinopathy Study (ETDRS) VA chart in the eye scheduled for surgery using an external telescope; and
- Adequate peripheral vision in the eye not scheduled for surgery; and
- Agree to undergo 2 to 4 pre-surgical training sessions with low vision specialist (optometrist or occupational therapist); and
- Evidence of a visually significant cataract (grade 2 or higher); and
- No active wet ARMD (no sign of active CNV in either eye); and
- No sign of eye disease other than well-controlled glaucoma; and
- Not been treated for wet ARMD in the previous 6 months; and
- Stable, untreated ARMD disease present in both eyes (end-stage, geographic atrophy or disciform scar) as determined by fluorescein angiography; and
- Visual acuity poorer than 20/160, but not worse than 20/800 in both eyes; and
Willingness to participate in a post-operative visual rehabilitation program.

As a condition of FDA approval, the manufacturer must conduct 2 post-approval studies: (i) VisionCare must continue follow-up on the subjects from its long-term follow-up cohort for an additional 2 years, and (ii) an additional study of 770 newly enrolled subjects will include an evaluation of the ECD and related adverse events for 5 years after implantation.

The IMT is contraindicated in patients with any of the following:

- A history of steroid-responsive rise in intra-ocular pressure (IOP), uncontrolled glaucoma, or pre-operative IOP greater than 22 mm Hg while on maximum medication;
- Any ophthalmic pathology that compromises the patient’s peripheral vision in the fellow eye;
- Evidence of active CNV on fluorescein angiography or treatment for CNV within the past 6 months;
- Known sensitivity to post-operative medications;
- Previous intra-ocular or corneal surgery of any kind in the operative eye, including any type of surgery for either refractive or therapeutic purposes;
- Prior or expected ophthalmic related surgery within 30 days preceding IMT implant surgery;
- Significant communication impairments or severe neurological disorders;
- Stargardt’s macular dystrophy;
- The planned operative eye has any of the following:
  - A history of retinal detachment
  - A narrow angle (i.e., less than Schaffer grade 2)
  - An axial length less than 21 mm
  - An ocular condition that predisposes the patient to eye rubbing
  - Central anterior chamber depth less than 3.0 mm (measured from the posterior surface of the cornea (endothelium) to the anterior surface of the crystalline lens
- Cornea stromal or endothelial dystrophies or disorders, including guttata
- Diabetic retinopathy
- Endothelial cell counts below the following minimum baseline:
  - Aged 65 to 84 years with ECD below 2,000 cells/mm²
  - Aged 85 years or older with ECD below 1,800 cells/mm²
- Hyperopia greater than 4.0 diopters
- Inflammatory ocular disease
- Intraocular tumor
- Myopia greater than 6.0 diopters
- Optic nerve disease
- Retinal vascular disease
- Retinitis pigmentosa
- Untreated retinal tears
- Zonular weakness/instability of crystalline lens, or pseudoexfoliation

One of the internal components of the IMT implant containing stainless steel has been evaluated for magnetic resonance imaging (MRI) compatibility and determined to be MR-conditional.

The National Institute for Clinical Excellence's (NICE, 2008) guidance on implantable miniature lens systems for the treatment of ARMD stated that: "[e]vidence on the efficacy of implantation of miniature lens systems for advanced age-related macular degeneration (AMD) shows that the procedure can improve both vision and quality of life in the short-term. Short-term safety data are available for limited numbers of patients. There is currently insufficient long-term evidence on both efficacy and safety. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research." The National Institute for Clinical Excellence included a non-randomized
study and a case series study as part of the evidence review. In the non-randomized study of 217 patients, 67 % (128/192) and 68 % (130/192) of eyes with an implanted lens system improved by 3 or more lines of best-corrected distance and near VA, respectively, compared with 13 % (24/192) and 33 % (64/192) of non-implanted fellow eyes (p less than 0.0001) at 1-year follow-up. Loss of 2 or more lines of best-corrected distance VA was reported in 2 % of implanted eyes and 9 % of fellow eyes at 1-year follow-up (p = 0.005). Two patients developed corneal decompensation and underwent device removal and corneal transplantation more than 1 year after the initial surgery and 5 % of the procedures were aborted due to complications (e.g., posterior capsule rupture and choroidal effusion/hemorrhage). In a case series study of 35 patients (40 eyes), best-corrected distance VA improved in all patients after a mean of 20 months. Other complications in the non-randomized study and case series study included increased IOP requiring treatment (28 % [57/206]) and corneal edema (25 % [9/36], 7 % [14/206]). Two specialist advisors reported corneal endothelial cell loss as an adverse event. They considered additional theoretical complications to include corneal decomposition and corneal and macular edema. One specialist advisor commented that the procedure has more risks than standard cataract surgery. Furthermore, the Committee noted that there are several different lens systems available and that the technique is still evolving.

An UpToDate review on “Age-related macular degeneration: Treatment and prevention” (Arroyo, 2014) states that “Two procedures have been tried, with limited success, for AMD: submacular surgery and macular translocation surgery. Submacular surgery involves the removal of abnormal subretinal neovascularization and large submacular hemorrhages, if present. Clinical trials have been largely disappointing, showing lack of benefit and high rates of retinal detachment. There may be a role for submacular surgery, however, in patients with large peripapillary membranes. Macular translocation surgery is experimental and involves moving the macula to a less diseased area of the retina in
patients with subfoveal choroidal neovascularization. The advent of effective pharmacologic therapy has limited the use of this surgical modality to patients with large submacular hemorrhages. The surgical risks are substantial. External beam radiation therapy has been studied in patients with AMD. A meta-analysis of randomized, controlled trials concluded that there was no consistent evidence of benefit. The long-term safety of radiation therapy is unknown”.

Si and colleagues (2014) compared the safety and effectiveness of combination of ranibizumab with PDT versus ranibizumab monotherapy in the treatment of ARMD. The Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, PubMed, and Embase were searched. There were no language or data restrictions in the search for trials. Only RCTs were included. Methodological quality of the literatures was evaluated according to the Jadad Score. RevMan 5.2.6 software was used to do the meta-analysis. A total of 7 studies were included in this systematic review, among which 4 of them were included in quantitative analysis. The result showed that the ranibizumab monotherapy group had a better mean BCVA change versus baseline at month 12 compared with that of the combination treatment group, and the statistical difference was significant (WMD, -2.61; 95 % CI: -5.08 to -0.13; p = 0.04). However, after the removal of 1 study, the difference between the 2 groups showed no significant difference (WMD, -2.29; 95 % CI: -4.81 to 0.23; p = 0.07). Meanwhile, no significant central retinal thickness (CRT) reduction was found in the combination treatment group and the ranibizumab monotherapy group at 12 months follow-up. Nevertheless, the combination group tended to have a greater reduction in CRT (WMD, -4.13 µm; 95 % CI: -25.88 to 17.63, p = 0.71). The proportion of patients gaining more than 3 lines at month 12 in the ranibizumab group was higher than in the combination group and there was a significant difference (RR, 0.72; 95 % CI: 0.54 to 0.95; p = 0.02). Whereas there was no significant difference for the proportion of patients gaining more than 0 line at month 12 between the 2 groups (RR, 0.93; 95 % CI: 0.76 to 1.15; p = 0.52). The general tendency showed a reduction in ranibizumab re-treatment
number in the combination treatment group compared with the ranibizumab monotherapy group. As major adverse events, the differences in the number of eye pain, endophthalmitis, hypertension and arterial thromboembolic events were not significant between the 2 groups, and the incidence of serious adverse events in the 2 groups was very low. The authors concluded that for the maintenance of vision, the comparison of the combination of ranibizumab with PDT versus ranibizumab monotherapy showed no apparent difference. Compared with the combination of ranibizumab and PDT, patients treated with ranibizumab monotherapy may gain more VA improvement. The combination treatment group had a tendency to reduce the number of ranibizumab re-treatment. Both treatment strategies were well-tolerated.

Jiang et al (2014) noted that ranibizumab is used monthly or as-needed (PRN) for the treatment of ARMD. However, which treatment regimen is more effective remains unknown. These investigators compared the effectiveness of monthly versus as-needed quarterly treatment; and the effectiveness of ranibizumab 0.5 mg treatment with: (a) no anti-VEGF; (b) ranibizumab 0.3 mg; and (c) bevacizumab. This was a systematic meta-analytic review of RCTs of ranibizumab in neovascular AMD. Weighted multiple regression analyses were used to compare the monthly versus PRN/quarterly treatment. A total of 8 RCTs met inclusion criteria. Patients on the monthly ranibizumab treatment had higher VA letter gains ($\beta = 0.441, p < 0.05$) compared with patients on as-needed/quarterly treatment. More patients on the monthly treatment gained greater than or equal to 15 letters than as-needed/quarterly treatment ($\beta = 0.582, p < 0.05$). Ranibizumab produced significantly higher improvement in VA ($d = 1.20, z = 7.14, p < 0.05$) and led to a higher proportion of patients gaining greater than or equal to 15 letters (odds ratios [OR]: 6.67; 95% CI: 3.16 to 14.06; $p < 0.05$) when compared with non-anti-VEGF. Ranibizumab did not show any advantage in VA compared with bevacizumab. No significant differences were found between ranibizumab 0.3 mg and 0.5 mg. The authors concluded that this was the first meta-analysis to systematically evaluate the
effectiveness of different treatment regimens for anti-VEGF therapy. Ranibizumab 0.3 or 0.5 mg monthly treatment was more effective for neovascular AMD than non-anti-VEGF treatments; but is no better than bevacizumab.

MacLaren et al (2014) examined the effects of retinal gene therapy with an adeno-associated viral (AAV) vector encoding REP1 (AAV.REP1) in patients with choroideremia. In a multicenter clinical trial, a total of 6 male patients (aged 35 to 63 years) with choroideremia were administered AAV.REP1 (0.6 to 1.0×10^{10} genome particles, subfoveal injection). Visual function tests included BCVA, microperimetry, and retinal sensitivity tests for comparison of baseline values with 6 months after surgery. Despite undergoing retinal detachment, which normally reduces vision, 2 patients with advanced choroideremia who had low baseline BCVA gained 21 letters and 11 letters (more than 2 and 4 lines of vision). Four other patients with near normal BCVA at baseline recovered to within 1 to 3 letters. Mean gain in VA overall was 3.8 letters (SE 4.1). Maximal sensitivity measured with dark-adapted microperimetry increased in the treated eyes from 23.0 dB (SE 1.1) at baseline to 25.3 dB (1.3) after treatment (increase 2.3 dB [95 % CI: 0.8 to 3.8]). In all patients, over the 6 months, the increase in retinal sensitivity in the treated eyes (mean 1.7 [SE 1.0]) was correlated with the vector dose administered per mm(2) of surviving retina (r = 0.82, p = 0.04). By contrast, small non-significant reductions (p > 0.05) were noted in the control eyes in both maximal sensitivity (-0.8 dB [1.5]) and mean sensitivity (-1.6 dB [0.9]). One patient in whom the vector was not administered to the fovea re-established variable eccentric fixation that included the ectopic island of surviving retinal pigment epithelium that had been exposed to vector. The authors concluded that the initial results of this retinal gene therapy trial are consistent with improved rod and cone function that overcome any negative effects of retinal detachment. They stated that these findings lend support to further assessment of gene therapy in the treatment of choroideremia and other diseases, such as ARMD, for which intervention should ideally be applied before the onset of
Shin et al (2016) stated that clinical study findings regarding the association between repeated injections of intra-vitreal anti-VEGF and the risk of retinal nerve fiber layer (RNFL) thinning in patients with ARMD have been inconsistent. These researchers investigated this association by using a meta-analysis. In August 2015, these investigators systematically reviewed PubMed, Embase, and the Cochrane Central Register of Controlled Trials. Two independent evaluators identified eligible articles by using pre-determined selection criteria. Average RNFL thickness before and after intra-vitreal anti-VEGF injections was examined by using data obtained at baseline and at the last follow-up visit. A total of 6 studies on 288 eyes were ultimately included. The meta-analysis revealed that average RNFL thickness following repeated anti-VEGF injections was not significantly different from baseline (mean difference [MD] = -0.171, 95% CI: -0.371 to 0.029, p = 0.093) or control group measurements (MD = -0.091, 95% CI: -0.517 to 0.335, p = 0.674). However, subgroup analyses by the methodological quality of study revealed a significant RNFL thickness loss in 2 low-biased, controlled experimental studies (MD = -0.534, 95% CI: -0.783 to -0.286, p = 0.001), but not in 4 observational studies (MD = -0.038, 95% CI: -0.171 to 0.095, p = 0.576). The authors concluded that there was no association between anti-VEGF injections and RNFL thickness changes when all studies were examined together. However, when 2 low-biased, controlled clinical trials were separately examined, repeated anti-VEGF injection was associated with RNFL loss. They stated that large-scale, prospective studies are needed to determine long-term effects of anti-VEGF treatments on the RNFL in ARMD patients.

Prevention of ARMD:

In a meta-analysis, Chuo and colleagues (2007) examined the effect of lipid-lowering agents in the development of ARMD. Case-control and cohort studies presenting relative risks and 95% CI were identified through a literature review. Inclusion was
limited to studies where both the exposure of interest (lipid-lowering agents) and outcome (ARMD) were explicitly defined. Pooled estimates were computed using the random effects model. To quantify heterogeneity, these researchers calculated the proportion of total variance of between study variance using the Ri statistic. The Q statistic for heterogeneity was also calculated. Eight studies were identified. The pooled relative risk (RR) for all studies was 0.74 (95 % CI: 0.55 to 1.00). When only those studies examining the use of statins were pooled (n = 7), the RR was 0.70 (95 % CI: 0.48 to 1.03). Using the Ri statistic, the heterogeneity between studies was found to be 0.85 for all studies and 0.89 for studies examining statins. The authors concluded that lipid-lowering agents, including statins, do not appear to lower the risk of developing ARMD, although clinically significant effects can not be excluded. The use of these agents in the prevention of ARMD can not be recommended until well-designed prospective studies with long-term follow-up have demonstrated a benefit.

Evans and Henshaw (2008) stated that some observational studies have suggested that people who eat a diet rich in antioxidant vitamins (e.g., carotenoids, vitamins C and E) or minerals (e.g., selenium and zinc) may be less likely to develop ARMD. In a Cochrane review, these researchers examined the evidence as to whether or not taking vitamin or mineral supplements prevents the development of ARMD. They included all randomized trials comparing an antioxidant vitamin and/or mineral supplement (alone or in combination) to control; and included only studies where supplementation had been given for at least 1 year. Three RCTs were included in this review (23,099 people randomized). These trials investigated alpha-tocopherol and beta-carotene supplements. There was no evidence that antioxidant vitamin supplementation prevented or delayed the onset of ARMD. The pooled risk ratio for any age-related maculopathy (ARM) was 1.04 (95 % CI: 0.92 to 1.18), for ARMD (late ARM) was 1.03 (95 % CI: 0.74 to 1.43). Similar results were seen when the analyses were restricted to beta-carotene and alpha-tocopherol. The authors concluded that there is no evidence to date that the general
population should take antioxidant vitamin and mineral supplements to prevent or delay the onset of ARMD.

Oral supplementation with the Age-Related Eye Disease Study (AREDS) formulation (antioxidant vitamins C and E, beta carotene, and zinc) has been shown to reduce the risk of progression to advanced ARMD. Observational data suggested that increased dietary intake of lutein + zeaxanthin (carotenoids), omega-3 long-chain polyunsaturated fatty acids (docosahexaenoic acid [DHA] + eicosapentaenoic acid [EPA]), or both might further reduce this risk. The Age-Related Eye Disease Study 2 (AREDS2) RCT examined if adding lutein + zeaxanthin, DHA + EPA, or both to the AREDS formulation decreases the risk of developing advanced ARMD and evaluated the effect of eliminating beta carotene, lowering zinc doses, or both in the AREDS formulation. The AREDS2 is a multi-center, randomized, double-masked, placebo-controlled phase III study with a 2 × 2 factorial design, conducted in 2006 to 2012 and enrolling 4,203 participants aged 50 to 85 years at risk for progression to advanced ARMD with bilateral large drusen or large drusen in 1 eye and advanced ARMD in the fellow eye. Participants were randomized to receive lutein (10 mg) + zeaxanthin (2 mg), DHA (350 mg) + EPA (650 mg), lutein + zeaxanthin and DHA + EPA, or placebo. All participants were also asked to take the original AREDS formulation or accept a secondary randomization to 4 variations of the AREDS formulation, including elimination of beta carotene, lowering of zinc dose, or both. Main outcome measure was development of advanced ARMD. The unit of analyses used was by eye. Median follow-up was 5 years, with 1,940 study eyes (1,608 participants) progressing to advanced ARMD. Kaplan-Meier probabilities of progression to advanced ARMD by 5 years were 31% (493 eyes [406 participants]) for placebo, 29% (468 eyes [399 participants]) for lutein + zeaxanthin, 31% (507 eyes [416 participants]) for DHA + EPA, and 30% (472 eyes [387 participants]) for lutein + zeaxanthin and DHA + EPA. Comparison with placebo in the primary analyses demonstrated no statistically significant reduction in progression to advanced ARMD (hazard ratio [HR], 0.90 [98.7%]
CI: 0.76 to 1.07]; p = 0.12 for lutein + zeaxanthin; 0.97 [98.7 %
CI: 0.82 to 1.16]; p = 0.70 for DHA + EPA; 0.89 [98.7 % CI: 0.75 to
1.06]; p = 0.10 for lutein + zeaxanthin and DHA + EPA). There
was no apparent effect of beta carotene elimination or lower-
dose zinc on progression to advanced ARMD. More lung
cancers were noted in the beta carotene versus no beta
carotene group (23 [2.0 %] versus 11 [0.9 %], nominal p = 0.04),
mostly in former smokers. The authors concluded that addition
of lutein + zeaxanthin (Lutemax 2020), DHA + EPA, or both to
the AREDS formulation in primary analyses did not further
reduce risk of progression to advanced ARMD. However,
because of potential increased incidence of lung cancer in
former smokers, lutein + zeaxanthin could be an appropriate
carotenoid substitute in the AREDS formulation.

In a multi-center, phase III, RCT, Dugel et al (2013) evaluated the
safety and effectiveness of epi-macular brachytherapy (EMBT;
also known as epiretinal brachytherapy) for the treatment of
neovascular ARMD. A total of 494 participants with treatment-
naïve neovascular ARMD were included in this study.
Participants with classic, minimally classic, and occult lesions
were randomized in a 2:1 ratio to EMBT or a ranibizumab
monotherapy control arm. The EMBT arm received 2
mandated, monthly loading injections of 0.5 mg ranibizumab.
The control arm received 3 mandated, monthly loading
injections of ranibizumab then quarterly injections.
Both arms also received monthly as needed (pro re nata) re-
treatment. Main outcome measures included the proportion
of participants losing fewer than 15 ETDRS letters from
baseline VA and the proportion gaining more than 15 ETDRS
letters from baseline VA. At 24 months, 77 % of the EMBT
group and 90 % of the control group lost fewer than 15 letters.
This difference did not meet the pre-specified 10 % non-
inferiority margin. This end-point was non-inferior using a 20
% margin and a 95 % CI for the group as a whole and for
classic and minimally classic lesions, but not for occult lesions.
The EMBT did not meet the superiority end-point for the
proportion of participants gaining more than 15 letters (16 %
for the EMBT group versus 26 % for the control group): this
difference was statistically significant (favoring controls) for occult lesions, but not for predominantly classic and minimally classic lesions. Mean VA change was -2.5 letters in the EMBT arm and +4.4 letters in the control arm. Participants in the EMBT arm received a mean of 6.2 ranibizumab injections versus 10.4 in the control arm. At least 1 serious adverse event occurred in 54 % of the EMBT arm, most commonly post-vitrectomy cataract, versus 18 % in the control arm. Mild, non-proliferative radiation retinopathy occurred in 3 % of the EMBT participants, but no case was vision threatening. The authors concluded that the 2-year effectiveness data do not support the routine use of EMBT for treatment-naive wet ARMD, despite an acceptable safety profile. They stated that further safety review is needed.

Petrarca et al (2013) reported the optical coherence tomography (OCT) and fundus fluorescein angiography (FFA) results of the MERITAGE (Macular Epiretinal Brachytherapy in Treated Age-Related Macular Degeneration) study. In this prospective, multi-center, interventional, non-controlled clinical trial, a total of 53 eyes of 53 participants with chronic, active neovascular ARMD requiring frequent anti-VEGF re-treatment were enrolled. Participants underwent pars plana vitrectomy with a single 24-gray dose of EMBT, delivered with an intra-ocular, hand-held, cannula containing a strontium 90/yttrium 90 source positioned over the active lesion. Participants were re-treated with ranibizumab administered monthly as needed, using pre-defined re-treatment criteria. Patients underwent FFA at baseline, month 1, and month 12. Patients underwent OCT at baseline and then monthly for 12 months. The FFA and OCT images were evaluated by independent, central reading facilities. Main outcome measures included change in OCT center-point thickness and angiographic lesion size 12 months after EMBT. Mean center-point thickness increased by 50 μm, from 186 to 236 μm (p = 0.292), but 70 % of participants had an increase of less than the mean, with a median increase of only 1.8 μm. The FFA total lesion size increased slightly by 0.79 mm(2), from 14.69 to 15.48 mm(2) (p = 0.710). Total CNV area increased by 1.17 mm(2), from 12.94 to 14.12 mm(2) (p =
The classic CNV area decreased substantially by 3.70 mm(2), from 3.90 to 0.20 mm(2) (p < 0.01). Predominantly classic lesions showed the greatest response, with mean ETDRS VA improving by 1.5 letters (versus -4.0 for all participants combined); mean center-point thickness decreased by 43 μm (p = 0.875). The angiographic and OCT response did not correlate with lesion size at baseline. The authors concluded that in chronic, active, neovascular ARMD, EMBT is associated with non-significant changes in center-point thickness and FFA total lesion size over 12 months. Moreover, they stated that “Although EMBT may be most appropriate for the treatment of classic ARMD, larger studies are needed”.

**Ciliary Neurotrophic Factor:**

Zhang and colleagues (2011) stated that there is no treatment available for vision loss associated with advanced dry ARMD or geographic atrophy (GA). In a pilot, proof of concept phase II study, these investigators evaluated ciliary neurotrophic factor (CNTF) delivered via an intra-ocular encapsulated cell technology implant for the treatment of GA. They designed a multi-center, 1-year, double-masked, sham-controlled dose-ranging study. Patients with GA were randomly assigned to receive a high- or low-dose implant or sham surgery. The primary endpoint was the change in BCVA at 12 months. Ciliary neurotrophic factor treatment resulted in a dose-dependent increase in retinal thickness. This change was followed by VA stabilization (loss of less than 15 letters) in the high-dose group (96.3 %) compared with low-dose (83.3 %) and sham (75 %) group. A subgroup analysis of those with baseline BCVA at 20/63 or better revealed that 100 % of patients in the high-dose group lost less than 15 letters compared with 55.6 % in the combined low-dose/sham group (p = 0.033). There was a 0.8 mean letter gain in the high-dose group compared with a 9.7 mean letter loss in the combined low-dose/sham group (p = 0.0315). Both the implant and the implant procedure were well-tolerated. The authors concluded that these findings suggested that CNTF delivered by the encapsulated cell technology implant appears to slow the progression of vision
loss in GA, especially in eyes with 20/63 or better vision at baseline. The findings of this phase II clinical study need to be validated by well-designed studies.

**ForeseeHome Technology:**

Chew, et al. (2013) reported that home monitoring with the ForeseeHome device (Notal Vision Ltd, Tel Aviv, Israel), using macular visual field testing with hyperacuity techniques and telemonitoring, resulted in earlier detection of age-related macular degeneration-associated choroidal neovascularization (CNV), reflected in better visual acuity, when compared with standard care. For this nonmasked randomized controlled trial, 1970 participants 53 to 90 years of age at high risk of CNV development were screened. Of these, 1520 participants with a mean age of 72.5 years were enrolled in the Home Monitoring of the Eye study at 44 Age-Related Eye Disease Study 2 (AREDS2) clinical centers, a clinical trial of nutritional supplements for the prevention of AMD. Participants had either bilateral large drusen (potentially 2 study eyes) or large drusen in 1 eye (study eye) and advanced AMD in the fellow (nonstudy eye) and best-corrected visual acuity (BCVA) of 20/60 or better in the study eye(s). In the standard care and device arms arm, investigator-specific instructions were provided for self-monitoring vision at home followed by report of new symptoms to the clinic. Aids such as Amsler grids could be recommended. In the device arm, in addition to receiving standard care instructions, the device was provided with recommendations for daily testing. The device monitoring center received test results and reported changes to the clinical centers, which contacted participants for examination. The main outcome measure was the difference in best-corrected visual acuity scores between baseline and detection of CNV. The event was determined by investigators based on clinical examination, color fundus photography, fluorescein angiography, and optical coherence tomography findings. Masked graders at a central reading center evaluated the images using standardized protocols. Seven hundred sixty-three participants were randomized to device monitoring and 757
participants were randomized to standard care and were followed up for a mean of 1.4 years between July 2010 and December 2013. At the prespecified interim analysis, 82 participants progressed to CNV, 51 in the device arm and 31 in the standard care arm. The primary analysis achieved statistical significance, with the participants in the device arm demonstrating a smaller decline in visual acuity with fewer letters lost from baseline to CNV detection (median, -4 letters; interquartile range [IQR], -11.0 to -1.0 letters) compared with standard care (median, -9 letters; IQR, -14.0 to -0.0 letters; p = 0.021), resulting in better visual acuity at CNV detection in the device arm.

An editorialist (Han, 2014) commented that, “[d]espite its efficacy in the HOME trial, the effectiveness of the ForeSeeHome device in the ‘real world’ remains uncertain. Notably, the study experienced a 23% screen failure rate. A similar rate of failure in a clinical setting could be a factor in its effectiveness.” The editorialist also noted that the HOME study was not intended to compare the ForeSeeHome device with use of the Amsler grid as a stand-alone approach, and that it is possible that mandatory, supervised use of the Amsler grid may have increased the success rate in the control arm.

Guidelines on the management of neovascular age-related macular degeneration (AMD) from the European Society of Retina Specialists (EURETINA) (Schmidt-Erfurth, et al., 2014) state that “patients should be instructed to self-monitor their vision between routine office visits. By contrast with current home monitoring strategies, those with intermediate AMD (large drusen in one or both eyes) could benefit from home monitoring with PHP [preferential hyperacuity perimetry], whenever the device is available.”

An American Academy of Ophthalmology preferred practice pattern on age-related macular degeneration (AAO, 2014) states: “Electronic monitoring devices are now available to aid in the detection of neovascularization at an early stage. Such devices use hyperacuity perimetry (or Vernier acuity) to create
a quantified central visual map of metamorphosia. Further studies of a variety of such devices are ongoing.”

Chew and associates (2014) evaluated the effects of a home-monitoring device with tele-monitoring compared with standard care in detection of progression to CNV associated with ARMD, the leading cause of blindness in the US. The authors noted that the study design appeared to be feasible despite challenges to conducting such a multi-site randomized study for a tele-monitoring device, resulting in the enrollment of greater number of participants than the anticipated sample size in a large number of clinics, with potential for answering an important clinically relevant research question. Limitation of the study includes decreased generalizability of the results for all persons with intermediate ARMD as an anticipated number of participants may not successfully pass the screening for the testing. However, the results may have impact on the management of persons with ARMD, a disease of public health importance.

Chaikitmongkol et al (2015) described clinical and imaging findings in 2 eyes with new onset subtle neovascular ARMD that was detected by the regular use of a home monitoring device based on preferential hyper-acuity visual field testing. The authors concluded that this report demonstrated the potential utility of a home monitoring program in a clinical setting. They stated that although both patients described in this report were participants in a home monitoring program study, and thus, might be better trained and experienced in using the device than a typical patient in a clinic, the cases nevertheless demonstrated the potential value of the device in detecting the earliest manifestation of the CNV.

Chew and colleagues (2016) determined the effectiveness of different monitoring modalities to detect incident neovascularization associated with ARMD. They concluded that tele-monitoring may alter the management of patients with ARMD and improve vision outcomes. They stated that a key limitation of the home monitoring device is the exclusion of
persons with ARMD who were not able to use the technology or to establish the crucial reproducible baseline values for future comparisons. Furthermore, the utility of the device is not known for those individuals who are monitored more frequently such as patients receiving monthly intra-vitreal injections of anti-VEGF in their fellow eye. To fully explore the utility for this subset of individuals, further studies are needed.

Low-Vision Rehabilitation:

Hamade and colleagues (2016) examined the effect of various low-vision rehabilitation strategies on reading speed and depression in patients 55 and older with ARMD. Computer databases including Medline (OVID), Embase (OVID), BIOSIS Previews (Thomson-Reuters), CINAHL (EBSCO), Health Economic Evaluations Database (HEED), ISI Web of Science (Thomson-Reuters) and the Cochrane Library (Wiley) were searched from the year 2000 to January 2015. Included papers were research studies with a sample size of 20 eyes or greater focused on ARMD in adults aged 55 or older with low vision (20/60 or lower). Two independent reviewers screened and extracted relevant data from the included articles. Standardized mean difference (SMD) was chosen as an effect size to perform meta-analysis using STATA. Fixed- and random-effect models were developed based on heterogeneity. Main outcomes were reading speed and depression scores. A total of 9 studies (885 subjects) were included. Overall, a significant improvement in reading speed was found with a SMD of 1.01 [95 % CI: 0.05 to 1.97]. Low-vision rehabilitation strategies including micro-perimetric biofeedback, microscopes teaching program significantly improved reading speed. Eccentric viewing training showed the maximum improvement in reading speed. In addition, a non-significant improvement in depression scores was found with a SMD of -0.44 [95 % CI: -0.96 to 0.09]. The authors concluded that a considerable amount of research is needed in the area of low-vision rehabilitation strategies for patients with ARMD. They stated that based on current research, low-vision rehabilitation aided in improving reading speed; however, they did not have a
significant effect on depression scores in those 55 and older with ARMD.

**ABCA1 rs1883025 Polymorphism Testing:**

Wang et al (2016) evaluated the association of the ABCA1 rs1883025 polymorphism and susceptibility to ARMD. They conducted a systematic search of the PubMed, Embase, and ISI web of science databases to identify eligible published studies without language restrictions up to September 2015. Pooled ORs with 95 % CIs were estimated under different genetic models using meta-analytic methods. Stratified analysis and sensitivity analysis were performed to explore potential sources of heterogeneity. A total of 12 articles with 25,445 cases and 36,460 controls were eligible in this meta-analysis. The ABCA1 rs1883025 variant showed significant association with the lower risk of overall ARMD under the allelic model (OR = 0.81, 95 % CI: 0.74 to 0.89). Stratified analysis based on ethnicity demonstrated a strong association between rs1883025 polymorphism and ARMD in the Caucasian population, but not in Asian population. For late ARMD, the ABCA1 rs1883025 variant was observed to have a significant association with the lower risk of this disease (OR = 0.81, 95 % CI: 0.72 to 0.91). In early-stage ARMD, significant associations of the rs1883025 polymorphism with lower risk of early ARMD were observed in different genetic models (OR ranging from 0.45 to 0.65, all p < 0.05). The authors concluded that the present meta-analysis indicated that the T allelic in rs1883025 variant was significantly associated with the risk of developing ARMD, especially at the early stage. They stated that the associations of the ABCA1 locus with ARMD risk in various populations need further exploration.

**CX3CR1 Polymorphism Testing:**

Li and colleagues (2015) noted that studies investigating the associations between CX3CR1 genetic polymorphisms and ARMD have reported controversial results. In a meta-analysis, these investigators examined the effects of CX3CR1 T280M and
V249I polymorphisms on ARMD risk. Results from 6 studies were pooled in the meta-analysis. Relevant studies were selected through an extensive search of PubMed, Embase, and the Web of Science databases. Pooled ORs and 95% CIs were calculated using random-effects model. A total of 6 studies with were included in this systematic review and meta-analysis. There was no significant association between CX3CR1 T280M polymorphism and risk of AMD under all genetic models (TT versus CC/CT: OR = 1.57, 95% CI: 0.87 to 2.84; CC versus TT/CT: OR = 0.75, 95% CI: 0.54 to 1.06; TT versus CC: OR = 0.58, 95% CI: 0.30 to 1.14; CT versus CC: OR = 1.25, 95% CI: 0.91 to 1.70). The CX3CR1 V249I polymorphism also did not significantly affect the ARMD risk (AA versus GG/AG: OR = 1.23, 95% CI: 0.98 to 1.55; AG/AA versus GG: OR = 0.56, 95% CI: 0.29 to 1.07; AA versus GG: OR = 1.43, 95% CI: 0.97 to 2.09; AG versus GG: OR = 1.07, 95% CI: 0.85 to 1.36). The authors concluded that the findings of this meta-analysis suggested that CX3CR1 T280M and V249I polymorphisms may not be associated with an increased risk of ARMD based on current published data. They stated that given the limited sample size, the finding on CX3CR1 polymorphisms needs further investigation.

TLR3 rs3775291 Polymorphism Testing:

Ma and colleagues (2016) noted that association of a polymorphism rs3775291 in the toll-like receptor 3 (TLR3) gene in patients with ARMD had been investigated intensively, with variable results across studies. These researchers conducted a meta-analysis to verify the effect of rs3775291 on ARMD. They searched for genetic association studies published in PubMed, Embase and Web of Science from start dates to March 10, 2015. A total of 235 reports were retrieved and 9 studies were included for meta-analysis, involving 7,400 cases and 13,579 controls. Summary ORs with 95% CIs for alleles and genotypes were estimated. TLR3 rs3775291 was associated with both geographic atrophy (GA) and neovascular ARMD (nARMD), with marginally significant pooled-p values. Stratification analysis by ethnicity indicated that rs3775291 was associated with all
forms of ARMD, GA and nARMD only in Caucasians (OR = 0.87, 0.78 and 0.77, respectively, for the TT genotype) but not in East Asians. However, the associations could not withstand Bonferroni correction. The authors concluded that the findings of this meta-analysis revealed suggestive evidence for TLR3 rs3775291 as an associated marker for ARMD in Caucasians but not in Asians. They stated that this SNP may have only a small effect on ARMD susceptibility; further studies in larger samples are needed to confirm its role.

Y402H Polymorphism Testing:

Hong and associates (2016) examined if the complement factor H (CFH) polymorphism rs1061170/Y402H is associated with responsiveness to anti-VEGF agents in ARMD. These investigators reviewed the English literature to examine the association between the polymorphism rs1061170/Y402H of the CFH gene and responsiveness to treatment with anti-VEGF drugs in ARMD patients. A meta-analysis of eligible studies was also performed. Pooled ORs and 95 % CIs were estimated using Stata V.12.0. Statistical heterogeneity was measured using Q-statistic testing. A total of 14 relevant studies including a total of 2,963 ARMD patients were eligible. In ARMD patients without a treatment history, individuals carrying the rs1061170/Y402H TT genotype were more likely to achieve a better outcome (OR = 1.932, 95 % CI: 1.125 to 3.317, p = 0.017) than those carrying the CC genotype. The authors concluded that polymorphism rs1061170/Y402H might be a genetic predictor of treatment response to anti-VEGF therapy in ARMD patients. They stated that further prospective research including a larger number of patients is needed to validate this finding.

CPT Codes / HCPCS Codes / ICD-10 Codes

<table>
<thead>
<tr>
<th>Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by &quot;*&quot;:</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT codes covered if selection criteria are met:</td>
</tr>
<tr>
<td>CPT Code</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>67028</td>
</tr>
<tr>
<td>67221</td>
</tr>
<tr>
<td>+ 67225</td>
</tr>
</tbody>
</table>

**CPT codes not covered for indications listed in the CPB:**

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0016T</td>
<td>Destruction of localized lesion of choroid (e.g., choroidal neovascularization), transpupillary thermotherapy</td>
</tr>
<tr>
<td>0017T</td>
<td>Destruction of macular drusen, photocoagulation</td>
</tr>
<tr>
<td>0190T</td>
<td>Placement of intraocular radiation source applicator</td>
</tr>
<tr>
<td>0378T</td>
<td>Visual field assessment, with concurrent real time data analysis and accessible data storage with patient initiated data transmitted to a remote surveillance center for up to 30 days; review and interpretation with report by a physician or other qualified health care professional [ForeseeHome device]</td>
</tr>
<tr>
<td>0379T</td>
<td>Visual field assessment, with concurrent real time data analysis and accessible data storage with patient initiated data transmitted to a remote surveillance center for up to 30 days; technical support and patient instructions, surveillance, analysis and transmission of daily and emergent data reports as prescribed by a physician or other qualified health care professional [ForeseeHome device]</td>
</tr>
<tr>
<td>38232</td>
<td>Bone marrow harvesting for transplantation; autologous</td>
</tr>
<tr>
<td>38240</td>
<td>Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor</td>
</tr>
<tr>
<td>38241</td>
<td>autologous transplantation</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>38242</td>
<td>Allogeneic lymphocyte infusions</td>
</tr>
<tr>
<td>61793</td>
<td>Stereotactic radiosurgery (particle beam, gamma ray or linear accelerator), one or more sessions</td>
</tr>
<tr>
<td>77432</td>
<td>Stereotactic radiation treatment management of cranial lesion(s) (complete course of treatment consisting of one session)</td>
</tr>
<tr>
<td>77520</td>
<td>Proton treatment delivery; simple, without compensation</td>
</tr>
<tr>
<td>77522</td>
<td>simple, with compensation</td>
</tr>
<tr>
<td>77523</td>
<td>intermediate</td>
</tr>
<tr>
<td>77525</td>
<td>complex</td>
</tr>
</tbody>
</table>

**HCPCS codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C9257</td>
<td>Injections, Bevacizumab, 0.25 mg</td>
</tr>
<tr>
<td>J2503</td>
<td>Injection, pegaptanib sodium, 0.3 mg</td>
</tr>
<tr>
<td>J2778</td>
<td>Injection, ranibizumab, 0.1 mg</td>
</tr>
<tr>
<td>J3396</td>
<td>Injection, verteporfin, 0.1 mg</td>
</tr>
<tr>
<td>J9035</td>
<td>Injection, bevacizumab, 10 mg</td>
</tr>
<tr>
<td>J0178</td>
<td>Injection, aflibercept, 1 mg</td>
</tr>
</tbody>
</table>

**HCPCS codes not covered for indications listed in the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J3300</td>
<td>Injection, triamcinolone acetonide, preservative free, 1 mg</td>
</tr>
<tr>
<td>J3301</td>
<td>Injection, triamcinolone acetonide, per 10 mg</td>
</tr>
<tr>
<td>J9212</td>
<td>Injection, interferon alfacon-1, recombinant, 1 mcg</td>
</tr>
<tr>
<td>J9213</td>
<td>Interferon alfa-2A, recombinant, 3 million units</td>
</tr>
<tr>
<td>J9214</td>
<td>Interferon alfa-2B, recombinant, 1 million units</td>
</tr>
<tr>
<td>J9215</td>
<td>Interferon alfa-N3, (human leukocyte derived), 250,000 IU</td>
</tr>
<tr>
<td>S2140</td>
<td>Cord blood-derivedstem cell transplantions, allogenic</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>-------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>2150</td>
<td>Bone marrow or blood-derived stem cells (peripheral or umbilical), allogenic or autologous, harvesting, transplantation, and related complications; including; ( \text{pheresis and cell preparation/storage; \text{marrow ablative therapy; \text{drugs, supplies, hospitalization with outpatient follow-up; \text{medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre- and post-transplant care in the global definition.}}))</td>
</tr>
<tr>
<td>S9559</td>
<td>Home injectable therapy; interferon, including administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drug and nursing visits coded separately), per diem</td>
</tr>
</tbody>
</table>

**ICD-10 codes covered if selection criteria are met:**

- H35.32 Exudative age-related macular degeneration

**ICD-10 codes not covered for indications listed in the CPB:**

- H35.051 - H35.059 Retinal neovascularization, unspecified [associated with age-related macular degeneration]
- H35.30 Unspecified macular degeneration [age-related]
- H35.31 Nonexudative age-related macular degeneration

**Implantable Miniature Telescope (IMT):**

**CPT codes covered if selection criteria are met:**

- 0308T Insertion of ocular telescope prosthesis including removal of crystalline lens or intraocular lens prosthesis

**ICD-10 codes covered if selection criteria are met [covered for ages 65 and above only]:**

- H35.31 Nonexudative age-related macular degeneration
- H35.32 Exudative senile macular degeneration
- H53.413 Scotoma involving central area, bilateral [associated with end-stage ARMD]
The above policy is based on the following references:


10. Chuo JY, Wiens M, Etminan M, Maberley DA. Use of lipid-


20. Sullivan T, Hiller J. Implantable miniature telescope for


37. CATT Research Group, Martin DF, Maguire MG, Ying GS, et al. Ranibizumab and bevacizumab for neovascular


46. Age-Related Eye Disease Study 2 Research Group. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: The Age-Related Eye Disease


50. Arroyo JG. Age-related macular degeneration: Treatment and prevention. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed June 2014.


54. VisionCare Ophthalmic Technologies, Inc. FDA approves VisionCare's Telescope Implant for macular degeneration in patients 65 years and older. Press Release. Saratoga,


60. Chaikitmongkol V, Bressler NM, Bressler SB. Early detection of choroidal neovascularization facilitated with a home monitoring program in age-related macular degeneration. Retinal cases & Brief Reports. 2015;9:33-37.


with age-related macular degeneration and Stargardt's macular dystrophy: Follow-up of two open-label phase 1/2 studies. Lancet. 2015;385(9967):509-516.


Amendment to
Aetna Clinical Policy Bulletin Number: 0765
Age-Related Macular Degeneration

There are no amendments for Medicaid.

www.aetnabetterhealth.com/pennsylvania
Updated 04/2017