A separate copy of this form must accompany each policy submitted for review. Policies submitted without this form will not be considered for review.

<table>
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<tr>
<th>Plan: Aetna Better Health</th>
<th>Submission Date: 11/01/2018</th>
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<tr>
<td>Policy Number: 0609</td>
<td>Effective Date:</td>
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<td>Policy Name: Laser Photocoagulation of Drusen</td>
<td>Revision Date:</td>
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**Type of Submission – Check all that apply:**
- [x] New Policy*
- [ ] Revised Policy
- [ ] Annual Review – No Revisions

*All revisions to the policy must be highlighted using track changes throughout the document. Please provide any clarifying information for the policy below:

**CPB 0609 Laser Photocoagulation of Drusen**

Policy is new to Aetna Better Health of Pennsylvania.

<table>
<thead>
<tr>
<th>Name of Authorized Individual (Please type or print):</th>
<th>Signature of Authorized Individual:</th>
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<tbody>
<tr>
<td>Dr. Bernard Lewin, M.D.</td>
<td>![Signature]</td>
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</table>
Laser Photocoagulation of Drusen

Policy

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

Aetna considers laser photocoagulation of macular drusen experimental and investigational for the prevention and treatment of age-related macular degeneration because it has not been shown to be effective and may be associated with loss of visual acuity.

See

CPB 0701 - Vascular Endothelial Growth Factor Inhibitors
also for Ocular Indications (../700_799/0701.html).

Background

Drusen are deposits located deep in the sensory retina that are seen characteristically in eyes with age-related macular degeneration (ARMD). As multiple large drusen are a risk factor for the development of visual loss from ARMD, laser strategies to cause drusen to resorb have been devised. Studies that have been performed thus far have been small and short-term. Two large, randomized controlled trials
(RCTs) using laser photocoagulation prophylactically for the treatment of ARMD are underway to determine the efficacy of such treatment.

In an update of a pilot RCT on the use of laser treatment in eyes with large drusen, it was found that throughout 4 years of follow-up, there were no statistically significant differences in change in visual acuity (VA), contrast threshold, critical print size, or incidence of geographic atrophy. With additional follow-up, the large increase in the incidence of choroidal neovascularization observed within 18 months of treatment was maintained; however, by 30 months, the incidence in the 2 treatment groups was the same. Most drusen resolution in treated eyes occurred within 24 months of the initial treatment. Treated eyes that received higher-intensity laser burns had an increased risk of choroidal neovascularization. Among eyes developing choroidal neovascularization in each treatment group, most lesions (2/3 or more) were composed of occult neovascularization only. It was concluded that laser treatment as applied in the Choroidal Neovascularization Prevention Trial (CNVPT) caused an excess risk of choroidal neovascularization in the first year or so after treatment. The increased early incidence of choroidal neovascularization was not associated with either a harmful or beneficial effect in this pilot study (CNVPT, 2003).

Furthermore, in an interim report of the Drusen Laser Study (DLS) on the use of laser photocoagulation in treating high-risk age-related maculopathy, Owens et al (2003) noted that there were 156 patients included in the interim analysis, and timed information was available on 153. Choroidal revascularization (CNV) occurred in 21 of 81 (26 %) patients in the treatment group and in 13 of 75 (17 %) patients in the no treatment group (p = 0.19). Visual acuity loss at 2 years occurred in 9 of 54 (17 %) patients in the treatment group compared to the 2 of 48 (4 %) patients in the no treatment group (p = 0.056). The authors stated that they were only the second group to identify
possible laser-induced CNV despite other similar studies in progress. Equipoise of the DLS investigators was lost, and recruitment was halted.

Ruiz-Moreno et al (2003) stated that macular atrophy can occur after green argon laser photocoagulation of soft drusen. The development of macular atrophy was associated with a significant decrease in best-corrected VA (BCVA).

In a multi-center, prospective, RCT, Friberg et al (2006) determined the effects of sub-threshold 810-nm-diode laser treatment on the rate of development of CNV (primary end point) and the effect on VA in participants with multiple large drusen in 1 eye and a pre-existing neovascular ARMD lesion in the other. A total of 244 patients 50 years of age or older and with a neovascular or advanced ARMD lesion in 1 eye and, in the fellow "study" eye, (i) at least 5 drusen of 63 mum or greater in diameter, (ii) Early Treatment Diabetic Retinopathy Study BCVA of 20/63 or better, and (iii) no evidence of neovascularization at baseline were enrolled in the study. Patients were randomized to treatment or observation of their study eye at each of 22 centers. At each visit, the protocol specified that BCVA, a complete retinal examination, and fluorescein angiography be documented. Treated eyes had a grid of 48 extra-foveal, sub-threshold diode (810 nm) laser spots, 125 mum in diameter, placed in an annulus outside of the foveola. Patients were seen at baseline and at 3, 6, 12, 18, 24, 30, and 36 months after randomization. No re-treatments were allowed. Main outcome measures were development of choroidal neovascularization (as confirmed by fluorescein angiography) and change in BCVA. Throughout follow-up, the rate of choroidal neovascularization events in treated eyes consistently exceeded that in observed eyes. At 1 year, the difference was 15.8 % versus 1.4 % (p = 0.05). Most of the inter-group differences in choroidal neovascularization events occurred during the first 2 years of follow-up. Treated eyes showed a
higher rate of VA loss (3 lines or more) at 3- and 6-month follow-ups relative to observed eyes (8.3 % versus 1 %; p = 0.02; and 11.4 % versus 4 %; p = 0.07, respectively). After 6 months, no significant differences were observed in VA loss between groups. These investigators concluded that prophylactic sub-threshold 810-nm-diode laser treatment to an eye with multiple large drusen in a patient whose fellow eye has already suffered a neovascular event places the treated eye at higher risk of developing choroidal neovascularization. The authors advised against using prophylactic sub-threshold diode laser treatment in these eyes. These findings by Friberg et al (2006) are in agreement with those by Owen et al (2006) who noted that results of their prospective RCT (n = 139) do not support prophylactic laser of the fellow eye of patients with neovascular age-related maculopathy.

Bylsma and Guymer (2005) stated that established treatments for ARMD include argon laser photocoagulation of extra-foveal CNV and photodynamic therapy of selected sub-foveal CNV. Newer approaches are targeting the angiogenic pathway in CNV development. Currently, other treatment modalities, such as radiotherapy and transpupillary thermotherapy do not have a clear role to play. Surgical options are experimental and only available in some centers for selected patients. Prevention of ARMD remains elusive. Dietary supplements may have a role, while statins and prophylactic laser photocoagulation of drusen remain experimental.

Figueroa et al (2006) stated that presently it is unclear if removal of drusen after photocoagulation is beneficial to the patients. In a non-randomized non-masked clinical study, Nili-Ahmadabadi et al (2007) examined the effect of prophylactic sub-threshold laser macular grid photocoagulation on drusen area and assessed the visual outcome and incidence of choroidal neovascularization in patients with soft drusen maculopathy. A total of 18 patients (36 eyes) with bilateral soft drusen maculopathy were studied. For each patient, 1 eye was treated with 48 sub-threshold (invisible end-point)
applications of 532-nm KTP-laser in a macular grid pattern and the fellow eye was observed. Soft drusen areas were calculated and compared between the 2 groups at baseline and follow-up visits at 3, 6, 12, and 30 months of therapy. Best corrected visual acuity was also compared in observed and laser-treated eyes. Reduction of drusen area, change in VA, and rate of CNV were assessed in both groups. At baseline, there was no significant difference in the mean drusen surface area between the 2 groups (p = 0.90). The mean surface area of soft drusen in treated eyes was 6.51 mm$^2$ after 30 months and 7.58 mm$^2$ (p = 0.50) in the control eyes. There was a trend towards reduction in the mean soft drusen area after 30 months from baseline in laser-treated eyes (6.51 versus 6.97 mm$^2$). In treated eyes, there was no statistically significant difference between the mean BCVA at the baseline (0.28 logMAR) and after 30 months (0.32 logMAR) (p = 0.40). The authors concluded that sub-threshold macular grid photocoagulation with 532-nm KTP-laser did not seem to reduce drusen surface area significantly and did not improve BCVA after 30 months.

In a Cochrane review, Parodi and colleagues (2009) examined the effectiveness and adverse effects of laser photocoagulation of drusen in ARMD. Randomized controlled trials of laser treatment of drusen in ARMD in which laser treatment had been compared with no intervention or sham treatment were selected. Two types of trials were included. Some trials studied 1 eye of each patient (unilateral studies); other studies recruited patients with bilateral drusen and randomized 1 eye to photocoagulation or control and the fellow eye to the other group. Two review authors independently selected studies and extracted data. Data were pooled from unilateral and bilateral studies using a random-effects model. For the bilateral studies, these researchers estimated the within-patient correlation coefficient from 1 study and assumed it was valid for the others. They found 9 studies that randomized 2,216 people: 4 unilateral trials, 3 bilateral trials and 2 trials that included both a unilateral and a
bilateral study arm. Overall, the studies were of moderate quality. Only half of the trials reported adequate allocation sequence generation, allocation concealment and masking of VA outcome assessors. Although 2 (of the 9) studies reported significant drusen disappearance at 2 years, photocoagulation did not appear to affect the development of CNV at 2 years follow-up (9 studies, 1,767 people followed-up, odds ratio (OR) 1.04, 95% confidence interval [CI]: 0.71 to 1.51) or the loss of 3 or more lines of visual acuity (6 studies, 1,628 people followed-up, OR 1.17, 95% CI: 0.75 to 1.82). The authors concluded 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 results in a reduction in the risk of developing CNV, geographic atrophy or VA loss.

A review of treatment for age-related macular degeneration in *BMJ Clinical Evidence* concluded that the effectiveness of laser to drusen is unknown (Arnold & Heriot, 2006). The authors stated that we don't know whether laser treatment of drusen prevents progression of disease, and it may increase short-term rates of choroidal neovascularisation.

Friberg and colleagues (2009) determined the prophylactic and therapeutic value of a single sub-threshold 810-nanometer laser treatment in patients with high-risk drusen as a manifestation of dry ARMD in both eyes. This study enrolled 1,278 eyes of 639 subjects who were 50 years or older with at least 5 drusen 63-microm or more in diameter in each eye. Treatment consisted of the placement of an annular grid of 48 extra-foveal, sub-threshold 810-nm diode laser applications centered at but sparing the foveola in 1 eye of each subject, with the fellow eye serving as a control. Development of choroidal neovascularization and change in BCVA were compared between treated and untreated eyes. Sub-threshold laser treatment did not decrease the incidence of choroidal neovascularization in treated versus untreated eyes. A modest VA benefit in treated eyes was found at 24 months.
(1.5 letter difference; \( p = 0.04 \)) and in the treated eyes of subjects with a baseline VA between 20/32 and 20/63 (4.0 letter difference; \( p = 0.0034 \)). However, this treatment effect was not sustained at 3 years. The authors concluded that a single sub-threshold 810-nanometer laser treatment to eyes of patients with bilateral high risk drusen is not an effective prophylactic strategy against choroidal neovascularization.

Mojana et al (2011) examined the long-term effect of subthreshold diode laser treatment for drusen in patients with non-exudative ARMD with spectral domain optical coherence tomography (OCT) combined with simultaneous scanning laser ophthalmoscope. A total of 8 eyes of 4 consecutive ARMD patients with bilateral drusen previously treated with subthreshold diode laser were imaged with spectral domain OCT/scanning laser ophthalmoscope. Abnormalities in the outer retinal layers’ reflectivity as seen with spectral domain OCT/scanning laser ophthalmoscope were retrospectively analyzed and compared with color fundus pictures, and autofluorescence images were acquired immediately before and after the laser treatment. A focal discrete disruption in the reflectivity of the outer retinal layers was noted in 29% of the laser lesions. The junction in between the inner and outer segment of the photoreceptor was more frequently affected, with associated focal damage of the outer nuclear layer. Defects of the retinal pigment epithelium were occasionally detected. These changes did not correspond to threshold burns on color fundus photography but corresponded to focal areas of increased autofluorescence in the majority of the cases. The authors concluded that subthreshold diode laser treatment causes long-term disruption of the retinal photoreceptor layer as analyzed by spectral domain OCT/scanning laser ophthalmoscope. The concept that subthreshold laser treatment can achieve a selected retinal pigment epithelium effect without damage to rods and cones may be flawed.
Huang et al (2011) prospectively evaluated the safety and effectiveness of prophylactic laser treatment in Chinese patients with bilateral soft drusen; these researchers examined the structure and function of the macula 8 years after treatment. A total of 10 patients with more than 10 soft drusen (greater than 125 mm) and BCVA greater than or equal to 20/25 in each eye participated in the study. One eye, with relatively more drusen, was exposed to an argon laser (514 nm) to achieve a barely visible retinal lesion. The contralateral eye was used as a control. Fluorescein angiography, Amsler tests, Fourier-domain OCT and visual evoked potential tests were carried out 8 years later. No choroidal neovascularization was seen in the laser-treated eyes or control eyes. There were no significant differences in visual acuity or P100 latency and amplitude between the laser treated eyes and contralateral eyes ($t = 1.685, 1.184; p > 0.05$). The thickness of the retinal pigment epithelium of the treated eyes was less than that of the contralateral eyes ($t = -4.540; p < 0.05$). The full retinal thickness in treated eyes was slightly, but insignificantly, reduced relative to contralateral eyes ($t = -1.746; p > 0.05$). The authors concluded that the treatment was associated with a reduction in retinal pigment epithelium thickness elevation compared with the contralateral eyes; macular function was not impaired.

In a prospective, interventional case-series study, Lenassi and colleagues (2013) examined if laser treatment to the retinal pigment epithelium anterior to drusen in eyes of patients with EFEMP1-related maculopathy affects visual acuity, deposit volume, and retinal sensitivity. In 11 patients with autosomal dominant drusen and confirmed disease-causing EFEMP1 mutation, the worse-seeing eye was treated with Argon green laser (10 to 15 laser spots; 200-μm spot size, 0.1-second duration, 80 to 120 mW). Patients were examined before treatment and 1, 3, 6, and 12 months after the procedure. Clinical assessment included VA, fundus-controlled perimetry, spectral-domain OCT, and auto-fluorescence imaging. Custom-made software allowed for co-registration of fundus-
controlled perimetry and spectral-domain OCT data sets. The main outcome measures were change in VA, retinal sensitivity, and drusen volume. The untreated eyes lost an average of 0.8 letters, whereas the treated eyes gained an average of 4.9 letters. For fundus-controlled perimetry, locus-by-locus differences in sensitivity were calculated between pre-treatment and post-treatment assessments; subsequently, the overall difference in the treated and untreated eye was compared. Five patients showed significant improvement in retinal sensitivity, 5 patients showed no change, and 1 patient showed significant deterioration. An increase in mean drusen thickness was observed in the untreated eyes, but not in the treated eyes (p = 0.0322). The thickness of the drusen correlated with retinal sensitivity (p = -0.49; p < 0.0001). Safety was demonstrated and no adverse events were observed. The authors concluded that low-energy laser treatment is safe and may be effective in the treatment of autosomal dominant drusen. Moreover, they stated that further evaluation with long-term assessment is needed to confirm the benefits.

In a Cochrane review, Virgili et al (2015) examined the effectiveness and adverse effects of laser photocoagulation of drusen in ARMD. These investigators searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (2015, Issue 7), Ovid Medline, Ovid MedlineInProcess and Other Non-Indexed Citations, Ovid Medline Daily, Ovid OldMedline (January 1946 to August 2015), Embase (January 1980 to August 2015), Latin American and Caribbean Health Sciences Literature Database (LILACS) (January 1982 to August 2015), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) . These researchers did not use any date or language restrictions in the electronic searches for trials. They last searched the electronic databases on August 3, 2015. Randomized controlled trials of laser treatment of drusen in
Laser Photocoagulation of Drusen

ARMD in which laser treatment had been compared with no intervention or sham treatment. Two types of trials were included. Some trials studied 1 eye of each participant (unilateral studies); other studies recruited participants with bilateral drusen and randomized 1 eye to photocoagulation or control and the fellow eye to the other group. Two review authors independently selected studies and extracted data. The authors pooled data from unilateral and bilateral studies using a random-effects model. For the bilateral studies, these researchers estimated the within-person correlation coefficient from 1 study and assumed it was valid for the others. The update of this review found 2 additional studies, totaling 11 studies that randomized 2,159 participants (3,580 eyes) and followed them up to 2 years, of which 6 studies (1,454 participants) included people with 1 eye randomized to treatment and 1 to control. Studies were conducted in Australia, Europe and North America. Overall, the risk of bias in the included studies was low, particularly for the larger studies and for the primary outcome development of CNV. Photocoagulation did not reduce the development of CNV at 2 years’ follow-up (OR 1.07, 95 % CI: 0.79 to 1.46, 11 studies, 2,159 participants (3,580 eyes), high quality evidence). This estimate meant that, given an overall occurrence of CNV of 8.3 % in the control group, these investigators estimated an absolute risk reduction by no more than 1.4 % in the laser group, according to the lower CI limit. Only 2 studies investigated the effect on the development of geographic atrophy and could not show a difference, but estimates were imprecise (OR 1.30, 95 % CI: 0.38 to 4.51, 2 studies, 148 participants (148 eyes), low quality evidence). Among secondary outcomes, photocoagulation led to drusen reduction (OR 9.16, 95 % CI: 6.28 to 13.4, 3 studies, 570 participants (944 eyes), high quality evidence) but was not shown to limit loss of 3 or more lines of VA (OR 0.99, 95 % CI: 1.81 to 1.22, 9 studies, 2,002 participants (2,386 eyes), moderate quality evidence). In a subgroup analysis, no difference could be shown for conventional visible (8 studies) versus sub-threshold invisible (4 studies) photocoagulation for
the primary outcomes (p value = 0.29). The effect in the sub-threshold group did not suggest a relevant benefit (OR 1.27, 95 % CI: 0.82 to 1.98). No study used micro-pulse sub-threshold photocoagulation. No other adverse effects (apart from development of CNV, geographic atrophy or visual loss) were reported. The authors concluded that the trials included in this review confirmed the clinical observation that laser photocoagulation of drusen led to their disappearance.

However, treatment did not result in a reduction in the risk of developing CNV, and was not shown to limit the occurrence of geographic atrophy or VA loss. They stated that ongoing studies are being conducted to examine if the use of extremely short laser pulses (i.e., nanosecond laser treatment) cannot only lead to drusen regression but also prevent neovascular ARMD.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

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<th>Code</th>
<th>Code Description</th>
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<td>ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):</td>
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<tr>
<td>H31.101 - H31.109</td>
<td>Choroidal degeneration, unspecified</td>
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<tr>
<td>H31.111 - H31.119</td>
<td>Age-related choroidal atrophy</td>
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<tr>
<td>H31.121 - H31.129</td>
<td>Diffuse secondary atrophy of choroid</td>
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<tr>
<td>H35.30 - H35.3293</td>
<td>Age-related macular degeneration</td>
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<tr>
<td>H35.361 - H35.369</td>
<td>Drusen (degenerative) of macula</td>
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The above policy is based on the following references:


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<th>Code</th>
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<tr>
<td>H47.321 - H47.329</td>
<td>Drusen of optic disc</td>
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AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0609 Laser Photocoagulation of Drusen

There are no amendments for Medicaid.

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