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Bronchial Thermoplasty for Asthma (Alair®)

Policy # 00266
Original Effective Date: 07/21/2010
Current Effective Date: 08/20/2014

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Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers bronchial thermoplasty for the treatment of asthma to be **investigational.***

Background/Overview

Bronchial thermoplasty is a newly available potential treatment option for patients with severe persistent asthma. It consists of radiofrequency energy delivered to the distal airways with the aim of decreasing smooth muscle mass believed to be associated with airway inflammation.

Asthma, a chronic lung disease, affects approximately 8% of adults and 9.5% of children in the U.S. and, in 2011, accounted for approximately 440,000 hospitalizations and 3,400 deaths. Asthma symptoms include episodic shortness of breath that is generally associated with other symptoms such as wheezing, coughing, and chest tightness. Objective clinical features include bronchial hyper-responsiveness and airway inflammation and reversible airflow obstruction (at least 12% improvement in forced expiratory volume in 1 second [FEV-1] post-bronchodilator, with a minimum of 200 mL improvement). However, there is substantial heterogeneity in the inflammatory features of patients who are diagnosed with asthma, and this biological diversity is responsible, at least in part, for the variable response to treatment in the asthma population.

Management of asthma consists of environmental control, patient education, management of co-morbidities, and regular follow-up for all affected individuals, as well as a stepped approach to medication treatment. Guidelines from the National Heart, Lung and Blood Institute (NHLBI) define 6 pharmacologic steps: step 1 for intermittent asthma and steps 2-6 for persistent asthma. The preferred daily medications: step 1: short-acting beta-agonists as needed; step 2: low-dose inhaled corticosteroids (ICS); step 3: ICS and long-acting beta-agonists (LABA) or medium-dose ICS; step 4: medium-dose ICS and LABA; step 5: high-dose ICS and LABA; and, step 6: high-dose ICS and LABA, and oral corticosteroids.

Despite this multidimensional approach, many patients continue to experience considerable morbidity. In addition to ongoing efforts to optimally implement standard approaches to asthma treatment, new therapies are being developed. One new therapy is bronchial thermoplasty, the controlled delivery of radiofrequency energy to heat tissues in the distal airways. Bronchial thermoplasty is based on the premise that patients with asthma have an increased amount of smooth muscle in the airway and that contraction of this smooth muscle is a major cause of airway constriction. The thermal energy delivered via bronchial thermoplasty aims to reduce the amount of smooth muscle and thereby decrease muscle-mediated bronchoconstriction with the ultimate goal of reducing asthma-related morbidity. Bronchial thermoplasty is intended as a

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supplemental treatment for patients with severe persistent asthma (i.e., steps 5 and 6 in the stepwise approach to care).

Bronchial thermoplasty procedures are performed on an outpatient basis, and each session lasts approximately 1 hour. During the procedure, a standard flexible bronchoscope is placed through the patient's mouth or nose into the most distal targeted airway and a catheter is inserted into the working channel of the bronchoscope. After placement, the electrode array in the top of the catheter is expanded, and radiofrequency energy is delivered from a proprietary controller and used to heat tissue to 65 degrees Centigrade over a 5-mm area. The positioning of the catheter and application of thermal energy is repeated several times in contiguous areas along the accessible length of the airway. At the end of the treatment session, the catheter and bronchoscope are removed. A course of treatment consists of 3 separate procedures in different regions of the lung scheduled about 3 weeks apart.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
In April 2010, the Alair®‡ Bronchial Thermoplasty System (Asthmatx, Inc., Sunnyvale, CA now part of Boston Scientific Corporation) was approved by the U.S. FDA through the premarket approval (PMA) process for use in adults with severe and persistent asthma whose symptoms are not adequately controlled with inhaled corticosteroids and LABAs. Use of the treatment is contraindicated in patients with implantable devices and those with sensitivities to lidocaine, atropine or benzodiazepines. It should also not be used while patients are experiencing an asthma exacerbation, active respiratory infection, bleeding disorder, or within 2 weeks of making changes in their corticosteroid regimen. The same area of the lung should not be treated more than once with bronchial thermoplasty.

Centers for Medicare and Medicaid Services (CMS)
No national coverage determination.

Rationale/Source

Three randomized, controlled trials (RCTs) evaluating the efficacy and safety of bronchial thermoplasty have been published. All of the RCTs were supported by Asthmatx, the manufacturer of the Alair system. The individual trials are described below:

Research in Severe Asthma (RISA) trial: This small study, published by Pavord and colleagues in 2007, was conducted at 8 centers in the U.K., Brazil, and Canada. Eligibility criteria included age 18 or older; asthma diagnosis; uncontrolled symptoms despite treatment with high-dose ICS (at least 750 *u*g fluticasone propionate per day or equivalent) and long-acting beta-agonists (LABAs) (at least 100 *u*g salmeterol per day or equivalent), with or without other medications including oral prednisone or leukotriene modifiers; FEV-1 at least 50% of predicted; demonstrated airway hyper-responsiveness by challenge with methacholine or reversible bronchoconstriction during the prior 12 months; abstinence from smoking for at least 1 year, and a past smoking history of less than 10 pack-years. After a 2-week run-in period, 34 participants were randomly assigned to a control group (n=17) that received continued medical management alone or medical management plus treatment with the Alair Bronchial Thermoplasty System (n=17). The bronchial thermoplasty group received 3 procedures at least 3 weeks apart (weeks 0-6). During

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weeks 6-22, all participants remained on a stable dose of steroids, and then during weeks 22-36, an attempt was made to reduce the dose of oral corticosteroids (or inhaled corticosteroids for patients not taking the oral medication). Between weeks 36 to 52, patients took the reduced dose of steroids. A total of 32 of the 34 participants (94%) completed the study.

The primary outcomes of the study were the rate of adverse events and serious adverse events (defined as any event that was fatal, required prolonged hospitalization, caused substantial immediate risk of death, resulted in permanent impairment, or required intervention to prevent permanent impairment). In the initial treatment period, 4 patients in the bronchial thermoplasty group experienced 7 serious adverse events requiring hospitalization; none occurred in the control group. During the remainder of the study, 3 patients in the bronchial thermoplasty group experienced 5 serious adverse events, and 1 patient in the control group experienced 4 serious adverse events; all of these events required hospitalization. There were an additional 5 severe adverse events in 2 bronchial thermoplasty group patients and 1 event in a control group patient that were medically treated without hospitalization (the authors did not report whether these were the same patients who were hospitalized). No overall statistical analysis was done that compared serious adverse events in the two groups.

The authors also reported a number of efficacy variables as secondary outcomes. At the end of the study at 52 weeks, bronchial thermoplasty patients had a significantly greater improvement in beta-agonist use than control patients (decrease of 26 puffs versus 6 puffs per week, respectively, $p<0.05$). There was no significant difference between groups in other efficacy variables including morning and evening peak expiratory flow, symptom scores, number of symptom-free days, improvement in FEV-1 predicted, and several quality-of-life measures. The small sample size resulted in limited power to detect differences in the efficacy outcomes.

Asthma Intervention Research (AIR) trial: Cox and colleagues published findings of the AIR trial in 2007, which was designed to evaluate symptom control and adverse events following bronchial thermoplasty. Patients were recruited from the same 3 countries as the RISA study plus Denmark. The eligibility criteria included age 18-65 years with moderate to severe persistent asthma requiring daily therapy with inhaled corticosteroids (equivalent to at least 200 *u*g beclomethasone) and LABAs (at least 100 *u*g salmeterol or equivalent). Also required for study entry were an FEV-1 of 60-85% predicted, airway hyper-responsiveness and stable asthma in the 6 weeks before enrollment, no current respiratory infection, and not more than 2 lower respiratory infections requiring treatment in the past year. An additional criterion was worsening asthma control during a 2-week baseline test period during which time LABAs were withheld. A total of 112 individuals met eligibility following the baseline test phase and were randomly assigned to receive medical management with inhaled corticosteroids and LABAs (n=56) or the same medical management strategy plus bronchial thermoplasty 3 sessions approximately 3 weeks apart), (n=56). After follow-up visits at 3, 6, and 12 months, there was a 2-week period of abstinence from LABAs, during which data on exacerbations were collected. Between data collection periods, patients could use all maintenance therapies.

The primary outcome was the difference between groups in change in rate of mild exacerbations from the baseline 2-week abstinence period. An exacerbation was defined as the occurrence on 2 consecutive days of a reduction in the morning peak expiratory flow of at least 20% below the average value (recorded during

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the week before the abstinence period), the need for more than 3 additional puffs of rescue medication compared to the week before the abstinence period, or nocturnal awakening caused by asthma symptoms. The study was powered to detect a difference between groups of 8 mild exacerbations per person per year. Data were available at 3 months for 100 of 112 patients (89%) and at 12 months for 101 patients (90%); all patients were included in the safety analysis.

The mean number of mild exacerbations per person per week in the bronchial thermoplasty group was 0.35 (standard deviation [SD]: 0.32] during the baseline test period and 0.18 (SD: 0.31) per person per week at 12 months (a decrease of 0.17 per person per week). In the control group, the mean number of mild exacerbations per person per week was 0.28 (SD: 0.31) at baseline and 0.31 (SD: 0.46) at 12 months (an increase of 0.03 per person per week). Compared to the control group, the bronchial thermoplasty group had a significantly greater reduction in mild exacerbations at the 12-month follow-up (p=0.003). Overall, the average number of exacerbations during the 2-week data collection periods at 3, 6, and 12 months decreased in the bronchial thermoplasty group, a mean decrease of 0.16 (SD: 0.37) per person per week but not in the control group, which had a mean increase of 0.04 (SD: 0.29) mild exacerbations. This resulted in a mean difference of .20 mild exacerbations per week or about 10 per year. In contrast, there was not a significant difference between the number of severe exacerbations at any time point, compared to baseline, but the study may not have had sufficient statistical power for this outcome. At the 12-month follow-up, the mean number of severe exacerbations in the bronchial thermoplasty group was 0.01 (SD: 0.08) per person per week compared to 0.07 (SD: 0.18) at baseline. The number of severe exacerbations in the control group was 0.06 (SD: 0.24) per person per week compared to 0.09 (SD: 0.31) at baseline.

The rate of adverse events was higher in the bronchial thermoplasty group during the active treatment period, but the proportion of adverse events was similar in the 2 groups in the post-treatment period. Post-treatment, 3 individuals in the bronchial thermoplasty group required hospitalization and 2 patients in the control group required a total of 3 hospitalizations. A limitation of the study is the lack of a sham intervention and consequently, an inability to blind patients to treatment group.

In 2011, Thomson and colleagues published 5-year data from the AIR trial. All study participants who completed the 1-year follow-up visit were invited to participate in the extension study; 45 of 52 (87%) in the bronchial thermoplasty group and 24 of 49 (49%) in the control group opted to participate. Follow-up was done on an annual basis. Patients in the control group were followed for 2 additional years, and patients in the bronchial thermoplasty group were followed for 5 years. Twenty-one of 24 (88%) patients in the control group and 42 of 45 (93%) in the bronchial thermoplasty group completed the final follow-up. No instances of pneumothorax, intubation, mechanical ventilation, cardiac arrhythmias or death were reported over the course of the extension study. As previously stated, data were collected on both treatment groups during the first 2 years of the extension study. In the first year (Year 2 of the study), the rate of hospitalizations was 3 of 45 (7%) in the bronchial thermoplasty group and 0 in the control group (p=0.55). In Year 3, the rate of hospitalizations in the bronchial thermoplasty group was again 3 of 45 (7%), and 1 of 21 (5%) patients in the control group was hospitalized (p=1.00). Rates of emergency department visits in Year 2 were 3 (7%) and 3 (12.5%) in the bronchial thermoplasty and control groups, respectively, p=0.41, and in Year 3, rates were 3 (5%) and 3 (5%), respectively (p=1.00). There was one hospitalization each year in the bronchial thermoplasty group in Years 4 and 5.

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In the extension study, unlike the initial follow-up period, respiratory adverse events with multiple symptoms were recorded as a single adverse event. This could give a misleading impression of the total number of adverse events or relative number in the two groups. The incidence of respiratory adverse events during Year 2 was 24 of 45 (53%) in the bronchial thermoplasty group and 13 of 24 (54%) in the control group. During Year 3, incidence was 24 of 43 (56%) in the bronchial thermoplasty group and 12 of 21 (57%) in the control group; differences between groups were not statistically significant in Year 2 or 3. The incidence of respiratory adverse events in the bronchial thermoplasty group was similar in subsequent years; rates were 23 of 43 (53%) in Year 4 and 22 of 42 (52%) in Year 5.

The Thompson et al. study also reported two measures of lung function, post-bronchodilator FEV-1 and forced vital capacity (FVC). Exact numbers were not reported, but post-bronchodilator FEV-1 did not go below 80% of predicted in either group during Years 2 to 5. The group comparisons of safety and efficacy in this follow-up trial was limited by the differential rate of follow-up between the two groups, with a lower percent of patients in the control group agreeing to participate in the follow-up study.

Asthma Intervention Research 2 (AIR2) trial: The AIR2 trial was an RCT evaluating the efficacy of bronchial thermoplasty conducted at 30 sites in 6 countries including the U.S.; findings were published in 2010 by Castro and colleagues. Unlike the other two RCTs, the control condition was a sham intervention, and the trial was double-blind. Eligibility criteria were similar to those in the AIR trial; key differences were that a higher initial dose of inhaled corticosteroids was required (equivalent to at least 1,000 *u*g beclomethasone), and patients were required to have experienced at least 2 days of asthma symptoms during the 4-week baseline period and have a baseline score on the Asthma Quality of Life Questionnaire (AQLQ) of no more than 6.25. (The possible range of the AQLQ score is 1 to 7, with a higher number representing a better quality of life.) Also different from the AIR trial, patients were not required to experience symptom worsening during a period of abstinence from LABAs. Patients were stable on their asthma medication and continued their medication regimen during the study. The primary outcome was the difference between groups in the change from baseline in the AQLQ score, with scores from the 6-, 9-, and 12-month follow-ups averaged (integrated AQLQ score). A related outcome was the proportion of patients who achieved a change in their AQLQ score of 0.5 or greater, generally considered the minimally important difference for this scale. Bayesian analysis was used. The target posterior probability of superiority (PPS) of bronchial thermoplasty over sham was 95%, except for the primary AQLQ endpoint; there the target was 96.4% to adjust for 2 interim looks at the data. The prior for the analysis was not reported in the article.

A total of 297 individuals were randomly assigned, 196 to a bronchial thermoplasty group and 101 to a sham control group. The intervention for all participants consisted of 3 bronchoscopy procedures, performed 3 weeks apart. Participants and outcome assessment was blinded, but the intervention team was unblinded. The sham intervention was identical to the active treatment, except that no radiofrequency energy was delivered. Nine participants withdrew consent before beginning treatment, and 288 underwent bronchoscopy and were included in the intention to treat (ITT) population. One hundred and eight-five participants in the treatment group and 97 in the sham control group underwent the second bronchoscopy, and the same numbers of individuals had the third bronchoscopy (it is not clear whether these were exactly the same patients). A total of 278 out of the 297 enrolled patients (94%) completed the 12-month visit, 181 in the treatment group and 97 in the sham control group.

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The superiority of bronchial thermoplasty was not achieved in the ITT population for the primary effectiveness outcome, mean change in the integrated AQLQ score. Mean change was 1.35 (SD: 1.10) in the bronchial thermoplasty group and 1.16 (SD: 1.23) in the sham control group. Using Bayesian analysis, the posterior probability of superiority was 96%. This did not surpass the target PPS of 96.4%. However, superiority of bronchial thermoplasty on a related outcome was achieved. In the ITT population, the percentage of patients achieving an AQLQ score change of 0.5 or greater (i.e., at least the minimal important difference) was 79% in the bronchial thermoplasty group and 64% in the control group. The posterior probability of superiority at 99.6% surpassed the target probability for secondary outcomes of 95%. Additional analysis of data from the active treatment group suggests that responders (defined as a change in AQLQ score of at least 0.5) were more likely to have a lower baseline score than nonresponders (mean of 4.1 vs. 5.1, respectively).

Several secondary outcomes favored bronchial thermoplasty over the sham control group. These include a reduction in the proportion of patients reporting asthma worsening during follow-up (27.3% vs. 42.9%, respectively, PPS: 99.7%) and a reduction in the number of emergency department visits (0.07 vs. 0.43 visits per person per year, respectively, PPS: 99.9%). Moreover, there was a reduction in severe exacerbations of 0.47 per person per year in the bronchial thermoplasty group compared to 0.70 per person per year in the control group (the PPS was 95.5%). There was no significant difference between groups in other secondary efficacy outcomes including morning peak expiratory flow, number of symptom-free days, symptom score, and rescue medication use.

Regarding safety outcomes, during the treatment phase, there was a higher rate of respiratory adverse events in the active treatment group (85% of participants, mean of 1.0 events per bronchoscopy) compared to the sham group (76% of participants, mean of 0.7 events per bronchoscopy). A total of 16 patients (8.4%) in the active treatment group required 19 hospitalizations for respiratory symptoms during the treatment phase compared to 2 patients (2%) in the sham group who required 1 hospitalization each. However, during the post-treatment period, 70% of patients in the bronchial thermoplasty group and 80% of patients in the sham group reported adverse respiratory events. During this phase of the study, 5 patients (2.6%) in the bronchial thermoplasty group had a total of 6 hospitalizations for respiratory symptoms, and 4 patients (4.1%) in the sham group had 12 hospitalizations (1 patient had 9 hospitalizations).

In the AIR2 study, the sham group had a relatively high rate of response, e.g., 64% experienced a clinically significant increase in the AQLQ. Blinding appeared to be initially successful and remained so for the sham group. After the first bronchoscopy, participants in both groups were unable to correctly guess their treatment group after the first bronchoscopy. During subsequent assessments, this continued among patients in the sham group, whereas in the bronchial thermoplasty group, a larger proportion guessed correctly.

Two-year follow-up data on patients in the bronchial thermoplasty group of AIR2 study were published in 2011 by Castro and colleagues. A total of 166 of 190 (87%) individuals randomized to the bronchial thermoplasty group completed the 2-year evaluation. In the second year after treatment, the proportion of participants who experienced severe exacerbations was 23.0 (95% confidence interval [CI]: 16.6 to 29.5%). This compares to a 30.9% (95% CI: 24.2 to 37.7%) rate of exacerbations during Year 1. The proportion who

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experienced asthma adverse events in Year 2 was 26.5% (95% CI: 19.8- 33.2). The rate in Year 1 was 28.7 (95% CI: 22.1 to 35.3%). The follow-up study is limited in that follow-up data are not being collected on patients randomized to the sham group, and therefore outcomes such as rate of exacerbations and hospitalizations, cannot be compared in patients who did and did not receive bronchial thermoplasty.

In 2011, Wu and colleagues published a meta-analysis of safety and efficacy findings of the 3 published RCTs. In all analyses reported here, data from the 3 trials were pooled. A pooled analysis found greater mean improvement in asthma quality of life in the bronchial thermoplasty compared to control groups (weighted mean difference [WMD]: 0.63, 95% CI: 0.10 to 1.15). The authors did not discuss a possible placebo effect that might impact quality-of-life reporting in the medication trials. In addition, there was significantly greater improvement in the peak expiratory flow with bronchial thermoplasty treatment compared to control (WMD: 21.78, 95% CI: 8.06 to 35.50). Adverse events were also reported. During the treatment period (beginning on the day of the first treatment session and lasting 6 weeks after the last session), there were more respiratory adverse events in the bronchial thermoplasty groups (1,113 events in 257 patients) compared with the control groups (369 events in 164 patients) (*p* value not reported). Also during the treatment period, there was a significantly higher risk of hospitalization with bronchial thermoplasty than control (risk ratio [RR]: 3.78, 95% CI: 1.39 to 10.24). In the post-treatment period (end of treatment to the 12-month follow-up visit), there was not a significant difference between groups in the risk of hospitalization between groups (RR: 1.15, 95% CI: 0.47 to 2.79). The authors also noted that there were no patient deaths and no permanent disability in any study participant.

Ongoing Clinical Trials

RISA Extension Study (NCT00401986): The purpose of this study is to follow patients who were treated with the Alair device in the RISA study for an additional 4 years to identify any long-term safety issues. This study is sponsored by Asthmatx.

AIR2 Extension Study (NCT01350414): This study is following patients who were treated with the Alair device in the AIR2 study for an additional 4 years to determine the long-term efficacy of the device. The primary outcome is the rate of asthma exacerbations in Years 2-5 compared to Year 1 (the initial AIR2 study. This study is sponsored by Asthmatx. Two-year data were published in 2011.

Bronchial Thermoplasty in Severe Persistent Asthma (PAS2) (NCT01350336): This study is being conducted as part of the conditions of the pre-market approval for the Alair system. Asthmatx, the study sponsor, is required by the FDA to evaluate the long-term safety and efficacy of the system in the intended use population in the United States. The study is being conducted at 3 U.S. sites and is including adults with asthma who are taking regular maintenance medication with pre-bronchodilator FEV-1 at least 60% of predicted. The estimated study completion date is December 2019.

A Prospective Observational Study of Biopredictors of Bronchial Thermoplasty Response in Patients With Severe Refractory Asthma (BTR Study) (NCT01185275): This is a prospective observational study of adults with asthma who have been taking regular maintenance medication for the past 12 months. Additional eligibility includes prebronchodilator FEV-1 at least 50% of predicted and asthma symptoms on at least 2 days or 1 night per week over the past 2 weeks. The study will assess the relationship between baseline

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clinical, physiologic, biologic, and imaging markers and response to bronchial thermoplasty. The expected study completion date is August 2017. This study is sponsored by the Washington University School of Medicine.

Summary
Three industry-sponsored RCTs on bronchial thermoplasty have been published. The largest RCT with the most rigorous methodology was the AIR2 trial. This was the only published trial that was double-blind and sham-controlled, and also the only published RCT with sites in the United States. Over one year, bronchial thermoplasty was not found to be superior to sham treatment on the investigator-designated primary efficacy outcome, mean change in quality-of-life score, but was found to be superior on a related outcome, improvement in quality of life of at least 0.5 points on the AQLQ scale. There was a high rate of response in the sham group of the AIR2 trial, which suggests a large placebo effect, particularly for subjective outcomes such as quality of life. On the secondary outcomes, bronchial thermoplasty provided greater benefit than sham treatment on some, but not all, of the outcomes. In the AIR trial and RISA trial, there were improvements in quality of life for the bronchial thermoplasty group. However, given the lack of benefit in the AIR2 trial, it is possible that the differences in quality of life for these other trials were due to placebo effect.

There are longer-term (3-year) comparative published data from the AIR trial. Rates of hospitalizations and respiratory adverse events did not differ significantly in the groups that received bronchial thermoplasty versus medication in Years 2 and 3. Data up to 5 years in the bronchial thermoplasty group did not suggest delayed complications. For the sham-controlled AIR2 trial, 2-year follow-up data are available only for bronchial thermoplasty group. In Year 2, patients did not experience an increase in severe exacerbations or asthma adverse events compared to Year 1.

Findings on adverse events from the three trials suggest that bronchial thermoplasty is associated with a relatively high rate of adverse events including hospitalizations during the treatment period, but not in the post-treatment period. Additional safety data from published RCTs on patients who were treated with bronchial thermoplasty are being collected in extension studies.

The uncertain degree of benefit and the presence of substantial adverse events leave a large degree of uncertainty about the impact of bronchial thermoplasty on the net health outcome. In addition, there is a lack of data on patient selection factors for this procedure, and as a result, it is not possible to determine which patients receive the most benefit. As a result, bronchial thermoplasty is considered investigational as a treatment for asthma.

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Coding

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Code Type	Code
CPT	31660, 31661
HCPCS	No codes
ICD-9 Diagnosis	All relative diagnoses
ICD-9 Procedure	32.27

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08/15/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/01/2013	Medical Policy Committee review
08/21/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/07/2014	Medical Policy Committee review
08/20/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 08/2015

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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