Catheter Ablation as Treatment for Atrial Fibrillation

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider the use of transcatheter radiofrequency ablation (RFA) or cryoablation to treat atrial fibrillation (AF) for certain indications to be eligible for coverage.

Patient Selection Criteria

The use of transcatheter radiofrequency ablation (RFA) or cryoablation as a treatment for atrial fibrillation (AF) may be eligible for coverage for the following indications which have failed to respond to adequate trials of antiarrhythmic medications:

- Symptomatic paroxysmal or symptomatic persistent atrial fibrillation (AF); or
- As an alternative to atrioventricular (AV) nodal ablation and pacemaker insertion in patients with class II or III congestive heart failure and symptomatic atrial fibrillation (AF).

Based on review of available data, the Company may consider transcatheter radiofrequency ablation (RFA) or cryoablation to treat atrial fibrillation to be eligible for coverage as an initial treatment for patients with recurrent symptomatic paroxysmal atrial fibrillation in whom a rhythm-control strategy is desired.

Based on review of available data, the Company may consider repeat radiofrequency ablation (RFA) or cryoablation in patients with recurrence of atrial fibrillation (AF) and/or development of atrial flutter following the initial procedure may be considered eligible for coverage. (See Note)

When 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 the use of transcatheter radiofrequency ablation or cryoablation as a treatment for cases of atrial fibrillation that do not meet the criteria outlined above, to be investigational.*

There is not 1 single procedure for catheter ablation, but several variations. Electrical isolation of the pulmonary vein musculature (pulmonary vein isolation) is the cornerstone of most atrial fibrillation (AF) ablation procedures, but additional ablation sites may also be included during the initial ablation. Potential additional ablation procedures include: creation of linear lesions within the left atrium; ablation of focal triggers outside the pulmonary veins; ablation of areas with complex fractionated atrial electrograms; and
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ablation of left atrial ganglionated plexi. The specific ablation sites may be determined by electroanatomic mapping to identify additional sites of excitation. As a result, sites may vary from patient to patient, even if they are treated by the same physician. Patients with long-standing persistent atrial fibrillation (AF) may need more extensive ablation. Similarly, repeat ablation procedures for recurrent atrial fibrillation (AF) generally involve more extensive ablation than do initial procedures.

As many as 30% of patients will require a follow-up (repeat) procedure due to recurrence of atrial fibrillation (AF) or to developing atrial flutter. In most of the published studies, success rates were based on having as many as three separate procedures, although these repeat procedures may be more limited than the initial procedure.

Background/Overview
Radiofrequency ablation using a percutaneous catheter-based approach is widely used to treat supraventricular arrhythmias. Atrial fibrillation frequently arises from an abnormal focus at or near the junction of the pulmonary veins and the left atrium, thus leading to the feasibility of more focused ablation techniques directed at these structures. Catheter-based ablation, using both RFA and cryoablation, is being studied in the treatment of various types of AF.

Atrial fibrillation is the most common cardiac arrhythmia, with a prevalence estimated at 0.4% of the population, increasing with age. The underlying mechanism of AF involves an interplay between electrical triggering events and the myocardial substrate that permits propagation and maintenance of the aberrant electrical circuit. The most common focal trigger of AF appears to be located within the cardiac muscle that extends into the pulmonary veins.

Atrial fibrillation accounts for approximately one-third of hospitalizations for cardiac rhythm disturbances. Symptoms of AF, i.e., palpitations, decreased exercise tolerance, and dyspnea, are primarily related to poorly controlled or irregular heart rate. The loss of AV synchrony results in a decreased cardiac output, which can be significant in patients with compromised cardiac function. In addition, patients with AF are at higher risk for stroke, and anticoagulation is typically recommended. Atrial fibrillation is also associated with other cardiac conditions, such as valvular heart disease, heart failure, hypertension, and diabetes. Although episodes of AF can be converted to normal sinus rhythm using either pharmacologic or electroshock conversion, the natural history of AF is one of recurrence, thought to be related to fibrillation-induced anatomic and electrical remodeling of the atria.

Atrial fibrillation can be subdivided into three types:
- Paroxysmal (episodes that last fewer than seven days and are self-terminating),
- Persistent (episodes that last for more than seven days and can be terminated pharmacologically or by electrical cardioversion), or
- Permanent.

Treatment strategies can be broadly subdivided into rate control, in which only the ventricular rate is controlled and the atria are allowed to fibrillate, or rhythm control, in which there is an attempt to re-establish and maintain normal sinus rhythm. Rhythm control has long been considered an important
treatment goal for management of AF, although its primacy has recently been challenged by the results of several randomized trials that reported that pharmacologically maintained rhythm control offered no improvement in mortality or cardiovascular morbidity compared to rate control.

Currently, the main indications for a rhythm control are for patients with paroxysmal or persistent AF who have hemodynamic compromise associated with episodes of AF or who have bothersome symptoms despite adequate rate control. A rhythm-control strategy involves initial pharmacologic or electronic cardioversion, followed by pharmacologic treatment to maintain normal sinus rhythm. However, antiarrhythmic medications are often not effective in maintaining sinus rhythm. As a result, episodes of recurrent AF are typical, and patients with persistent AF may require multiple episodes of cardioversion. Implantable atrial defibrillators, which are designed to detect and terminate an episode of AF, are an alternative in patients otherwise requiring serial cardioversions, but these have not yet achieved widespread use. Patients with paroxysmal AF, by definition, do not require cardioversion but may be treated pharmacologically to prevent further arrhythmic episodes.

Treatment of permanent AF focuses on rate control, using either pharmacologic therapy or ablation of the AV node, followed by ventricular pacing. Although AV nodal ablation produces symptomatic improvement, it does entail lifelong anticoagulation (due to the ongoing fibrillation of the atria), loss of AV synchrony, and lifelong pacemaker dependency. Implantable defibrillators are contraindicated in patients with permanent AF.

The cited treatment options are not considered curative. A variety of ablative procedures have been investigated as potentially curative approaches, or perhaps modifying the arrhythmia such that drug therapy becomes more effective. Ablative approaches focus on interruption of the electrical pathways that contribute to AF through modifying the arrhythmia triggers and/or the myocardial substrate that maintains the aberrant rhythm. The Maze procedure, an open surgical procedure often combined with other cardiac surgeries (i.e., valve repair), is an ablative procedure that involves sequential atriotomy incisions designed to create electrical barriers that prevent the maintenance of AF. Because of the highly invasive nature of this procedure, it is currently mainly reserved for patients who are undergoing open heart surgery for other reasons, such as valve repair or coronary artery bypass grafting.

**Catheter Ablation for Atrial Fibrillation**

Radiofrequency ablation using a percutaneous catheter-based approach is a widely used technique for a variety of supraventricular arrhythmias, in which intracardiac mapping identifies a discrete arrhythmogenic focus that is the target of ablation. The situation is more complex for AF, because there is no single arrhythmogenic focus. Since the inception of ablation techniques in the early 1990s, there has been a progressive understanding of the underlying electrical pathways in the heart that are associated with AF. In the late 1990s, it was recognized that AF most frequently arose from an abnormal focus at or near the junction of the pulmonary veins and the left atrium, thus leading to the feasibility of more focused, percutaneous ablation techniques. The strategies that have emerged for focal ablation within the pulmonary veins originally involved segmental ostial ablation guided by pulmonary vein potential (electrical approach) but currently more typically involve circumferential pulmonary vein ablation (anatomic approach).
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The individual lesion set (in addition to the pulmonary vein isolation) and the degree to which the pulmonary vein antrum is electrically isolated vary. Research is ongoing into specific ablation/pulmonary vein isolation techniques is ongoing. Evidence from a randomized controlled trial (RCT) comparing pulmonary vein isolation alone with pulmonary vein isolation plus ablation of electrograms showing complex fractionated activity and with pulmonary vein isolation plus additional linear ablation across the left atrial roof and mitral valve isthmus suggests that the more extensive lesion sets do not reduce the AF recurrence rate.1 Meta-analyses have found that the addition of complex fractionated atrial electrogram ablation to pulmonary vein isolation alone did not improve rates of freedom from recurrent AF, although at least 1 RCT has reported that patients with ablation of dormant conduction sources outside the pulmonary veins had fewer arrhythmia recurrences than those treated with pulmonary vein isolation alone.

Circumferential pulmonary vein ablation using radiofrequency energy is the most common approach at the present time. The procedure also can be done using cryoa blation technology. Use of currently available radiofrequency catheters for AF has a steep learning curve because they require extensive guiding to multiple ablation points. One of the potential advantages to cryoablation techniques is that cryoablation catheters have a circular or shaped end point, allowing a “one-shot” ablation. Other types of radiofrequency catheters, such as Medtronic’s radiofrequency-based Pulmonary Vein Ablation Catheter™, which incorporate circular or otherwise shaped end points, may also be used.

Repeat procedures following initial RFA are commonly performed if AF recurs or if atrial flutter develops postprocedure. The need for repeat procedures may, in part, depend on clinical characteristics of the patient (eg, age, persistent vs paroxysmal AF, atrial dilatation), and the type of initial ablation performed. Repeat procedures are generally more limited than the initial procedure. For example, in cases where electrical reconnections occur as a result of incomplete ablation lines, a “touch up” procedure is done to correct gaps in the original ablation. In other cases when atrial flutter develops after ablation, a “flutter ablation” is performed, which is more limited than the original AF procedure. A number of clinical and demographic factors have been associated with the need for a second procedure, including age, length of AF, permanent AF, left atrial size, and left ventricular ejection fraction.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

In February 2009, the Navistar® ThermoCool® Irrigated Deflectable Diagnostic/Ablation Catheter and EZ Steer ThermoCool NAV Catheter (Biosense Webster South Diamond Bar, CA,) received expanded approval by the FDA through the pre-market approval (PMA) process for RFA for treatment of drug-refractory recurrent symptomatic paroxysmal atrial fibrillation.

Devices using laser or cryoa b lation techniques for substrate ablation have been approved by FDA through the PMA process for atrial fibrillation (FDA product code: OAE). These devices include:

- Arctic Front™ Cardiac CryoAblation Catheter and CryoConsole (Medtronic, Minneapolis, MN) in December 2010.
- TactiCath™ Quartz Catheter and TactiSysQuartz® Equipment (St. Jude Medical, St. Paul, MN) in October 2014.
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- HeartLight® Endoscopic Ablation System (Cardiofocus, Marlborough, MA) in April 2016.

In addition, numerous catheter ablation systems have been approved by FDA for other ablation therapy for arrhythmias such as supraventricular tachycardia, atrial flutter, and ventricular tachycardia. FDA product code: LPB.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD).

Rationale/Source
This policy is updated periodically with literature review. The most recent literature search was performed through March 29, 2016. Following is a summary of the key literature to date.

In patients with paroxysmal or persistent AF, pulmonary vein ablation may be considered an alternative to drug therapy. In patients with permanent AF, pulmonary vein ablation may be considered an alternative to drug therapy or to AV nodal ablation and pacing. For all types of AF, it is possible that pulmonary vein ablation may not be curative as a sole treatment but might alter the underlying myocardial triggers or substrate in such a way that subsequent pharmacologic therapy may become more effective.

There is ongoing controversy regarding the relative benefits of rhythm versus rate control in AF, which underlies the evaluation of evidence on catheter ablation. Randomized trials of pharmacologic therapies have not demonstrated the superiority of rhythm versus rate control. However, the apparent equivalency of these two strategies with pharmacologic therapy cannot be extrapolated to the rhythm control achieved with ablation. Antiarrhythmic medications used for rhythm control are only partially effective and have serious complications, including proarrhythmic properties that can be lethal. Therefore, nonpharmacologic strategies for rhythm control have the potential to achieve superior outcomes than have been seen with pharmacologic strategies.

Outcome Assessment in Atrial Fibrillation
A variety of outcomes for treatment of AF may be considered. The mortality and morbidity related to AF, such as cardiovascular mortality, stroke, and heart failure, are the most important clinical outcomes. However, these are uncommon events, and currently available trials are not powered to detect differences in these outcomes. Quality of life (QOL) is also an important outcome, as these measures reflect important manifestations of AF, such as symptoms and reduced exercise tolerance. Atrial fibrillation has been shown to be associated with lower QOL scores, and maintenance of sinus rhythm has been associated with higher QOL scores for patients with paroxysmal AF.

Recurrence of AF is a more problematic outcome measure, since the intermittent and often transient nature of recurrences makes accurate measurement difficult. This outcome measure has been reported in different ways. For example, the proportion of patients in sinus rhythm at the end of the study, the time to first recurrence, and the number of recurrences within a time period have been reported. A recent publication highlights the difficulties in measuring AF recurrence and recommends a measure of AF “burden,” defined as the percentage of time an individual is in AF, as the optimal measure of treatment efficacy. However,
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this parameter requires continuous monitoring over a relatively long period of time, which is inconvenient for patients, resource intensive, and usually not pragmatic in patients who do not already have an implanted pacemaker.

Recommendations for outcome assessment in trials of AF treatment were included in the 2006 American College of Cardiology/American Heart Association practice guidelines for the treatment of AF. These guidelines pointed out that the appropriate endpoints for evaluation of treatment efficacy in patients with paroxysmal or persistent AF have little in common. For example, in studies of persistent AF, the proportion of patients in sinus rhythm at the end of follow-up is a useful endpoint, but this is a less useful measure in studies of paroxysmal AF. Given all these variables, ideally, controlled clinical trials would report a range of outcomes (including QOL) and complications in homogeneous patient groups and compare to the most relevant treatment alternatives, such as pharmacologic therapy; defibrillator therapy; and AV nodal ablation, depending on the classification of AF (paroxysmal, persistent, or permanent).

Radiofrequency Ablation for AF
Overall Efficacy of Radiofrequency Ablation for Symptomatic Paroxysmal or Persistent AF

Systematic Reviews
The literature review for this evidence review was originally based on a 2008 technology evaluation center (TEC) Assessment. Six RCTs met the inclusion criteria for this TEC Assessment. The trials differed in their patient populations, the specific catheter ablation techniques used, and comparisons made. The trials addressed 3 distinct indications for catheter ablation: (1) patients with paroxysmal AF, as a first-line treatment option (1 trial); (2) patients with symptomatic paroxysmal or persistent AF who have failed treatment with antiarrhythmic drugs (4 trials); and (3) patients with symptomatic AF and heart failure who have failed treatment with standard medications for rate control and who would otherwise be considered for AV nodal ablation and pacemaker insertion (1 trial).

All 6 trials reported that maintenance of sinus rhythm was improved for the catheter ablation group. Recurrence rates of AF at 1 year ranged from 11% to 44% for the catheter ablation groups compared with 63% to 96% for the medication groups. Four of the 6 trials reported QOL outcomes. One of these only reported within-group comparisons, as opposed to between-group comparisons. The other 3 trials reported improvements in QOL associated with catheter ablation. None of the available trials reported meaningful data on cardiovascular morbidity and mortality associated with AF. The Assessment concluded that catheter RFA is more effective than medications in maintaining sinus rhythm across a wide spectrum of patients with AF and across different variations of catheter ablation. The evidence on QOL is suggestive, but not definitive, of a benefit for patients undergoing catheter ablation. For other outcomes, the evidence did not permit conclusions. Based on these findings, TEC criteria were met for 2 indications: patients with symptomatic paroxysmal or persistent AF who have failed treatment with antiarrhythmic drugs and patients with symptomatic AF and heart failure who have failed treatment with standard medications for rate control and who would otherwise be considered for AV nodal ablation and pacemaker insertion. For the first indication, the conclusion followed from the premise that reducing episodes of recurrent AF for this population will reduce or eliminate the symptoms associated with episodes of AF. For the other indication, the single multicenter RCT available was judged sufficient to conclude that catheter ablation improved
outcomes compared with the alternative, AV nodal ablation and pacemaker insertion. While this trial was relatively small, it was judged to be otherwise of high quality and reported improvements of a relatively large magnitude across a range of clinically important outcome measures, including QOL, exercise tolerance, left ventricular ejection fraction (LVEF), and maintenance of sinus rhythm.

Since the publication of the 2008 TEC Assessment, additional systematic reviews and meta-analyses of catheter ablation for AF have been published.

In 2015, Vaidya et al reported results of a systematic review and meta-analysis of RCTs comparing pulmonary vein isolation, pharmacologic rate control, atrioventricular (AV) junction ablation with pacemaker insertion for AF. Subgroup analyses focused on patients with congestive cardiac failure. The review identified 7 RCTs, 2 comparing AV junction ablation with pacemaker insertion with pharmacologic rate control, 1 comparing AV junction ablation with pacemaker insertion with pharmacologic rate control and pacemaker insertion, 1 comparing pulmonary vein isolation with AV junction ablation and biventricular pacing, and 3 comparing pulmonary vein isolation with pharmacologic rate control. Studies ranged in size from 36 to 99 patients, with 425 patients in total across the 7 studies. When pulmonary vein isolation was compared with pharmacologic rate control, based on 3 RCTs, pulmonary vein isolation-treated patients had higher increases in left ventricular ejection fraction (LVEF; weighted mean difference [WMD] +6.5; 95% confidence interval [CI], 0.6 to 12.5; p=0.03). When pulmonary vein isolation was compared with AV junction ablation and pacemaker insertion, based on 1 RCT, pulmonary vein isolation-treated patients had higher increases in LVEF (WMD = +9.0; 95% CI, 6.3 to 11.7; p<0.01). Patients treated with pulmonary vein isolation had greater improvements in heart failure symptoms, measured by the Minnesota Living with Heart Failure Questionnaire (MLHFQ) compared with pharmacologic rate control, in 3 RCTs that included only patients with congestive cardiac failure (WMD = -11.0; 95% CI, -19.4 to -2.6; p=0.01). MLHFQ score was also improved when pulmonary vein isolation was compared with AV junction ablation with pacemaker insertion.

Also in 2015, Shi et al reported results of a meta-analysis of RCTs comparing catheter ablation with antiarrhythmic drug therapy for AF. The meta-analysis included 11 trials (total N=1763 patients), of which 4 included only patients with paroxysmal AF, 2 included only patients with persistent AF, and 5 included patients with paroxysmal or persistent AF. Eight RCTs included only patients who were drug-refractory or drug-intolerant, and the remaining 3 included patients treated with catheter ablation as first-line therapy. Catheter ablation-treated patients had lower rates of AF recurrence than antiarrhythmic drug therapy-treated patients (RR 0.47; 95% CI, 0.38 to 0.58; p<0.001; I2=62%, p=0.003).

A Cochrane review of catheter ablation for paroxysmal and persistent AF was published in 2012. It included 7 RCTs of catheter ablation versus medical therapy. The review’s main conclusions were that catheter ablation was superior at reducing the recurrence of AF (RR=0.27; 95% confidence interval [CI], 0.18 to 0.41) but that there were no differences in mortality (RR=0.50; 95% CI, 0.04 to 5.65), embolic complications (RR=1.01; 95% CI, 0.18 to 5.60), or death from thromboembolism (RR=3.04; 95% CI, 0.13 to 73.4).

In 2013, Ganesan et al published results from a systematic review and meta-analysis of studies reporting long-term outcomes after percutaneous catheter ablation for paroxysmal and nonparoxysmal AF. The
authors included 19 studies (RCTs, case-control and cohort studies, case series) that reported catheter ablation outcomes at 3 years or more after the index ablation procedures. Sample sizes in these studies ranged from 39 to 1404 (total N=6167 patients) included overall. For a single procedure, the pooled overall success rate at 12 months postprocedure was 64.2% (95% CI, 57.5% to 70.3%). At late follow-up, the overall single-procedure success, defined as freedom from atrial arrhythmia at latest follow-up, was 53.1% (95% CI, 46.2% to 60.0%). The pooled overall multiple-procedure long-term success rate was 79.8% (95% CI, 75.0% to 83.8%). The analysis was unable to identify any predictors of short- or long-term recurrence. Reporting of periprocedural complications was heterogeneous across the studies, but complication rates were generally low.

Earlier systematic reviews and meta-analyses comparing RFA with antiarrhythmic drug therapy for AF have reported improved rates of freedom from arrhythmias with catheter ablation. Nair et al included 6 RCTs comparing RFA with antiarrhythmic drug therapy for AF, 5 of which were included in the TEC Assessment. Two systematic reviews published in 2008 synthesized the RCT evidence on catheter ablation versus alternative therapy. They included 4 of the 6 trials reviewed for the TEC Assessment. Noheria et al included 3 of these 4 RCTs, as well as a small RCT of 30 patients not included in the TEC Assessment. Gjesdal et al included 5 RCTs in their analysis, including the 4 trials in the Noheria systematic review, and 1 additional trial (included in the TEC Assessment) that compared catheter ablation plus antiarrhythmic drugs with antiarrhythmic drugs alone. All 3 systematic reviews concluded that catheter ablation was more effective than pharmacologic treatment in maintaining normal sinus rhythm. Nair et al demonstrated a pooled relative risk for AF at 1 year after procedure of 0.35 compared with antiarrhythmic drug therapy. In combined analysis, Noheria et al reported AF-free survival at 1 year to be 75.7% in the catheter ablation group compared with 18.8% in the comparison group. The relative risk for maintaining sinus rhythm was 3.73 (95% CI, 2.47 to 5.63) for the catheter-ablation group compared with alternative treatment. Gjesdal et al concluded that the available evidence was of moderate quality and consistent in reporting that AF-free survival was superior for the catheter ablation group. However, due to unexplained heterogeneity, these authors did not perform a combined analysis.

Additional systematic reviews have assessed the effect of RFA on specific AF-related outcomes. In 2014, Zhuang et al conducted a meta-analysis to evaluate the effect of RFA on left atrial (LA) volume and function in patients with AF. In a summary of data from 26 studies enrolling 1821 patients, RFA was associated in improvements in LA volume measurements compared with preablation (eg, for LA diameter); the weighted mean difference was -1.52 mm (95% CI, -2.57 to -0.47 mm). There were no significant improvements in LA function.

Randomized Controlled Trials

Since the TEC Assessment, three additional RCTs comparing RFA versus pharmacologic treatment have been identified. Wilber et al. enrolled 167 patients who had failed at least one antiarrhythmic medication and had at least 3 AF episodes in the prior 6 months. Patients were randomly assigned to either catheter ablation or continued drug therapy and followed for 9 months. At the end of follow-up, 66% of patients in the ablation group were free of recurrent AF compared to 16% of patients in the medication group. Adverse events related to treatment occurred in 4.9% (5/103) of patients treated with ablation and in 8.8% (5/57) of patients treated with medications.
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Forleo et al. randomly assigned 70 patients with type 2 diabetes and AF to either RFA or an antiarrhythmic medication. Follow-up was for 1 year, with the primary outcome being recurrence of AF. At the end of the trial, 42.9% of patients in the medication group were free of AF compared to 80% of patients in the ablation group. There was also a significant improvement in QOL for patients in the ablation group. Adverse events from medications occurred in 17.2% (6/35) patients, whereas complications from ablation occurred in 2.9% (1/35).

Mont et al conducted an RCT comparing radiofrequency catheter ablation with antiarrhythmic drug therapy among 146 patients with symptomatic persistent AF. Patients were randomized in a 2:1 fashion to catheter ablation (n=98) or antiarrhythmic drug therapy (N=48). Although the study was terminated before the planned sample size of 208 was met due to lower than expected enrollment, at 12 months of follow up, the proportion of patients who were free of sustained episodes of AF was higher in the catheter ablation group than the antiarrhythmic drug therapy group (70.4% vs 43.7%, p=0.002). QOL scores did not significantly differ between the groups. Longer term outcomes were not reported.

RFA as First-Line Therapy for AF
Since the 2008 TEC Assessment which found that the evidence was insufficient to support the use of catheter ablation as first-line therapy for individuals with paroxysmal AF, the evidence has continued to evolve.

Systematic Reviews
In 2015, Hakalathi et al reported on a systematic review and meta-analysis of RCTs comparing RFA with antiarrhythmic drug therapy as first-line therapy for symptomatic AF which included 3 trials (total N=491 patients). Included were the RAAFT-2 and MANTRA-PAF trials (described below) and the earlier RAAFT-1 trial. RAAFT-2 and MANTRA-PAF were considered to be at low risk of bias. RFA was associated with lower risk of recurrence of AF (risk ratio, 0.63; 95% CI, 0.44 to 0.92; p=0.02; I²=38%).

Randomized Controlled Trials
The 2 RCTs considered at lowest risk of bias are described in additional detail. In 2014, Morillo et al published results of the RAAFT-2 trial, an RCT comparing RFA to antiarrhythmic drug therapy as first-line therapy for paroxysmal AF. Eligible patients had symptomatic recurrent paroxysmal AF lasting more than 30 seconds, with 4 or fewer episodes in the prior 6 months, and had no previous antiarrhythmic drug treatment. The study enrolled 127 patients at 16 centers; 66 were randomized to RFA and 61 to antiarrhythmic drug therapy, at the discretion of the treating physician. In the RFA group, 63 underwent ablation; during follow-up, 9 underwent reablation and 6 crossed over to receive antiarrhythmic drug therapy. In the drug therapy group, 26 crossed over to undergo ablation and 24 discontinued antiarrhythmic drug therapy but continued in the trial. Analysis was intention-to-treat. Patients were followed with biweekly scheduled transtelephonic monitor recordings and symptomatic recordings through the 24-month follow-up period. The study's primary outcome (recurrence of any atrial tachyarrhythmia lasting longer than 30 seconds) occurred in 72.1% (n=44) in the antiarrhythmic drug group compared with 54.5% (n=36) in the ablation group (hazard ratio [HR], 0.56; 95% CI, 0.35 to 0.90; p=0.02). Fewer patients in the RFA group had recurrence of symptomatic AF, atrial flutter, or atrial tachycardia (47% vs 59%; HR=0.56; 95% CI, 0.33 to 0.95; p=0.03) or recurrence
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of symptomatic AF (41% vs 57%; HR=0.52; 95% CI, 0.3 to 0.89; p=0.02). QOL measures did not differ significantly between groups.

An earlier RCT of RFA as the initial therapy for paroxysmal AF was published in 2012. A total of 294 patients were randomized to initial treatment with catheter ablation or pharmacologic therapy. Patients were followed for up to 24 months for the primary outcomes of burden of AF (percentage of time in AF on Holter monitor) at each time point and cumulative burden of AF over all time points. For the individual time points, the burden of AF was lower in the catheter RFA group at 24 months (9% vs 18%, p=0.007), but not at other time points. The 90th percentile cumulative burden did not differ significantly between groups (13% vs 19%; p=0.10). The secondary outcome of percent of patients free from AF at 24 months was greater for the catheter ablation group (85% vs 71%, p=0.004), as was the secondary outcome of freedom from symptomatic AF (93% vs 84%, p=0.01). There was 1 death in the ablation group (due to a procedural-related stroke) and 3 patients in the ablation group developed cardiac tamponade following the procedure.

RFA for AF in the Setting of Heart Failure
Based on one available multicenter RCT, the TEC Assessment concluded that the evidence was sufficient to conclude that catheter ablation improves outcomes compared with the alternative, AV nodal ablation and pacemaker insertion. RCTs and multiple observational studies have compared catheter ablation to medical therapy for AF in the setting of heart failure.

In 2016, Anselmino et al reported on a systematic review of available observational studies and RCTs evaluating catheter ablation for AF in patients with chronic heart failure or structural cardiomyopathies. For the population of patients with chronic heart failure, the authors identified 17 observational studies, 4 RCTs, and 4 meta-analyses. In the 4 RCTs, 1 compared catheter ablation with AV node ablation and biventricular pacemaker insertion and 3 compared catheter ablation with optimal medical therapy and rate control. In pooled analysis, the mean efficacy of catheter ablation in maintaining sinus rhythm was 59% after a single procedure, increasing to 77% after patients who underwent a repeat procedure were included.

The 2 most recent RCTs comparing RFA to medical rate control are described next. While these studies do not directly provide evidence on use of catheter ablation as an alternative to AV nodal ablation in patients who have failed rate control, they support use of catheter ablation to treat AF in this population.

Hunter et al conducted an RCT comparing catheter RFA to medical rate control for patients with persistent AF and symptomatic heart failure, with adequate rate control at the time of enrollment. There was no requirement for patients to have failed antiarrhythmic drug therapy. The study's primary end point was difference between groups in LVEF at 6 months postprocedure. Fifty patients were randomized, 26 to catheter ablation and 24 to medical management. At 6 months, 81% of the catheter ablation group was free from recurrent AF and antiarrhythmic drugs. LVEF at 6 months after procedure was 40% (±12%) in the catheter ablation group compared with 31% (±13%, p=0.015) in the medical management group. Catheter ablation was also associated with improvements in health-related QOL.

Jones et al reported results from an RCT comparing catheter ablation to medical rate control for patients with symptomatic heart failure, LVEF 35% or less, and persistent AF. Fifty-two patients were randomized,
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26 each to catheter ablation or medical rate control. At 12 months after procedure, sinus rhythm was maintained in 88% of the catheter ablation group, with a single-procedure success rate of 68%. For the study’s primary outcome (peak oxygen consumption at 12 months postprocedure), there was a significant increase in peak consumption the catheter ablation group (+3.07 mL/kg/min) compared with the medical management group 95% CI, 0.56 to 5.59 mL/kg/min; p=0.018).

Comparisons of RFA Techniques
Techniques for RFA for pulmonary vein isolation or substrate ablation have evolved over time. Specifying RFA techniques is not the focus of the present review, but recent large studies are described briefly.

In 2015, Reddy et al reported results of a noninferiority RCT comparing a contact force-sensing RFA catheter with a standard (noncontact force-sensing) catheter in 300 patients with treatment-refractory paroxysmal AF. The study’s primary effectiveness end point was a composite end point of acute ablation success and long term ablation success (freedom from symptomatic AF, atrial tachycardia, or atrial flutter at 12 months off antiarrhythmic drugs, after a 3-month blanking period). In the modified intention-to-treat population, patients in the contact force-sensing catheter group (n=149) were noninferior to control catheter group patients (n=141; 67.8% vs 69.4%, respectively; absolute difference, -1.6%; lower limit of 1-sided 95% CI; -10.7; p=0.007 for noninferiority.)

A second, smaller RCT published in 2015 (Nakamura et al) compared a contact force-sensing RFA catheter with a standard catheter (total N=120) and reported lower rates of pulmonary vein reconnections in those treated with a contact force-sensing catheter.

A 2015 systematic review and meta-analysis by Afzal et al, which included 9 studies (1 RCT) but not the Reddy RCT, also compared RFA with contact force-sensing or noncontact force-sensing catheters. At 12-month follow-up, contact force-sensing catheter-treated patients had lower AF recurrence at 12 months compared with standard catheter-treated patients (relative risk, [RR] 0.63; 95% CI, 0.44 to 0.91; p=0.01).

Longer Term Outcomes
The available RCTs mainly report on short-term outcomes (>1 year) and, therefore, do not evaluate the rate of late recurrences after 1 year. Longer term outcomes have been reported, and have generally found rates of early recurrence in the range of 20% to 30%, requiring repeat ablations. Rates of longer term recurrence are lower if early recurrence does not occur, in the range of 1% to 2% per year.

Hussein et al reported on 831 patients treated in 2005 (median follow-up, 55 months). During the first year following ablation, 23.8% had a recurrence of AF. During the remaining follow-up, recurrences occurred in 8.9% additional patients. The overall rate free of arrhythmia and medications was 79.4% at 55 months. An additional 10.5% of patients were arrhythmia-free on drugs, for a total clinical improvement rate of 89.9%. In a smaller study (N=509) with follow-up to 5 years after initial ablation, Teunissen et al reported that after a single procedure 41.3% of patients had long-term maintenance of sinus rhythm.

In 2013, Bunch et al reported results from a prospective cohort study comparing risk of stroke between patients with AF who had undergone catheter ablation, patients with AF who did not undergo ablation, and
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patients without a history of AF. A total of 4212 patients with AF who had undergone catheter ablation were age- and sex-matched in a 1:4 ratio to 16,848 subjects in each of the other groups. Mean follow-up time was 3.9 years. At 1 year postprocedure, significantly more patients with AF who had not undergone ablation had a stroke (3.5%) than those with AF who had had ablation (1.4%) or had no history of AF (1.4%; p<0.001 for trend). During the follow-up period, for all ages and CHADS2 profiles, patients with AF who had ablation had a lower stroke risk than those with AF who had not.

Several smaller studies have also reported longer term follow-up after catheter RFA. Weerasooriya et al reported 5-year follow-up in 100 patients treated with catheter ablation. Recurrences were most common within the first 6 months, with repeat procedures being common during that period. At 1, 2, and 5 years after ablation, arrhythmia-free survival was 87%, 81%, and 63%, respectively. Tzou et al reported long-term follow-up for 123 patients who had a previous successful ablation, defined as free of AF at 1 year. At 3-year follow-up, 85% of patients were still free of AF and off of all medications; at 5 years, 71% remained free of AF. The authors estimated a late recurrence rate of 7% per year for patients with an initially successful procedure. In a similar study, Bertaglia et al reported outcomes after 6 years of follow-up for 229 patients who had a single, successful ablation.47 At 1-year follow-up, 77% (177/229) of patients were free of AF and off of all medications. After a mean additional follow-up of 49.7±13.3 months for these 177 patients, 58% remained free of AF. Sawhney et al reported 5-year success rates in 71 patients who underwent ablation in 2002 or 2003. Freedom from symptomatic AF while off medications was achieved in 86% of patients at 1 year, 79% at 2 years, and 56% at 5 years. A substantial minority of patients (22.5%) had recurrence at points more than 2 years after ablation. A 2013 study by Anselmino et al followed 196 patients who underwent catheter RFA for paroxysmal or persistent AF and had LVEF of 50% or less for a mean of 46.2 months. During follow-up, 29.6% of patients required repeat ablation procedures. At the end of follow-up, 37.8% had at least 1 episode of AF, atrial flutter, or ectopic atrial tachycardia. Takigawa et al reported long-term follow-up for 1220 patients who underwent RFA for symptomatic paroxysmal AF. AF recurrence-free survival probabilities at 5 years were 59.4% after the initial procedure and 81.1% after the final ablation procedure (average procedures per patient, 1.3).

Section Summary: Radiofrequency Ablation for AF
Numerous RCTs of RFA for isolation of the pulmonary veins versus medical management have reported that freedom from AF at 1 year is higher with RFA than with medical management. The trials mainly included patients who failed antiarrhythmic medications. These studies reported that most patients undergoing RFA were free of AF at 1 year. QOL was also improved in these trials for patients undergoing catheter ablation. A smaller number of studies have evaluated outcomes longer than 1 year and reported that late recurrences occur up to 5 years but were uncommon after the first year. Complications from RFA were reported at low rates in the RCTs, but the numbers of patients in these trials are too low to accurately estimate rates of uncommon events. Two RCTs have evaluated the use of catheter ablation as an initial strategy for paroxysmal AF; one RCT demonstrated reduced rates of AF recurrence, while the other reported reduced cumulative overall AF burden.
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Cryoablation of the Pulmonary Veins
Earlier studies reporting on outcomes after cryoablation for AF were mainly case series and cohort studies reporting success rates in the range of those reported for RFA. Since 2013, several RCTs have compared cryoablation to medical therapy or RFA.

Systematic Reviews
In 2015, Cheng et al reported on a meta-analysis of RCTs and observational studies comparing cryoablation and RFA for AF. The meta-analysis included 11 studies (3 RCTs, 11 observational studies) with a total of 1216 patients. One RCT included only patients undergoing repeat treatment after an initial failed ablation procedure. In pooled analysis, 66.9% of those treated with cryoablation and 65.1% of those treated with RFA were free of AF after a mean 16.5 months follow up (RR=1.01; 95% CI, 0.94 to 1.07; p=0.87; I²=5%, p=0.39).

In 2014, Xu et al reported on a meta-analysis of studies comparing cryoablation and RFA for AF, which included 14 studies (total N=1104 patients). Two RCTs were included in the analysis, although in 1 cryoablation was compared with laser ablation, so may not be representative of RFA studies. In pooled analysis, there were no significant differences between RFA and cryoablation in terms of ablation success rates (odds ratio [OR], 1.34; 95% CI, 0.53 to 3.36; p=0.538; I²=74.8%, p=0.003) or AF recurrence (OR=0.75; 95% CI, 0.3 to 1.88; p=0.538; I²=74.8%, p=0.003)

A systematic review of studies of cryoablation was published in 2011. This analysis included the STOP-AF trial in abstract form and a total of 22 other nonrandomized studies, primarily case series. Procedural success was reported in over 98% of cases. At 1 year, the rates of success, as defined by no recurrent AF, were 73% (95% CI, 69% to 77%) for paroxysmal AF and 60% (95% CI, 54% to 66%) for persistent AF. Complications were inconsistently reported among the available studies. The most common complication reported was phrenic nerve palsy, which occurred in 6.4% of patients. Other rates of reported complications included pericardial effusion or tamponade (1.5%), groin complications at insertion site (1.8%), stroke (0.3%), and pulmonic stenosis (0.9%).

These systematic reviews provide some evidence that there are no significant differences in efficacy between cryoablation and RFA for AF; however, all 3 do not include key RCTs published from 2015 to 2016, which are discussed at more length below.

Randomized Controlled Trials
Cryoablation Compared With Medical Therapy
In 2013, Packer et al reported results of the STOP AF trial, an RCT of cryoablation versus antiarrhythmic medications. This trial enrolled 245 patients with paroxysmal AF who had failed at least 1 (median, 1.2) membrane-active antiarrhythmic medications. Patients were randomized in 2:1 fashion to cryoballoon ablation (n=163) or drug therapy (n=82). At 1-year follow-up, 69.9% of patients in the ablation group were free of AF versus 73.7% in the medication group. The single-procedure success rate was 57.7%. There was also a significantly greater reduction in symptoms for the ablation group. Seventy-nine percent of the drug treatment group crossed over to cryoablation during the 12-month study follow-up because of recurrent, persistent AF. Cryoablation procedure-related adverse events occurred in 5 patients (3.1%); major AF
events occurred in 3.1% of the cryoablation group compared with 8.5% of the drug-treatment group (noninferiority p<0.001). Phrenic nerve injury occurred at a rate of 13.5%, with 86% resolved at 12 months.

In 2014, Andrade et al published a follow-up analysis of the STOP AF trial to evaluate the incidence and significance of early recurrence of AF after ablation. Of the 163 subjects randomized to cryoablation, 84 (51.5%) patients experienced early recurrence of AF, defined as any recurrence of AF lasting more than 30 seconds between 3 and 12 months postablation. The presence of early AF recurrence was associated with late AF recurrence: late AF recurrence occurred in 41 (25.1%) patients, and was more likely in those with early recurrence (55.6% in those with early recurrence vs 12.7% in those without early recurrence; p<0.001).

Cryoablation Compared With RFA
In 2016, Kuck et al reported results of the FIRE AND ICE Trial, a multicenter RCT with a noninferiority design and blinded end point assessment, which compared RFA with cryoablation in individuals with symptomatic, treatment-refractory paroxysmal AF. The study enrolled 769 patients, of whom 750 were randomized and included in a modified intention-to-treat analysis (n=376 in the RFA group, n=374 in the cryoablation group). The study’s tested the hypothesis that the cryoballoon would be noninferior to RFA in terms of a prespecified efficacy end point, which was time to the first documented clinical failure occurring more than 90 days after the index ablation period (“blanking period”). The study defied clinical failure as recurrence of AF or occurrence of atrial flutter or atrial tachycardia on ECT or 24-hour Holter monitoring, prescription of class I or III antiarrhythmic drugs, or repeat ablation. After 90 days, the primary efficacy end point occurred in 138 cryoablation group patients and in 143 RFA group patients (1-year Kaplan-Meier event rate estimates, 34.6% and 35.9%, respectively; HR=0.96; 95% CI, 0.76 to 1.22; p<0.001 for noninferiority). Cryoablation group patients had shorter total procedure time (124 minutes vs 141 minutes, p<0.001) and left atrial dwell time (92 minutes vs 109 minutes, p<0.001), but longer fluoroscopy time (22 minutes vs 17 minutes, p<0.001). The study’s primary safety end point , a composite of death from any cause, stroke or transient ischemic attack form any cause, and serious adverse events, occurred in 40 patients in the cryoablation group and 51 patients in the RFA group (1-year Kaplan-Meier event rate estimates, 10.2% and 12.8%, respectively; HR=0.78; 95% CI, 0.52 to 1.18; p=0.024). In the cryoablation group, phrenic nerve injury was the most common adverse event reported (2.7%).

In 2015, Luik et al reported results of the FreezeAF trial, an RCT with a noninferiority design which compared RFA with an irrigated catheter with cryoablation in individuals with treatment-refractory paroxysmal AF. The study included 315 patients with paroxysmal AF refractory to treatment with at least 1 antiarrhythmic drug, who were randomized to RFA (n=159) or cryoablation (n=156). The study tested the null hypothesis that cryoablation was noninferiority to RFA in terms of a coprimary endpoint: the absence of AF in combination with absence of persistent complications at 6- and 12-month follow-ups. The coprimary end point was reached in 63.1% and in 64.1% of the RFA and cryoablation groups, respectively, at 6 months, and in and 73.6% and 73 % of the RFA and cryoablation groups, respectively, at 12 months. At 12 months postablation, the null hypothesis was rejected (null hypothesis risk difference, ≤ -0.15; risk difference, 0.029; 95% CI, -0.074 to 0.132; p<0.001).
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An additional RCT published in 2015 compared point-by-point RFA with cryoablation, but in one comparison group pulmonary vein isolation could be achieved with RFA if cryoablation was unsuccessful, and in the second comparison group a hybrid procedure (cryoablation following RFA) was used, which makes isolating the relative efficacy of cryoablation difficult.

The Mesh Ablator versus Cryoballoon Pulmonary Vein Ablation of Symptomatic Paroxysmal AF (MACPAF) study was a single-center RCT comparing cryoablation with RFA with the HD Mesh Ablator Catheter (Bard Electrophysiology, purchased by Boston Scientific in 2013) for AF. The HD Mesh Ablator Catheter, which is not cleared for use in the United States, is a multielectrode RFA catheter that uses a mesh electrode to deliver radiofrequency energy to multiple points of contact. Primary short-term results for MACPAF were reported by Koch et al in 2012. The study randomized symptomatic paroxysmal AF to catheter ablation with the Arctic Front cryoablation catheter (Medtronic) or the HD Mesh Ablator Catheter. The study’s primary end point was complete isolation of the pulmonary veins at the end of the procedure. Enrollment was initially planned for 108 patients with symptomatic paroxysmal AF inadequately controlled using antiarrhythmic drug treatment. However, at interim analysis, the HD Mesh Ablator demonstrated a lack of efficacy for the primary end point, and the study’s data safety monitoring board terminated the trial early. Forty-four patients with drug-resistant paroxysmal AF were randomized at the time the study was terminated and comprised the intention-to-treat analysis cohort. The per-protocol analysis cohort included 32 patients. Three patients withdrew before the catheter procedure; 9 additional patients were excluded from analysis due to use of a noncompliant catheter (n=2), identification of a trigger arrhythmia, which was subsequently ablated (n=1), failure of transseptal puncture (n=1), or ablation occurring after the interim analysis (n=5). For the primary end point, by intention-to-treat analysis (complete pulmonary vein isolation), was achieved in 13 (56.5%) of 23 patients in the cryoablation group compared with 2 (9.5%) of 21 patients in the mesh ablator group (p=0.001). In the per-protocol cryoablation group, 76.5% of subjects had complete pulmonary vein isolation. Major complications included 1 case of retroperitoneal hematoma in the cryoablation group and 1 case of pericardial tamponade requiring drainage in the mesh ablator group.

Malmborg et al reported results from an RCT comparing cryoablation with the Arctic Front cryoballoon catheter to RFA with the Pulmonary Vein Ablation Catheter. One hundred ten patients with paroxysmal or persistent AF were randomized, 54 to cryoablation and 56 to RFA. Complete pulmonary vein isolation was achieved in 98% of the cryoablation group compared with 93% of the RFA group (p=0.37). At 6-month follow-up, freedom from AF (absence of symptoms and no AF episodes on 7-day Holter monitoring or 12-lead electrocardiogram) without antiarrhythmic drug treatment was achieved in 52% of the cryoablation group and 38% of the RFA group (p=0.13).

Nonrandomized Studies
Case series of cryoablation published before the RCTs discussed above have reported success rates in the range of those reported for RFA. A prospective noncomparative interventional study reported in 2008 evaluated cryoablation in 346 patients; 74% of patients with paroxysmal AF, but only 42% of those with persistent AF, were free from AF at 12-month follow-up. One small analysis compared 20 patients undergoing cryoablation with 20 patients undergoing RFA, matched for age, sex, LVEF, and AF history. There were no significant differences between groups, including freedom from AF at 6 months, which was 55% in the cryoablation group and 45% in the RFA group.
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In the largest nonrandomized comparative study identified, Aryana et al compared ablation with a second-generation cryoballoon with RFA in a retrospective cohort of 1196 patients with paroxysmal and persistent AF. Of the overall study population, 76% had paroxysmal AF; 773 were treated with cryoablation and 423 with RFA. Procedural success and complication rates did not differ significantly between groups. For the study’s primary end point, freedom from AF or atrial flutter or tachycardia at 12 months following a single ablation procedure without the use of antiarrhythmic medications was significantly higher for cryoablation-treated patients (76.6% vs 60.4%, p<0.001).

In a large, 2014 nonrandomized study, Schmidt et al used data from a prospective German registry of catheter ablation procedures to compare RF with cryoablation for paroxysmal AF. The cohort included 905 patients who underwent cryoablation and 2870 patients who underwent RFA, all of whom were enrolled from January 2007 to August 2011. The 2 groups were generally similar, with the exception that patients who underwent RFA were significantly more likely to have had valve disease (8.1% vs 3.0%, p<0.001) and an ejection fraction of 40% or less (2.4% vs 1.2%, p<0.05). Rates of acute success were similar for the 2 groups (97.5% for cryoablation vs 97.6% for RFA, p=0.92), as were rates of major procedure-related adverse cardiac and cerebrovascular events (0.4% for cryoablation vs 0.2% for RFA, p=0.15). Overall procedural complication rates were similar (4.6% for each group, p=1.0); the rate of postprocedural phrenic nerve palsy was significantly higher for the cryoablation group (2.1% for cryoablation vs 0% for RFA, p=0.15).

In a subsequent study, Schmidt et al compared 1-year outcomes for patients treated with RFA or cryoablation in the German registry described above. This cohort included 2306 patients with symptomatic paroxysmal AF who underwent ablation from January 2007 to January 2010 (n=607 cryoablation; n=1699 RFA). The groups did not differ significantly in rates of reduction of symptomatic AF at 1 year (77.7% in RFA patients vs 79.5% in cryoablation patients; p=0.42). At 1 year, fewer cryoablation-treated patients were taking an antiarrhythmic drug (27.5% vs 32.1%, p<0.05). Rates of major clinical adverse events did not differ significantly between groups at 1 year, with the exception of phrenic nerve paralysis, which was more common in cryoablation patients (1.1% vs 0.3%, p<0.05).

Some studies have reported on comparisons between newer and older generations of devices, including 2 nonrandomized studies comparing cryoablation with a second generation device with RFA with a contact-force sensing catheter. One smaller nonrandomized study reported lower rates of atrial tachycardias after cryoablation than after RFA, but with greater magnitude of effect with cryoablation with a second generation device. 70 Another smaller nonrandomized study reported shorter procedure times with cryoablation than with RFA, with no significant differences in resolution of AF.

Several studies have also reported on methods to reduce the risk of phrenic nerve injury with cryoballoon ablation, including fluoroscopy of spontaneous breathing and recordings of diaphragmatic electromyograms.

**Longer Term Follow-Up**
Similar to RFA, the available RCTs for cryoablation report primarily on short-term outcomes. Longer term outcomes after cryoablation have been reported by several authors.
Vogt et al reported longer term follow-up for 605 patients who underwent cryoablation for symptomatic, paroxysmal or persistent AF. Follow-up data beyond 12 months were available for 451 patients (median follow-up, 30 months). Of those with follow-up available, 278 (61.6%) were free of AF recurrence with no need for repeat procedures after a 3-month blanking period. After 1, 2, and 3 repeat procedures, rates of freedom from AF were 74.9%, 76.2%, and 76.9%, respectively. Phrenic nerve palsy was the most common adverse event, occurring in 2% of patients, all of which resolved within 3 to 9 months. There were 2 periprocedural strokes, and 1 case each of periprocedural pericardial tamponade and pericardial effusion.

Smaller studies have reported longer term outcomes. Neumann et al reported 5-year outcomes after a single cryoablation procedure among 163 patients with symptomatic, drug-refractory paroxysmal AF. Fifty-three percent of subjects were free from recurrent AF, atrial tachycardia, or atrial flutter at 5 years of follow-up with no additional procedures (after a 3-month blanking period). Boho et al reported on follow-up to a median of 3 years after cryoablation for 205 patients with symptomatic paroxysmal or early persistent AF treated at a single institution. At the 6-, 12-, 24-, and 36-month follow-up, 88%, 71%, 49%, and 31% had no documented recurrence of AF. Davies et al reported AF recurrence rates (median follow up 56 months) for 200 patients with paroxysmal or persistent AF after cryoablation. During the follow up period, 46.7% and 35.6% of those with paroxysmal and persistent AF, respectively, had recurrence of symptomatic AF after a single procedure.

Section Summary
The evidence related to cryoablation for AF includes RCTs and numerous uncontrolled case series. The STOP AF trial, which compared cryoablation with antiarrhythmic medication therapy, reported that cryoablation is superior to medical management and that rates of freedom from arrhythmia at 1 year in the cryoablation group were in the range reported for RFA. Interpretation of the MACPAF trial is limited by early termination due to the unexpectedly low efficacy of the RFA method used. While the Malmborg study suggests that cryoablation is comparable with RFA, success in the RFA group was also unusually low. Two RCTs published subsequently found that cryoablation is noninferior to RFA for pulmonary vein isolation.

Other Ablation Procedures
Most of the currently available research on ablation procedures for pulmonary vein isolation focus on RFA or cryoablation. Other energy sources are under investigation. The CardioFocus Endoscopic Ablation System, which is under investigation in the United States, involves a visually-guided balloon that uses laser energy to ablate cardiac tissue. A 2015 RCT compared the visually guided laser balloon (VGLB) with RFA in patients with drug-refractory paroxysmal AF. Overall, 342 (170 VGLB, 172 RFA) underwent ablation, and 334 (167 VGLB, 167 RFA) were included in the primary efficacy end point analysis after 12 months of follow-up. The study’s primary efficacy end point was freedom from treatment failure, which included documented symptomatic AF, ablation-induced or unknown origin left atrial flutter or atrial tachycardia, failure to acute isolate all pulmonary veins, use of any antiarrhythmic drugs, or left heart ablation surgery or implantable cardioverter defibrillator placement for AF. In a prespecified noninferiority analysis, 61.1% of those in the VGLB group met the primary efficacy end point, compared with 61.7% of the RFA group (absolute difference, -0.6%; p=0.003 for noninferiority). Overall, rates of primary adverse events did not differ significantly between groups (14.1% in the VGLB group vs 15.7% in the RFA group, p=NS). However, VGLB group patients had a lower rate of pulmonary valve stenosis (0% for VGLB group vs 2.9% for RFA).
group, p=0.03), but a higher rate of diaphragmatic paralysis (3.5% for VGLB group vs 0.6% for RFA group, p=0.05).

Repeat Procedures
Repeated procedures for recurrent AF or atrial flutter were commonly performed in most of the clinical trials included in this policy statement. Of the 10 RCTs reviewed that compared RFA with medical management, only 223, did not include repeated procedures. In the other 5 studies, 1 or more repeated procedures were allowed, and success rates reported generally incorporated the results of up to 3 procedures. In 4 studies that reported these data, repeated procedures were performed in 8.2%, 9%, 20%, and 32% of patients randomized to ablation. In their RCT of catheter ablation of AF in patients with heart failure, Hunter et al report that repeat procedures were required in 65.4% of the catheter ablation group. Stabile et al did not report specifics on how many patients actually underwent repeated procedures, but limited data in the publication indicated that up to 30% of treated patients were eligible for repeated procedures. In the Jais et al study, patients underwent a mean of 1.8 procedures per patient and a median of 2 procedures per patient, indicating that approximately 50% of patients in the ablation group underwent at least 1 repeated procedure.

Because of this high rate of repeated procedures, the results reported in these studies do not reflect the success of a single procedure. Rather, they more accurately estimate the success of an ablation strategy that includes repeated procedures for recurrences that occur within the first year of treatment. Nonrandomized evidence suggests that early reablation increases the success of the procedure, when defined as maintenance of sinus rhythm at 1 year. There is variability in the protocol for when repeated procedures should be performed. There is also uncertainty concerning other details on repeated procedures, such as how soon after the initial procedure it should be done, the threshold of AF recurrence that should prompt a repeat, and whether medications should be tried prior to a repeated procedure.

Pokushalov et al reported results of an RCT comparing repeat catheter ablation with antiarrhythmic drug therapy for patients with paroxysmal AF who had failed an initial pulmonary vein isolation procedure. After an initial postablation blanking period, 154 patients with symptomatic AF recurrence were randomized to drug therapy (n=77) or repeat ablation (n=77). Patients were followed for 3 years with an implanted cardiac monitor. At the 3-year follow up, 58% (45/77) of the repeat ablation group were free from AF or atrial tachycardia on no antiarrhythmic drugs, compared with 12% (9/77) of the antiarrhythmic therapy group (p<0.01). In the antiarrhythmic drug group, 43 patients (56%) crossed over to receive repeat ablation; in the repeat ablation group, 21 patients (27%) required antiarrhythmic drug therapy. By intention-to-treat analysis, 65% (50/77) of the repeat ablation group and 45% (35/77) of the drug therapy group were free from AF or atrial tachycardia (p=0.02).

Complications
Individual clinical trials and case series report relatively low rates of complications, but may be limited in their ability to detect uncommon outcomes due to their small size. In 2013, Gupta et al reported results from a systematic review and meta-analysis of periprocedural complications following catheter ablation for AF. The authors included 192 studies that included at least 100 participants undergoing catheter ablation for symptomatic AF and that reported complications. The total sample size was 83,236 patients. The overall
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Acute complication rate was 2.9% (95% CI, 2.6 to 3.2), with significant heterogeneity across studies. The most common complications were vascular complications (1.4%), cardiac tamponade (1.0%), pericardial effusion (0.7%), stroke/transient ischemic attack (TIA) (0.6%), and pulmonary vein stenosis (0.5%).

In addition to the complication rates reported in available clinical trials and case series, there have been a number of database studies and postmarketing surveillance that report complications in larger numbers of patients than are in the clinical trials. A representative sample of these studies is discussed next, some of which were included in the Gupta et al review (Shah et al, Dagres et al).

Waldo et al. reported the results of an FDA-directed post-marketing safety study involving 1,275 patients from 6 prospective, multicenter studies of RFA ablation using an open-irrigated catheter. A total of 4.9% (63/1275) of patients experienced any acute serious complication within 7 days of the procedure. Vascular access complications were most common, ranging from 0.5% to 4.7% across the 6 studies. Exacerbations of heart failure occurred in 1.5% of patients, and 2 patients experienced cardiac tamponade. There were no strokes or TIsAs reported post-procedure.

Shah et al. used data from a California hospital database to evaluate complications in 4,156 patients who underwent catheter ablation for AF. Major complications occurred in 5.1% (211/4,156) of patients, with approximately half of these (2.6%, 110/4,156) consisting of hemorrhage or hematoma at the vascular entry site. The most common cardiac complication was cardiac perforation and/or tamponade, which occurred in 2.5% (104/4,156) of patients. Less common rates of serious adverse events included death (0.02%), stroke/TIA (0.31%), and pneumothorax/hemothorax (0.1%). Factors that were predictive of complications were female gender, older age, prior hospitalizations for AF, and less hospital experience with ablation.

In a study of Medicare beneficiaries, Ellis et al. identified 6,065 admissions from 168 hospitals in which RFA for AF was performed. The total rate of in-hospital complications was 9.1%, with vascular complications accounting for over half of the total complications at a rate of 5.7%. The mortality rate was 0.4%, and 0.6% of patients suffered a stroke or TIA. Perforation or tamponade occurred in 3.1% of patients and pneumothorax occurred in 0.4% of patients. The presence of chronic obstructive pulmonary disease (COPD) or unstable angina was associated with a higher risk of complications, while obesity and hyperlipidemia were associated with a lower risk. Age and hospital volume were not significant predictors of risk, but low hospital volume was a significant predictor of in-hospital death.

Complications of catheter ablation were reported in a large cohort of 1,000 patients undergoing ablation at a high-volume center in Europe. There were no deaths definitely attributable to the procedure, but there were 2 deaths of uncertain cause within the first 30 days following ablation. Overall, 3.9% of patients had a major complication resulting from the procedure. Tamponade was the most serious life-threatening complication, occurring in 1.3% of patients. Major vascular complications occurred in 1.1%. Thromboembolism, cerebrovascular accident/TIA, atrio-esophageal fistula, and endocarditis were all reported complications that occurred at a rate of less than 1%.

Cappato et al. performed a multicenter, retrospective case series to estimate the overall mortality rate following ablation. Data were collected on 32,569 patients from 162 clinical centers worldwide. There were
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32 deaths reported, for a mortality rate of 0.98 per 1,000 patients. The most common causes of death were tamponade (n = 8), stroke (n = 5), atrio-esophageal fistula (n = 5), and pneumonia (n = 2).

In the MACPAF study, 1 goal was to identify adverse events, particularly cerebral thromboembolism through the use of serial magnetic resonance imaging (MRIs) and neuropsychologic testing. While there is some evidence that RFA for patients with AF improves stroke risk, a clinically significant stroke or TIA attack occurs in 0.1% to 0.8% of patients undergoing catheter ablation, and several case series have demonstrated peridural brain lesions on diffusion weighted MRI imaging in up to 18% of patients undergoing catheter ablation of the left atrium. Thus, the MACPAF investigators evaluated patients pre-and postcatheter ablation with brain MRI at 3 Tesla and neuropsychologic testing. Short-term outcomes from these evaluations were reported by Haeusler et al in 2013 and demonstrated that new ischemic lesions occurred in 41% of all patients. However, these brain lesions were not associated with cognitive dysfunction immediately after procedure. Longer-term follow-up was reported by Herm et al in 2013. At follow-up MRI at 6 months after procedure, 31.3% of the acute brain lesions had formed a persistent glial scar. Similar to the short-term findings, there was no significant effect of either the ablation procedure or the presence of persistent brain lesions on attention or executive functions, short-term memory, or learning after 6 months.

Section Summary
Several large, database studies estimate the rate of adverse events from catheter ablation in the clinical care setting. The range of major adverse events in these studies is from 4% to 9%. Deaths have been reported and occur at rates less than 1%. Vascular complications at the groin site are the most common adverse events, occurring at rates of up to 5%. Serious cardiovascular adverse events such as tamponade and stroke occur uncommonly, at rates of approximately 1% or lower. There is some evidence that new ischemic lesions are commonly found on MRI after procedure, but the clinical significance of these defects is unclear.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this policy are listed in Table 1.

Table 1. Summary of Key Trials

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<th>NCT No.</th>
<th>Trial Name</th>
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<td>A Randomized Ablation-based Atrial Fibrillation Rhythm Control Versus Rate Control Trial in Patients With Heart Failure and High Burden Atrial Fibrillation</td>
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<td>Sep 2016</td>
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<td>NCT01687166</td>
<td>Clinical Evaluation of the Blazer Open-Irrigated Ablation Catheter for the Treatment of Paroxysmal Atrial Fibrillation (ZERO-AF)</td>
<td>552</td>
<td>Dec 2016</td>
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<td>NCT02274857</td>
<td>Randomized Evaluation of Atrial Fibrillation Treatment With Focal Impulse and Rotor Modulation Guided Procedures (REAFFIRM)</td>
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<td>NCT02150902</td>
<td>Augmented Wide Area Circumferential Catheter Ablation for</td>
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<table>
<thead>
<tr>
<th>NCI</th>
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<td>Evaluating the Efficacy of Circumferential Pulmonary Vein Ablation (CPVA) Versus Segmental Pulmonary Vein Isolation (SPVI) in Paroxysmal Atrial Fibrillation</td>
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<td>NCT00911508</td>
<td>Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial (CABANA)</td>
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<td>NCT01696136</td>
<td>Multi-electrode Pulmonary Vein Isolation Versus Single Tip Wide Area Catheter Ablation for PAF a Randomized Multinational Multicenter Trial (MYSTIC-PAF)</td>
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<td>NCT01278953</td>
<td>A Prospective, Randomized, Multicenter, Interventional Study to Evaluate the Safety and Effectiveness of the TactiCath Percutaneous Ablation Catheter for the Treatment of Symptomatic Paroxysmal Atrial Fibrillation Using Contact Force Assisted Radiofrequency Ablation</td>
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<td>NCT01490814</td>
<td>A Controlled, Prospective, Non-Inferiority, Parallel-Group, Randomised, Interventional, Open, Blinded Outcome Assessment (PROBE-Design), Multi-centre Trial, Comparing Efficacy and Safety of Isolation of the Pulmonary Veins With a Cryoballoon Catheter Versus a Radiofrequency Ablation With a ThermoCool Catheter in Patients With Paroxysmal Atrial Fibrillation</td>
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<td>Jan 2016 (completed)</td>
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<td>NCT01925885</td>
<td>Focal Impulse and Rotor Modulation Ablation Trial for Treatment of Paroxysmal Atrial Fibrillation (FIRMAT-PAF)</td>
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NCT: national clinical trial.
a Denotes industry-sponsored or cosponsored trial.

Clinical Input Received From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2011 Input

In response to requests, input was received from 2 physician specialty societies (3 reviewers) and 2 academic medical centers while this policy was under review in 2011.

While the input was mixed, there was general agreement with the policy statements. One reviewer commented that use of cryoablation may have a specific role when ablation targets are close to the AV node.

2015 Input

In response to requests, input was received from 3 physician specialty societies (6 reviewers) and 4 academic medical centers while this policy was under review in 2015. Input was focused on the use of ablation as an initial procedure for symptomatic paroxysmal and persistent AF and on the use of cryoablation for AF. There was consensus supporting the use of RFA as an initial treatment for symptomatic
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paroxysmal AF, and the use of cryoablation as an alternative to RFA as treatment for AF. For the use of RFA as initial treatment for symptomatic persistent AF, support from clinical input was more mixed.

Summary of Evidence
For individuals who have symptomatic paroxysmal or persistent AF who have failed antiarrhythmic drugs who receive RFA or cryoablation, the evidence includes multiple RCTs and systematic reviews. Relevant outcomes are overall survival, symptoms, morbid events, and quality of life. RCTs that compare RFA with antiarrhythmic medications have reported that freedom from AF is more likely after ablation than after medications. Results of long-term follow-up (5-6 years) after ablation has demonstrated that late recurrences continue to occur in patients who are free of AF at 1 year. However, most patients who are AF-free at 1 year remain AF-free at 5 to 6 years. Multiple RCTs comparing cryoablation and RFA have found that cryoablation is noninferior to RFA for AF control. RFA and cryoablation differ in adverse effect profiles; for example, cryoablation is associated with higher rates of phrenic nerve paralysis, but may allow a shorter procedure time. Given currently available data, it would be reasonable to consider both RFA and cryoablation effective for catheter ablation of AF foci or pulmonary vein isolation, provided that there is a discussion about the risks and benefits of each. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have symptomatic AF and congestive heart failure who have failed rate control and antiarrhythmic drugs who receive RFA or cryoablation, the evidence includes a TEC Assessment, supported by RCTs. Relevant outcomes are overall survival, symptoms, morbid events, and quality of life. Based on 1 available multicenter RCT, the TEC Assessment found that the evidence was sufficient to conclude that catheter ablation improves outcomes more than the alternative, AV nodal ablation and pacemaker insertion. Findings from this RCT have been supported by other comparative studies, which have reported improvements in AF. It is reasonable to consider both RFA and cryoablation effective for catheter ablation of AF foci or pulmonary vein isolation, provided that there is a discussion about the risks and benefits of each. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have recurrent symptomatic paroxysmal AF who receive RFA or cryoablation as an initial rhythm-control strategy, the evidence includes RCTs and systematic reviews. Relevant outcomes are overall survival, symptoms, morbid events, and quality of life. Two RCTs with low risk of bias compared catheter ablation for pulmonary vein isolation to antiarrhythmic medications. One RCT demonstrated reduced rates of AF recurrence, while the other reported reduced cumulative overall AF burden. Together, these results suggest that, when a rhythm-control strategy is desired, catheter ablation is a reasonable alternative to antiarrhythmic drug therapy. While the RCTs comparing ablation to medical therapy were conducted using RFA, it is reasonable to consider both RFA and cryoablation effective for catheter ablation of AF foci or pulmonary vein isolation, provided that there is a discussion about the risks and benefits of each. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.
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References

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90. Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Developed in partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society of Thoracic Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the Heart Rhythm Society. Heart Rhythm. Apr 2012;9(4):832-696 e621. PMID 22386883

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Policy History
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09/09/2010 Medical Policy Committee review
09/01/2011 Medical Policy Committee review
09/14/2011 Medical Policy Implementation Committee approval. Coverage statements edited for clarity, but no change in intent of coverage statements. Note added at the end of coverage section.
10/11/2012 Medical Policy Committee review
01/23/2013 Coding updated
10/03/2013 Medical Policy Committee review
10/16/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/04/2014 Medical Policy Committee review
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/08/2015 Medical Policy Committee review
10/21/2015 Medical Policy Implementation Committee approval. Added new policy statement for ablation as initial treatment for paroxysmal atrial fibrillation. Title change.
10/06/2016 Medical Policy Committee review
10/19/2016 Medical Policy Implementation Committee approval. The policy statement for the use of catheter ablation for initial treatment of atrial fibrillation was clarified to state that there should be greater than one episode of atrial fibrillation.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
Next Scheduled Review Date: 10/2017

Coding
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Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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<td>CPT</td>
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<tr>
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*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 TEC or other nonaffiliated TEC(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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A. In accordance with nationally accepted standards of medical practice;

B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient’s illness, injury or disease; and

C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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