Healthy Blue

Medical Policy

Subject:	Irreversible Electroporation		
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Description/Scope

This document addresses use of irreversible electroporation (IRE, also known as pulsed field ablation [PFA] or pulsed electric field [PEF] therapy). This document exclusively addresses all uses of IRE as a specific form of tissue ablation.

Note: For information related to other ablative techniques for cancer treatment or heart arrhythmias, please see:

- CG-SURG-61 Cryosurgical, Radiofrequency, Microwave or Laser Ablation to Treat Solid Tumors Outside the Liver
- CG-SURG-78 Locoregional Techniques for Treating Primary and Metastatic Liver Malignancies

Position Statement

Investigational and Not Medically Necessary:

Irreversible electroporation is considered **investigational and not medically necessary** for all indications, including, but not limited to, ablation of soft tissue or of solid organs, such as the liver and pancreas.

Rationale

Tumor Ablation

The published evidence addressing IRE to date has consisted of studies with limited methodologies and low power. One single-center, prospective, nonrandomized cohort study was performed to investigate the safety of IRE for tumor ablation in 38 humans with advanced malignancy of the liver, kidney, or lung (Thomson, 2011). Transient ventricular arrhythmia occurred in 4 participants, and electrocardiographically (ECG) synchronized delivery was used subsequently in the remaining 30 participants with occurrence of two further arrhythmias (supraventricular tachycardia and atrial fibrillation). One subject developed obstruction of the upper ureter after IRE. One adrenal gland was unintentionally directly electroporated, which produced transient severe hypertension. There was no other evidence of adjacent organ damage related to the electroporation. Only 30-day outcomes were reported. Although not a primary aim of this preliminary study, complete target tumor ablation verified by computed tomography (CT) was achieved in 46 of the 69 tumors treated with IRE (66%). Most treatment failures occurred in renal and lung tumors. Biopsy in 3 participants showed coagulative necrosis in the regions treated by IRE. The authors concluded, “IRE appears to be safe for human clinical use provided ECG-synchronized delivery is used. Comparative evaluation with alternative ablative technologies is warranted”.

Verloh (2019) reported the results of a retrospective study involving 164 participants with hepatocellular carcinoma treated with either thermal ablation via microwave or radiofrequency ablation (RFA) (n=117) vs. IRE (n=47). In the post-operative period, 17.9% of participants experienced post-ablation syndrome in thermal ablation group vs. 14.9% in the IRE group (p=0.607). No significant differences between groups were reported with regard to the occurrence or the severity of a complication (p=0.864). The primary efficacy endpoint, defined as the percentage of target tumors successfully eradicated by the 6-week follow-up, was 84.3% in the thermal ablation group and 67.2% in the IRE group (no p-value provided). The authors concluded that their results suggest that thermal ablation with microwave or RFA vs. IRE ablation have comparable complication rates. No long-term health outcomes data were provided and lack of statistical data regarding the primary outcome weaken the utility of this study. While the comparative nature of this trial is favorable, the retrospective nature, lack of randomization, lack of blinding and other methodological weaknesses prevents the generalization of these findings.

A prospective trial involving 74 participants with locally advanced pancreatic cancer (LAPC) treated with IRE was published by Yang (2020). A total of 69 procedures (93%) were performed by the laparotomic method, and the remainder were conducted by the laparoscopic approach. A total of 42 participants (57%) received a gemcitabine-based induction chemotherapy regimen, and the other 32 participants (43%) received an oral TS-1 regimen (tegafur, gimeracil, and oteracil). A total of 30 IRE-related complications were reported in 13 participants (17.6%), including 7 (23.3%) Clavien-Dindo Grade I, 14 (46.7%) Clavien-Dindo Grade II, and 9 (30%) Clavien-Dindo Grade III complications. In a multivariate analysis using Cox regression for adverse events, two significant predictors were identified, electrode placement direction (anteroposterior vs craniocaudal, HR [hazard ratio]: 4.194, $p<0.004$) and GI tract tumor involvement (with GI tract involvement vs. without GI tract involvement HR: 15.73, $p<0.002$). The median serum CA19-9 level was significantly decreased after induction chemotherapy ($p<0.001$) and 3 months after IRE ($p<0.001$). There were no cases of post-IRE mortality during the same admission period and 3 months after IRE. Nine (12.2%) participants developed local recurrence, and 30 participants (40.5%) developed distant metastasis. The progression free survival (PFS) rates in 1 year, 3 years, and 5 years were 69.1%, 48.7%, and 28.8%, respectively, and the overall survival (OS) rates in 1 year, 3 years, and 5 years were 97.2%, 53%, and 31.2%, respectively. The authors concluded, “This study showed that combined induction chemotherapy and surgical IRE for LAPC is safe. For well-selected patients, IRE can achieve encouraging survival outcomes”. However, a complication rate of 17.6% should not be overlooked. Entry into this trial was limited to individuals who had responded to initial induction chemotherapy. Results may not be applicable to other individuals. Further prospective, randomized investigation is warranted to understand the risks and benefits of this treatment.

A small prospective, single-arm, phase II clinical trial was conducted at two centers to evaluate the safety and effectiveness of IRE as a treatment for lung cancers which failed to meet primary and secondary endpoints. The expected effectiveness was not met at interim analysis, and the trial was stopped prematurely after inclusion of 23 participants (Ricke, 2015).

Meijerink (2021) reported the results of the prospective, phase-2, single-arm COLDFIRE-2 trial investigating the use of IRE in 51 individuals with colorectal cancer liver metastases 5.0 cm or smaller that were unsuitable for surgical resection or thermal ablation. Percutaneous IRE was conducted in 39 participants, 14 of whom underwent

concurrent thermal ablation. Open IRE was conducted in 12 participants, 1 of which underwent additional surgery, 3 of which underwent concurrent thermal ablation, and 6 underwent concurrent thermal ablation and surgery. Participants were followed for 12 months after the initial IRE. Retreatment with IRE was reported in 8 participants, 6 with local tumor progression of a previously IRE-treated tumor and 2 with new tumors. Cases with recurrence of disease were treated with repeat IRE (n=12), thermal ablation (n=3), stereotactic body radiation therapy (n=3), or selective internal radiation therapy (n=1). Concomitant treatment with systemic therapy for disease progression was reported in 25 participants during the follow-up period. Overall, 76 tumors were treated with IRE, including repeat treatment and new metastases. Adverse events were reported in 23 participants with a total of 34 total events, resulting in a 40% overall complication rate. Reported events included infection (n=5), pneumothorax (n=3), periprocedural cardiac arrythmia (n=4), portal vein thrombosis (n=3) and biliary obstruction (n=3). At 1 year, 34 of the 50 participants (68%) were alive without long term progression. The per-tumor 1-year long term progression free survival rate was 79%. Median distant progression free survival was 5.3 months (95% confidence interval [CI]: 2.5, 8.1). The most frequent site of first recurrence was the liver. Following repeat procedures, local tumor control was eventually achieved in 74% of participants. The authors reported that for long term progression, the hazard ratio (HR) after univariable analysis was 2.5 (p=0.03) for participants with an American Society of Anesthesiologists score greater than 2, and 3.6 (p=0.004) for primary rectal tumors. They concluded "Irreversible electroporation was effective and relatively safe for colorectal liver metastases 5.0 cm or smaller that were unsuitable for partial hepatectomy, thermal ablation, or further systemic treatment". However, these results are limited in the lack of control group and blinding, as well as the use of concurrent procedures with IRE. Additionally, the predefined threshold in the sample size calculation was chosen arbitrarily.

Freeman (2021) reported a comparative trial involving the use of IRE in 18 participants (25 tumors) vs. 81 propensity-matched participants (149 tumors) who underwent RFA for the treatment of hepatocellular carcinoma. In total, 190 ablations took place (n=31 IRE and n=159 RFA). All but 2 of the procedures were conducted by a single surgeon. Median follow-up time was 19.4 months in the IRE group vs. 13.2 months in the RFA group. At baseline, the RFA cohort had significantly worse liver function with regard to MELD scores (7 vs. 10, p<0.001) and Child Pugh Grade (88% vs 58.8% Grade A, p=0.02). Two (8%) of the IRE lesions and 4 (2.7%) of the RFA lesions required a second ablation in order to achieve complete remission (CR, p=0.18). After propensity score matching, a total of 121 lesions (25 IRE and 96 RFA) were analyzed for local recurrence free survival (LRFS), and rate was similar between groups (40% IRE lesions vs. 28% RFA lesions, p=0.25). No significant differences between groups were noted with regard to LRFS after adjusting for MELD scores using Cox regression (HR, 1.14; p=0.71). Similarly, no differences between groups were reported when lesion size was taken into consideration (< 3 cm, p=0.79 or < 2 cm, p=0.99). There were no major procedure-related complications or deaths in either group. Pain was reported in 36.8% of IRE participants. Acute kidney injury, transient urinary retention and a small subcapsular hematoma secondary to needle insertion sites each occurred in single participants. In the RFA group, pain was documented in 7.5% of participants and single cases each of transient urinary retention, lower respiratory tract infection and minor bleeding were managed conservatively. The retrospective nature of this trial, lack of blinding or controls, conduct in a single treating center, as well as the low number of IRE participants limit the generalizability of these findings.

Blazevski (2021) described the results of IRE treatment of 50 participants with distal apical prostate cancer followed for at least 1 year post treatment. All procedures were conducted by a single surgeon. Median follow-up was 44 months. Forty-three participants (86%) had intermediate-risk disease, 5 (10%) had low-risk disease and 2 (4%) had high-risk disease. With regard to adverse events, 10 participants (20%) experienced dysuria, urgency, hematuria, and perineal pain. Nine participants (18%) experienced complications including urinary tract infections, severe urgency/frequency or incontinence (Clavien–Dindo 2). Results of the Expanded Prostate Cancer Index Composite (EPIC) quality of life tool (QoL) were reported. The results indicated no statistically significant difference in urinary QoL at baseline and 12 months post-treatment (p=0.063). All participants were dry at baseline, and none required leak protection pads at 24 months after treatment. However, 2 participants (4%) required one pad at 3 months and only 1 (2%) required one pad at 12 months. No significant difference was observed in the bowel QoL domain between baseline and 12 months (p=0.066) and no rectal injuries or fistulae were reported. Results on the sexual QoL domain at baseline vs. 12 months indicated a significant decrease in sexual function, with 94% of participants retaining sufficient function to engage in sexual intercourse post-IRE (p=0.001). No significant differences were reported with regard to urinary incontinence (p=0.439), urinary leakage (p=0.642), and erections sufficient for intercourse (p=0.894) post-treatment when the investigators compared treatment in the anterior vs. posterior segments of the prostate. Median PSA at 12 months decreased by 71% to 1.7 ng/mL. In-field recurrence at 12 months was reported in only 1 subject (2.5%). Out-of-field recurrence occurred in 8 (20%) participants. Overall, 78% of participants were free of significant disease after initial IRE and in participants with greater than 3-year follow-up (n=40), the failure free survival at 3 years was 90%. The authors concluded that IRE for prostate cancer in the "distal apex appears safe and feasible with acceptable early QoL and oncologic outcomes." However, several methodological issues limit the generalizability of these findings, including the use of retrospective data, lack of a control group or blinding, and performance of all procedures by a single surgeon.

In 2022, Wang and colleagues reported the results of a single-group, nonrandomized trial of extended focal ablation of localized prostate cancer using high-frequency IRE (H-FIRE). A total of 109 individuals with low or intermediate risk of biochemical recurrence of localized and locally advanced prostate cancer received H-FIRE. The primary outcome measurement was clinically significant prostate cancer at 6 months following treatment. Among the 100 participants who underwent biopsy at 6 months, the prostate cancer rate was 6.0% (95% CI, 2.2%-12.6%; p<0.001), which was superior to the rate of 20% observed in historical controls treated with thermal energy methods. The rate of complications in the H-FIRE group was low and only 9.0% of the participants had emergent sexual dysfunction. The authors concluded that the results of this study were encouraging in terms of efficacy and minimal effect on functional outcomes. However, they acknowledge that the sample size was relatively small and that "a major limitation of the current study was the use of a historical control rather than including a parallel control group."

Miñana López and colleagues (2023) published results of a single-center, phase II study of focal therapy of prostate cancer using IRE. This was a small study of 41 individuals with a median follow-up of 36 months. Recurrence was observed in 16 of 41 (39%) of the cohort. Recurrence in the treatment field was detected in 5 (15%) and out-of-field in 11 (33.3%). Complications were few with all participants having preserved urinary continence; potency was maintained in 91.8%. The authors concluded that treatment with IRE could delay radical treatments of participants

on active surveillance, however the risk of recurrence over time is a concern. This study is limited by lack of blinding or controls, conduct in a single treating center, as well as the low number of participants.

A multicenter, randomized, single-blind, 2-arm intervention study was published evaluating the results of IRE using the NanoKnife system for the ablation of localized prostate cancer (de la Rosette, 2023; Zhang, 2023). A total of 106 individuals were randomized into two IRE treatment groups, one in which participants underwent focal IRE at the site of the tumor and one in which participants underwent extended ablation of a larger area surrounding the tumor. The focal ablation group had better International Index of Erectile Function scores at 3 months post IRE, but from 6 months onward there was no significant difference in sexual function between the 2 groups. At 6 months post-treatment, the rate of residual clinically significant prostate cancer based on biopsy results was 18.8% and 13.2% in the focal and extended IRE groups, respectively, although the difference was not significant. Limitations of this study include a small sample size such that the study might not be adequately powered to detect small differences between the 2 groups. Since all participants received IRE treatment, the study results do not allow a comparison of IRE to more established prostate cancer treatments. In addition, longer term follow-up of recurrence rates and oncologic results is needed.

In 2021, two meta-analyses were published addressing the use of IRE for the treatment of liver tumors. The report by Yu and colleagues included 26 studies (n=807 participants and n=1115 lesions) and indicated that the pooled data indicated a complete ablation rate of 86% and complication rate of 23%. Gupta and colleagues reported on 25 studies (n=776, 15 prospective, 10 retrospective) and concluded that the pooled data showed that overall survival at 6, 12, 24, and 36 months was 93.28%, 81.29%, 61.47%, and 40.88%, respectively. The pooled progression-free survival at 6, 12, and 24 months was 79.72%, 64.19%, and 49.05% respectively. The overall complication rate was reported to be 23.7%, with major complications occurring in 6.9% of participants. While these results are promising, the pooled results of poorly designed and conducted trials is still weak data, and investigation in the form of larger, well-designed and conducted trials is needed.

Additional case series studies of IRE use in locally advanced pancreatic adenocarcinoma (LAPC) and liver tumors have been published (Ansari, 2017; Bhutiani, 2016; Bujis, 2021; Distelmaier, 2017; Dollinger, 2015; Hosein, 2014; Kalra, 2019; Langan, 2017; Lyu, 2017; Mafeld, 2019; Niessen 2016 and 2017; Scheffer, 2017; Schicho, 2018; Stillström, 2019; Sutter, 2017; Tasu, 2017; Wah, 2021). While favorable results have been almost uniformly reported, the data from these studies is hampered by weak methodology and low power. Data from well-designed and conducted trials with long term follow-up is needed to fully assess the health outcomes resulting from IRE.

In 2022, Sugumar and colleagues published a systematic review and meta-analysis of multimodal therapy with or without IRE for unresectable LAPC. A total of 48 studies were included for IRE (n=27) and without IRE (n=21) with data for 1420 (IRE) and 1348 (without IRE) individuals. Most of the included studies of IRE had small sample sizes and lack of a comparative arm. IRE was found to be associated with similar survival outcomes compared to chemotherapy with or without radiotherapy. Nevertheless, nearly 75% of participants progressed and nearly half died within 1 year of the IRE procedure compared to 70% progression and 20% death in the chemotherapy group. The authors noted that “There exists a striking paucity in studies directly comparing outcomes between IRE and

standard of care CT [chemotherapy] in LAPC." Furthermore, they concluded that "Given the lack of quality prospective data, IRE should remain experimental and be used with caution in LAPC."

Other available publications addressing IRE include small retrospective chart reviews and prospective pilot studies addressing treatment of hepatocellular carcinoma and tumors of the pancreas, liver, and bile ducts (Belfiore, 2020; Cannon, 2013; Djokic, 2021; Franken, 2022; Guo, 2021; Hsiao, 2020; Kingham, 2012; Kwon, 2021; Lyons, 2021; Månsson, 2020; Martin, 2012 and 2018; Moir, 2014). Some of these studies have reported limited short-term improvements with high rates of adverse events and trends toward recurrence in larger tumors (over 4 cm) also noted.

The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology™ for pancreatic adenocarcinoma (NCCN, V2.2024) notes that "due to concerns about complications and technical expertise, the panel does not currently recommend IRE for treatment of locally advanced pancreatic cancer." Similarly, the NCCN guideline for hepatocellular carcinoma (V2.2024) states, "Recurrences have been reported following IRE for larger tumors. Larger studies are needed to determine the effectiveness of IRE for local HCC treatment."

The use of IRE in combination with chemotherapy, also referred to as electrochemotherapy (ECT), has been reported in several studies. One retrospective study (He, 2020) described the results in 132 participants with advanced pancreatic cancer treated with chemotherapy plus IRE (n=36) vs. chemotherapy alone (n=96). Due to significant differences between groups at baseline, 36 pairs of participants were obtained from the study population after propensity score matching (PSM) analysis. Participants who received chemotherapy combined with IRE treatment had significantly higher cumulative 1-year and 2-year OS rates than participants who received chemotherapy alone ($p<0.001$). After the PSM analysis the 1-year and 2-year OS rates were 89.8% and 77.2% in the chemotherapy plus IRE group, respectively, and 18.1% and 18.1% in the chemotherapy group, respectively ($p<0.001$). Median PFS was 7.1 months in the chemotherapy plus IRE group and 4.9 months in the chemotherapy group after the finish of induction therapy ($p<0.001$). Similar results were reported after PSM ($p<0.001$). Participants in the chemotherapy group were 4.45 times more likely to have decreased PFS than participants in the chemotherapy plus IRE group. Two cases with pancreatic fistula and one case of biliary fistula were observed in the IRE group, with no intra-abdominal hemorrhage in participants after IRE therapy. Larger, prospective, randomized trials are needed to confirm this study's results.

Edhemovic (2020) reported a prospective phase II study of ECT in 39 participants with 84 metachronous colorectal liver metastases. ECT was performed during open surgery using bleomycin administered intravenously and electrodes having fixed geometry (59 metastases) or variable geometry (25 metastases). The procedure was feasible and safe in all participants, with no immediate or delayed IRE-related adverse events reported. According to the mRECIST criteria, objective response rate (ORR) was 75% for the 84 treated metastases (23% partial response). The median follow-up was 330 days. The response per subject was 44.0% complete response (CR), 15.0% PR, 2.5% stable disease (SD), and 38.5% progressive disease (PD). In participants who had two or more metastases treated, a lower complete response rate per subject was observed (44.0%) due to the partial or lack of response of some metastases. The response of smaller metastases (up to 3 cm in diameter) was significantly better compared to the larger metastases (larger than 3 cm; $p<0.035$). No differences in response were noted in participants with

peripheral vs. centrally located tumors. Participants with a good response to IRE also had significantly slower progression locally or systemically ($p<0.0016$) than participants with progressive disease. These results are promising, but investigation in a larger, more generalizable population is needed.

In 2022, several systematic reviews were published analyzing the use of ECT for skin cancer. Bastrup and colleagues evaluated 55 clinical studies (n=3729 participants) investigating ECT with intravenous bleomycin for individuals with cutaneous malignancies. The mean ORR was 81.5% with the standard dose of bleomycin while studies using lower doses of bleomycin observed a similar ORR (85.5%), suggesting that a lower dose may not be inferior. Ferioli and colleagues performed a systematic review of the efficacy and toxicity of ECT in the setting of skin metastases from malignant melanoma (MM). Altogether, 18 studies with 529 individuals were included in the analysis. Most studies used bleomycin as the chemotherapy drug but 2 used cisplatin and 1 study used both drugs. The pooled ORR was 80.6% and 1-year OS was 67–86.2%. Similar results were obtained by Petrelli and colleagues who conducted a systematic review and meta-analysis of available literature (27 studies; 1161 individuals) to evaluate the use of ECT with bleomycin or cisplatin in MM. One-year OS rates were 67-89% compared to 67-86% in the Ferioli study. In general, these studies concluded that ECT for MM yields favorable oncologic outcomes. However, there was significant heterogeneity between the studies included in these analyses based on different drugs, with different doses and routes of administration (intravenous vs. intratumoral), and variations in tumor size. In addition, some of the studies included were retrospective. It was also concluded that given the promising results, further prospective randomized studies with larger cohorts of participants are warranted to be able to standardize the use of ECT in clinical practice.

Heart Arrhythmia

IRE has been investigated for pulmonary vein isolation in participants with atrial fibrillation (AF). One case series study involving 10 participants has been reported by Loh (2020). The authors of this methodologically weak study reported technical success with no reconnections or complications developing during the study period. Reddy and others (2018) reported on a larger case series involving 22 participants who underwent AF ablation with IRE. They reported successful pulmonary vein isolation in 57 pulmonary veins of 15 participants undergoing endocardial procedures (100%). In epicardial procedures, surgical box lesions were successful in 6 of 7 participants (86%). There were no catheter-related complications, including deployment failure, cardiac perforation, or catheter entrapment. Additionally, there were no instances of atrial or ventricular tachyarrhythmias, as well as no evidence of significant repolarization abnormalities. The authors noted that IRE for pulmonary vein ablation was promising, but long-term results and safety data is needed from larger well-designed trials.

This same group published another case series study involving 25 participants who underwent pulmonary vein isolation with IRE of the cavotricuspid isthmus with adjunctive ablation of the left atrial posterior wall. Successful ablation in all participants were reported, with post-procedure esophagogastroduodenoscopy and repeat cardiac computed tomography indicating no mucosal lesions or pulmonary vein narrowing. Invasive remapping demonstrated durable isolation (defined by entrance block) in 82 of 85 veins (96%) and 21 of 21 left atrial posterior wall (100%). The authors indicated that their study demonstrated good safety and feasibility of IRE for pulmonary vein isolation and ablation of the left atrial posterior wall, but they concluded that larger future trials will be

necessary to confirm their study's conclusions (Kawamura, 2021). The authors of a systematic review and meta-analysis of 26 studies (n=2561 participants) investigating the use of PFA for AF reached a similar conclusion (Qamar, 2024). PFA was viewed as a promising technique but "Further prospective randomized controlled trials are needed to compare its long-term efficacy and safety with conventional ablation techniques."

In 2021, Reddy and colleagues conducted a pooled analysis of three separate, nonrandomized, prospective studies (IMPULSE, PEFCAT, and PEFCAT II) that used PFA to treat AF. The total cohort was 121 individuals. The 1-year Kaplan-Meier estimate for freedom from any atrial arrhythmia was 78.5 ± 3.8%. Safety of the procedure was deemed to be acceptable with primary adverse events occurring in 2.5% of individuals. Limitations of this study include the nonrandomized nature, lack of a comparator group, and follow-up was only to 1 year.

Reddy and colleagues (2023) conducted a randomized, single-blind, noninferiority trial (ADVENT) to compare PFA with conventional radiofrequency or cryoballoon ablation in individuals with drug-refractory paroxysmal AF. A total of 305 individuals were assigned to undergo PFA and 302 were assigned to undergo thermal ablation. The primary efficacy endpoint was freedom from a composite of initial procedural failure, documented atrial tachyarrhythmia, antiarrhythmic drug use, cardioversion, or repeat ablation. At 1 year post-treatment, the primary endpoint was met in 204 participants in the PFA group (estimated probability, 73.3%) and 194 participants in the thermal ablation group (estimated probability, 71.3%). PFA met the criterion for noninferiority (but not superiority) compared to thermal ablation with a posterior probability of more than 0.999. However, the rationale for choosing the specified noninferiority margin (δ=0.15) was not clearly described. The authors acknowledged that the devices used to detect AF in the follow up period may not have detected all episodes of asymptomatic AF. In addition, follow-up was limited to 1 year, so durability of the procedure and longer-term outcomes are unknown.

A secondary analysis of data from the ADVENT trial was conducted by Reddy and colleagues (2024) to assess the effect of ablation modality on post ablation atrial arrhythmia (AA) burden. The primary endpoint of the ADVENT trial was 1-year freedom from AA recurrence lasting at least 30 seconds over 1-year follow-up; AA burden measures the percentage of AA over the total duration of monitoring by Holter or transtelephonic electrocardiogram. Compared with thermal ablation, there was less residual AA burden after PFA. However, this report shares the limitations of the earlier report, including possible missed detection of AF episodes and short (1-year) follow up duration. The authors noted that further studies are needed to understand the relationship between AA burden over time based on ablation treatment modalities and clinical outcomes.

Verma and colleagues (2023) published results from the PULSED AF study, a prospective, multicenter, single-arm before-and-after study in which individuals with paroxysmal (n=150) or persistent (n=150) symptomatic AF were treated with PFA. PFA was found to be effective at 1 year in 66.2% (95% CI, 57.9 to 73.2) of individuals with paroxysmal AF and 55.1% (95% CI, 46.7 to 62.7) of individuals with persistent AF. This study is limited by its single-arm design with no control group. Follow-up was limited to 1 year so durability of the outcomes could not be assessed.

Turagam and colleagues (2023) reported results from a large, multicenter, observational registry (MANIFEST-PF) of individuals who underwent PFA to treat AF. A total of 1568 individuals were treated. The 1-year Kaplan-Meier

estimate for freedom from atrial arrhythmia was 78.1% (95% CI, 76.0%–80.0%). The treatment was more clinically effective in individuals with paroxysmal AF versus persistent AF (81.6% versus 71.5%; p = 0.001). However, this study is limited by being a retrospective, observational, and nonrandomized study with no control group. Randomized controlled trials comparing PFA versus radiofrequency/cryoablation, and follow-up longer than 1 year are needed to demonstrate effective and durable outcomes.

A study of the safety of PFA in more than 17,000 individuals with AF was conducted by Ekanem and colleagues (2024). The safety profile was found to be favorable especially by avoiding much of the collateral damage seen with conventional thermal ablation such as esophageal complications. However, this study is limited by being retrospective and observational without prospectively defined safety outcomes. Clinical outcomes with respect to the effectiveness of PFA in reducing AF were not reported.

In 2024, Della Rocca and colleagues published a retrospective review of patient registries comparing PFA, cryoballoon, and radiofrequency for the treatment of paroxysmal AF. PFA contributed to shorter procedural times and arrhythmia freedom at 1 year was not significantly different among technologies. The authors concluded that "future randomized trials comparing the safety and efficacy of different ablation strategies are warranted."

Based upon the studies of Reddy (2023), Turagam (2023) and Verma (2023), the Heart Rhythm Society released a position statement on the use of PFA for the treatment of AF (2024). The HRS believes that PFA should be made available to individuals with AF based on the best clinical judgment of the treating physician. It is the position of the HRS that adoption of this technology could lead to improved cardiovascular outcomes and quality of life with reduced costs associated with recurrent hospitalizations and the need for additional procedures.

There is currently inadequate evidence in the published literature to support the safety and efficacy of IRE or to demonstrate how treatment with this technology will impact clinical outcomes for any condition or indication.

Background/Overview

IRE is a low energy, direct current, nonthermal ablative device system for use in performing minimally invasive procedures intended for the destruction of soft tissues. The procedure is done with the use of the NanoKnife Oncobionic System, which received initial clearance from the U.S. Food and Drug Administration (FDA) on November 21, 2006 as a tissue ablation system indicated for surgical ablation of soft tissue, including cardiac and smooth muscle (FDA, 2006). Subsequent FDA clearance clarified the indications, "For the surgical ablation of soft tissue" (FDA, 2008). The NanoKnife System is classified by the FDA as an electrosurgical cutting and coagulation device (FDA, 2011).

Use of the NanoKnife Oncobionic System involves the process of using brief and controlled high voltage electric pulses to open microscopic pores in a targeted area. By increasing the number, strength, and duration of electric pulses, electroporation can be made permanent or irreversible. It is purported by the manufacturer that IRE technology allows for extreme precision in targeting soft-tissue cells of interest while blood vessels and other sensitive structures in the area remain functional.

On January 21, 2011 the FDA Center for Devices and Radiological Health (CDRH) issued a warning letter to the manufacturer, AngioDynamics, Inc. regarding the NanoKnife Oncobionic System branding and labeling indications listed on the manufacturer's website. The FDA requested that the words, "treat," "treatment," and "therapy" be removed and replaced with the word "ablation" throughout the labeling for the device, since the FDA clearance is not for any specific disease or condition. The FDA also requested that a precise definition of "Irreversible Electroporation or IRE" be provided, since this term was not part of the initial FDA application (FDA, 2011). The information currently available on the FDA web site for the NanoKnife refers to IRE device as, "A low energy, direct current, non-thermal ablation device" (FDA, 2019).

Definitions

Electroporation: The process of using brief and controlled electric pulses to open microscopic pores in a targeted area. By increasing the number, strength, and duration of electric pulses, electroporation can be made permanent or irreversible (IRE). After IRE, the pores in the cells remain open permanently with resultant microscopic damage to cells.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:

CPT	
0600T	Ablation, irreversible electroporation; 1 or more tumors per organ, including imaging guidance, when performed, percutaneous
0601T	Ablation, irreversible electroporation; 1 or more tumors, including fluoroscopic and ultrasound guidance, when performed, open
93799	Unlisted cardiovascular service or procedure [when specified as pulsed field ablation (PFA) or IRE for pulmonary vein isolation]
ICD-10 Procedure	
02583ZF	Destruction of conduction mechanism using irreversible electroporation, percutaneous approach
0F500ZF-0F504ZF	Destruction of liver using irreversible electroporation [by approach; includes codes 0F500ZF, 0F503ZF, 0F504ZF]
0F510ZF-0F514ZF	Destruction of right lobe liver using irreversible electroporation [by approach; includes codes 0F510ZF, 0F513ZF, 0F514ZF]

0F520ZF-0F524ZF	Destruction of left lobe liver using irreversible electroporation [by approach; includes codes 0F520ZF, 0F523ZF, 0F524ZF]
0F5G0ZF-0F5G4ZF	Destruction of pancreas using irreversible electroporation [by approach; includes codes 0F5G0ZF, 0F5G3ZF, 0F5G4ZF]

ICD-10 Diagnosis

All diagnoses

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Peer Reviewed Publications:

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Government Agency, Medical Society, and Other Authoritative Publications:

1. Heart Rhythm Society. Position Statement: Pulsed-Field Ablation (PFA) for Treatment of Atrial Fibrillation. Available at: https://www.hrsonline.org/sites/default/files/2024-04/PositionStatement_PFA-for-AFib-Treatement_042424.pdf. Accessed on July 26, 2024.
2. NCCN Clinical Practice Guidelines in Oncology™. © 2024. National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on July 26, 2024.
   - Hepatocellular Carcinoma (V2.2024). Revised July 2, 2024.
   - Pancreatic Adenocarcinoma (V2.2024). Revised April 30, 2024.
3. U.S. Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH). Oncobionic System with six probe output (Oncobionic, Inc., Rancho Santa Margarita, CA). Summary of Safety and Effectiveness. No. K080376. April 2, 2008. Available at: http://www.accessdata.fda.gov/cdrh_docs/pdf8/K080376.pdf. Accessed on July 19, 2024.
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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	08/08/2024	Medical Policy & Technology Assessment Committee (MPTAC) review. Revised Rationale and References sections.
Reviewed	05/09/2024	MPTAC review. Revised Description, Rationale, References and Index sections.
	04/01/2024	Updated Coding section with 04/01/2024 ICD-10-PCS changes; added 02583ZF.
Reviewed	05/11/2023	MPTAC review. Updated Rationale and References sections.
Reviewed	05/12/2022	MPTAC review. Updated Rationale and References sections.
Reviewed	05/13/2021	MPTAC review. Updated Rationale, References, and Index sections. Updated Coding section; added 93799 NOC.
Reviewed	05/14/2020	MPTAC review. References section was updated. Updated Coding section with 07/01/2020 CPT changes; added 0600T, 0601T replacing NOC codes.
Reviewed	06/06/2019	MPTAC review. References section was updated.
Revised	07/26/2018	MPTAC review. The document header wording was updated from "Current Effective Date" to "Publish Date." The acronym (IRE) was removed from the title and position statement. The Rationale and References sections were

		updated. Updated Coding section with 10/01/2018 ICD-10-PCS changes, added procedure codes for liver and pancreas IRE.
Reviewed	08/03/2017	MPTAC review. The Rationale and References sections were updated.
Reviewed	08/04/2016	MPTAC review. The Rationale and References were updated. Removed ICD-9 codes from Coding section.
Reviewed	08/06/2015	MPTAC review. The Rationale and References were updated.
Reviewed	08/14/2014	MPTAC review. The Rationale and References sections were updated.
Reviewed	08/08/2013	MPTAC review. The Rationale, Background and References were updated.
Revised	08/09/2012	MPTAC review. The document was revised to make clear that all uses of IRE are addressed and considered investigational and not medically necessary. Document was retitled: Irreversible Electroporation (IRE). The Scope, Rationale and References were updated.
New	08/18/2011	MPTAC. Initial policy development.