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Irreversible Electroporation (IRE)

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Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

Irreversible electroporation **may be considered medically necessary** in the treatment of intrahepatic cholangiocarcinoma under the following circumstances:

- Tumor(s) is amenable to complete ablation so that the tumor and a margin of normal tissue up to 1 cm can be treated; and
- For small single tumors <3 cm, whether recurrent or primary, ablation is a reasonable alternative to surgical resection.

Irreversible electroporation, including use of the NanoKnife, **is considered experimental, investigational and/or unproven** for treatment of primary or metastatic solid tumors, including but not limited to, tumors of the liver, pancreas, kidney, and lung.

Policy Guidelines

None.

Description

Irreversible Electroporation
Electroporation generates high-frequency electric pulses between two or more electrodes which produces an electric current that damages the cell membrane and allows molecules to pass into the cell passively. Electroporation can be temporary (reversible electroporation) or permanent (irreversible electroporation or IRE). In IRE the cell membrane is permanently damaged causing cell death due to the inability to maintain homeostasis. IRE achieves its action with no thermal effect. IRE appears to preserve vessels, nerves and the extracellular matrix. (1-3)

Regulatory Status
The NanoKnife System™ (Angiodynamics) was originally cleared through the 510(k) process (K102329) in 2011 for the surgical ablation of soft tissue. In December 2024, the FDA approved the NanoKnife System to treat prostate cancer. FDA product code: OAB.

Rationale

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Liver Tumors
Clinical Context and Therapy Purpose
The American Cancer Society estimates that there will be over 41,000 new cases of liver and intrahepatic bile duct cancer in 2024. Liver and intrahepatic-bile duct cancer death is the 5th most common cancer related death in males and the 7th most common in females.

(4) Approximately 75% of primary liver tumors are hepatocellular carcinoma (HCC) and the remaining cases are mostly cholangiocarcinoma (CCA). HCC is a primary liver malignant tumor that typically develops in the setting of chronic liver disease. (5) The prognosis following diagnosis depends on several factors including tumor mass and hepatic reserve.

Treatment options for HCC are categorized as potentially curative surgical therapies (i.e., resection and liver transplantation) and nonsurgical therapies (liver-directed or systemic). The best long-term survival is observed after curative surgical therapies but many patients are not eligible because of tumor extent or underlying liver dysfunction. National Comprehensive Cancer Network (NCCN) guidelines for treatment of HCC state that all patients with HCC should be evaluated for potential curative therapies. For most patients with liver-isolated HCC who are not candidates for resection or transplant, liver-directed, locoregional therapies, such as ablation, are preferable to systemic therapy. Ablative strategies are potentially curative for small lesions (≤3 cm). IRE is thought to have some advantages over thermal methods of ablation, for example, the lack of "heat sink" effect from radiofrequency ablation (RFA) and the ability to treat tumors near vessels, bile ducts, and other critical structures. (6)

Similarly for treatment of intrahepatic CCA, NCCN guidelines state that patients with intrahepatic CCA should be evaluated for potentially curative therapies (i.e., resection, ablation for lesions <3 cm). The guidelines also state that locoregional treatment such as ablation may be considered in patients who are not candidates for resection or to downstage for other treatments. (7)

The following PICO was used to select literature to inform this policy.

Populations
The main risk factor for HCC in the US is non-alcoholic fatty liver disease, followed by alcoholic liver disease, and hepatitis C virus and hepatitis B virus infections. (8) HCC is diagnosed more frequently in men than women. Asia-Pacific Islanders have higher rates of HCC compared with other racial and ethnic groups in the US. (9) Mortality rates are higher for Native American people. (4)

The relevant population(s) of interest are patients being treated with locoregional therapy for hepatocellular carcinoma (HCC) or intrahepatic cholangiocarcinoma (CCA). These patients are generally nonsurgical candidates with one or a few small localized HCC or intrahepatic CCA or those for whom local ablation is being used to downstage in preparation for other treatments. Ablative strategies may be used as a curative treatment for small lesions (≤3 cm).

IRE has also been used in patients with hepatic metastases.

Interventions
The therapy being considered is irreversible electroporation (IRE). The NanoKnife System is an IRE system cleared in the US for the surgical ablation of soft tissue and prostate tissue ablation.

The NanoKnife System is a software-controlled low-energy direct-current generator that includes single electrode probes and an optional probe spacer. Voltage is applied between pairs of probes in a series of pulses with adjustable waveform. (10)

The IRE procedure is performed under computed tomography guidance and electrocardiography synchronization due to the possibility of muscular spasms caused by high-voltage pulses. (11) IRE is performed under general anesthesia, either percutaneously or open. The physician places 2 to 6 electrodes to bracket the targeted tissue and then applies the series of electrical pulses. (12)

Comparators
NCCN states that the following ablation techniques are used for locoregional therapy in HCC: microwave/radiofrequency, surgical, or percutaneous ethanol injection. For patients who are candidates for locoregional therapy but cannot receive thermal ablation, arterial embolization and radiotherapy (including Stereotactic Body Radiation Therapy [SBRT]) are options. (6)

NCCN states that the following ablation techniques are used for locoregional therapy in intrahepatic CCA: cryoablation, radiofrequency ablation, microwave ablation. For patients who are candidates for locoregional therapy but cannot receive thermal ablation, arterial embolization and radiotherapy are options. (7)

Outcomes
Overall survival, disease-free survival, and recurrence, quality of life, complications and adverse events are outcomes of interest. IRE can cause cardiac arrhythmias and uncontrolled muscle contractions.

Median survival for HCC depends on etiology but is generally less than 1 year. (13) Median survival for intrahepatic CCA is generally less than 2 years. (14) Therefore trials with outcomes of 1 to 2 years of follow-up are preferred.

There is no consensus as to the optimal approach for or length of post-treatment surveillance in patients undergoing locoregional therapy for HCC.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Wade et al. (2023) reported results of a systematic review and meta-analysis of ablative and non-surgical therapies for early and very early HCC commissioned by the National Institute for Health Care Research in the U.K. (15) The objective was to review and compare the effectiveness of all current ablative and non-surgical therapies for patients with small HCC (≤ 3 cm). The authors included 37 RCTs (n>3700) comparing ablative and non-surgical therapies to any comparator in the network meta-analysis. The authors identified only 1 non-randomized, comparative study (Sugimoto et al) of IRE; the study compared IRE with RFA (n = 21 patients). The Sugimoto study was rated as having a high risk of bias using the Cochrane tool and is reviewed in the following section.

Randomized Controlled Trials

No RCTs were identified.

Nonrandomized Studies

The majority of studies of IRE for liver cancer have not included a comparator and have included samples sizes smaller than 50. (16-24)

Cannon et al. (2013) reported results of the largest single-arm study (n=44) which was from a prospective registry of patients undergoing IRE for hepatic tumors. (17) The patients had colorectal metastasis (n=20), HCC (n=14), and other metastatsis (n=10). 5 patients (11%) had 9 adverse events but all complications resolved within 30 days. Local recurrence free survival at 3, 6, and 12 months was 97%, 95%, and 60%, respectively.

Two comparative studies were identified. Sugimoto et al (2019) reported results of a prospective study in 21 patients with HCC comparing RFA (n = 11) to IRE (n = 10). However, they reported only physiological outcomes; no health outcomes were reported. (25)

Blaise et al. (2021) reported results of a retrospective comparative study including patients with HCC and tumor portal invasion treated by percutaneous ablation (n = 44) from one center compared to a control group drawn from an external RCT including patients treated with sorafenib or trans-arterial radioembolization. (26) The percutaneous ablation group included 26 patients treated by multi-bipolar radiofrequency ablation (MBP-RFA) alone, 15 by IRE alone and 3 by both MBP-RFA and IRE. 41 patients treated by percutaneous ablation (MBP-RFA or IRE) were matched using propensity-score matching with 41 patients either from TARE or sorafenib groups from an external RCT. Median overall survival was 16 months (95% CI, 13 to 24) in the ablation group versus 14 months (95% CI, 9 to 24) in the control group. Median progression-free survival was 7 months (95% CI, 3 to 10) in the ablation group versus 4 months (95% CI, 3 to 6) in the control group. (26)

Section Summary: Liver Tumors

Studies of IRE for liver tumors are primarily single-arm. One comparative study was identified reporting health outcomes but the study is retrospective and included 18 patients treated with

IRE. Therefore, there is insufficient data to determine how survival or adverse events compare to other methods for locoregional therapy. There are no studies reporting functional or quality of life outcomes. There is a lack of standardization on appropriate use. A protocol for patient selection, procedural parameters, perioperative care, and follow-up of IRE for the treatment of liver tumors has been proposed (27) but has not been tested.

Pancreatic Tumors

Clinical Context and Therapy Purpose

Pancreatic ductal adenocarcinoma has a poor prognosis. The American Cancer Society estimates that in 2024, there will be over 66,000 new cases of pancreatic cancer in the US and over 51,000 pancreatic cancer deaths. Pancreatic cancer is the third-leading cause of cancer death in men and women. (4)

Surgical resection is considered the only curative therapy although the majority of cases of pancreatic cancer are unresectable. Locally advanced pancreatic cancer accounts for 30% of newly diagnosed cases of pancreatic cancer and is usually unresectable due to local involvement of adjacent vessels. The 5-year overall survival rate is <5% for locally advanced, unresectable disease. (28)

The NCCN recommended treatment for patients with locally advanced pancreatic adenocarcinoma includes systemic therapy with FOLFIRINOX-based or gemcitabine-based therapy, potentially with radiation therapy, with the goal of shrinking the tumor enough for surgical resection. People who are unable to undergo surgery may continue systemic therapy. Depending on the kind of cancer and the genetic makeup some people may be candidates for immunotherapy or poly adenosine diphosphate-ribose polymerase (PARP) inhibitors. (29) Thermal (radiofrequency and microwave) ablation therapies are not commonly used due to the increased risk of trauma to the adjacent major anatomical structures. Irreversible electroporation (IRE) is being considered as an adjunct to systemic therapy because it may not cause thermal injury to nearby sensitive structures such as the superior mesenteric and portal veins, superior mesenteric and celiac arteries, bile duct adjacent nerves, or gastrointestinal structures.

The following PICO was used to select literature to inform this policy.

Populations

Risk factors for developing pancreatic cancer include: cigarette smoking, obesity, alcohol use, diabetes, pancreatitis and hereditary factors. (30)

The relevant population(s) of interest are patients with locally advanced pancreatic cancer.

Interventions

The therapy being considered is irreversible electroporation (IRE). The NanoKnife System is an IRE system cleared in the US for the surgical ablation of soft tissue and prostate tissue ablation.

The NanoKnife System is a software-controlled low-energy direct-current generator that includes single electrode probes and an optional probe spacer. Voltage is applied between pairs of probes in a series of pulses with adjustable waveform. (10)

The IRE procedure is performed under computed tomography guidance and electrocardiography synchronization due to the possibility of muscular spasms caused by high-voltage pulses. (11) IRE is performed under general anesthesia, either percutaneously or open. The physician places 2 to 6 electrodes to bracket the targeted tissue and then applies the series of electrical pulses. (12)

Comparators
The NCCN recommended treatment for patients with locally advanced pancreatic adenocarcinoma includes systemic therapy, potentially with radiation therapy, with the goal of shrinking the tumor enough for surgical resection. (29) Local ablation treatment is not currently recommended in NCCN guidelines and not commonly used due to concerns regarding the increased risk of thermal injury to the adjacent structures. The role of ablation treatments in addition to systemic therapy is unclear. However, local ablation with radiofrequency ablation (RFA) and microwave ablation (MWA) has been considered for some patients with persistent locally advanced disease after systemic therapy as a strategy to downstage.

Outcomes
Overall survival, disease-free survival, and recurrence, quality of life, complications and adverse events are outcomes of interest. IRE can cause cardiac arrhythmias and uncontrolled muscle contractions.

Locally advanced pancreatic Stage 3 cancer has a median survival of less 1 year. (31) Studies with at least one year follow-up are preferred.

The American Society of Clinical Oncology (ASCO) published recommendations from a meeting of a working group on outcomes in clinical trials of treatments for pancreatic cancer. The group concluded that a 3- to 4-month improvement in overall survival in gemcitabine-eligible and gemcitabine/albumin-bound paclitaxel-eligible patients and a 4- to 5-month improvement in overall survival for FOLFIRINOX-eligible patients was clinically meaningful. (32)

<u>Study Selection Criteria</u>
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.

- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Charallambous et al. (2020) reported results of a systematic review of 9 studies of IRE in 460 patients with with locally advanced pancreatic cancer published between 2000 and 2019. (33) 4 of the studies were prospective and 5 were retrospective. None of the studies were comparative. Sample sizes ranged from 10 to 152. Follow-up duration ranged from 3 to 29 months. Adverse events were reported were reported with varying methods across the studies. Intraoperative adverse events were described but rates were not given; hypertensive episodes, hypotensive episodes, and transient supraventricular tachycardia were noted in the studies. The rate of complications ranged from 14% to 53% across the studies but with varying definitions. IRE-related mortality was reported in 5 patients. (33)

Randomized Controlled Trials

No published RCTs were identified. The DIRECT RCT (NCT03899636; n=528) is registered on clinicaltrials.gov with a completion date of December 2023 but results have not been published. The DIRECT trial is a multicenter trial in the US designed to compare chemotherapy alone to chemotherapy followed by IRE in patients with stage III pancreatic cancer. In the United Kingdom, the Treatment of unresectable Locally Advanced Pancreas cancer with Percutaneous Irreversible Electroporation following initial systemic chemotherapy (LAP-PIE; ISRCTN14986389) is also designed to compare chemotherapy alone to chemotherapy plus IRE and scheduled to be completed in November 2025.

Nonrandomized Studies

The published studies for IRE in pancreatic cancer are single-arm. (34-44)

Holland et al. (2019) reported results of the largest prospective, multicenter study including 152 patients with locally advanced pancreatic cancer treated with IRE from 2015 to 2017 from the American Hepato-Pancreato-Biliary Association (AHPBA) Pancreatic Registry. (45) The registry had a standardized protocol for settings and delivery of energy during the IRE procedure. The median follow-up was 19 months following diagnosis. The overall adverse event rate was 18% and mortality was 2%. 19 (13%) patients experienced severe adverse events. Nine (6%) patients experienced local recurrence. Median time to progression, progression free survival, and overall survival from diagnosis were 27 months, 23 months, and 31 months, respectively. (45)

Raurus et al. (2020) reported results of the phase 2, prospective, single-arm study conducted in the Netherlands between 2012 and 2017 called the Percutaneous Irreversible Electroporation in Locally Advanced and Recurrent Pancreatic Cancer (PANFIRE-2; NCT01939665). (38) PANFIRE-2 consecutively enrolled 50 study participants: 40 with locally advanced pancreatic cancer and 10 with isolated local recurrence after pancreatic tumor resection. Participants were adults with a maximum tumor diameter of 5 cm. Individuals with ventricular cardiac arrhythmias, an implanted stimulation device, or compromised liver function were excluded. The median hospital stay was 4 days (range, 2 to 21 days). The median largest tumor diameter was 4.0 cm (IQR, 3.7 to 4.6 cm). 14 minor and 21 major adverse events occurred in 29 participants (58%

overall complication rate). Most minor adverse events involved gastrointestinal symptoms. Serious adverse events included biliary obstruction (n = 4; 11%), cholangitis and/or pancreatitis (n = 5; 14%) or pancreatic fistula (n = 1; 3%), severe hematemesis due to bleeding from a duodenal ulcer (n = 1; 3%), duodenal perforation (n = 1; 3%), high-grade stenosis of the superior mesenteric artery (n = 2; 6%), gastroparesis (n = 3; 9%), and chyle leakage (n = 1; 3%). 2 participants died less than 90 days after IRE. The median overall survival for participants with locally advanced pancreatic cancer was 17 months from the time of diagnosis (95% CI, 15 to 19) and 10 months from IRE (95% CI, 8 to 11). Median local tumor progression-free survival was 10 months (95% CI, 8 to 11). (38)

Section Summary: Pancreatic Tumors

There is a lack of consensus on the optimal IRE treatment protocol. (46) Studies of IRE for pancreatic tumors are single-arm. There is insufficient data to determine whether survival is improved with chemotherapy followed by IRE compared to chemotherapy alone; RCTs are underway. Prospective, single arm studies suggest a high complication rate. There are no studies reporting functional or quality of life outcomes.

Kidney Tumors

Clinical Context and Therapy Purpose

The American Cancer Society estimates that there will be over 81,000 new cases of kidney cancer and over 14,000 kidney cancer related deaths in 2024. (4) At diagnosis, approximately 65% of disease is localized disease. (47) Surgery is curative for most patients with localized kidney cancer and is therefore the preferred treatment. NCCN guidelines for kidney cancer recommend partial or radical nephrectomy for T1 kidney cancer, or ablation or active surveillance in select patients. The guidelines say that thermal ablation is an option for the management of clinical stage T1 renal lesion that are ≤3 cm and is an option for clinical T1b masses in select patients who not eligible for surgery. However, the guidelines caution that randomized phase III trials of ablative techniques with surgical resection have not been performed. (48)

The following PICO was used to select literature to inform this policy.

Populations

Kidney cancer is approximately two-fold more common in males compared to females. Mortality rates are two-fold higher for kidney cancers in Native American people compared to White people.[4,] There are many risk factors for kidney cancer such as smoking, hypertension, obesity, chronic kidney disease, exposure to analgesics, chemotherapy and certain toxic compounds, and kidney stones. (49-55)

The relevant population(s) of interest are patients being treated with local ablation for renal cell carcinoma. These are generally patients with T1a lesions that are ≤3 cm or T1b lesions that are not eligible for surgery.

Interventions

The therapy being considered is irreversible electroporation. The NanoKnife System is an IRE system cleared in the US for the surgical ablation of soft tissue and prostate tissue ablation.

The NanoKnife System is a software-controlled low-energy direct-current generator that includes single electrode probes and an optional probe spacer. Voltage is applied between pairs of probes in a series of pulses with adjustable waveform. (10)

The IRE procedure is performed under computed tomography guidance and electrocardiography synchronization due to the possibility of muscular spasms caused by high-voltage pulses. (11) IRE is performed under general anesthesia, either percutaneously or open. The physician places 2 to 6 electrodes to bracket the targeted tissue and then applies the series of electrical pulses. (12)

Comparators
Ablative procedures (e.g., cryosurgery, radiofrequency ablation, microwave ablation) may be an alternative to resection for patients with small renal masses or who are not surgical candidates. NCCN guidance also states that active surveillance is an option for certain patients with small renal masses (<3 cm), T1a tumors (≤ 4cm), and competing comorbidities, (48)

Outcomes
Overall survival, disease-free survival, and recurrence, quality of life, complications and adverse events are outcomes of interest. IRE can cause cardiac arrhythmias and uncontrolled muscle contractions.

The incidence of renal cell carcinoma recurrence after nephrectomy has been reported to be about 7% with a median time to recurrence of 38 months for T1 tumors. The greatest risk of recurrence after nephrectomy is within the first 5 years. (56) Therefore, studies should include follow-up of 3 to 5 years.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews
Hilton et al. (2022) reported results of a systematic review of e safety and early oncological outcomes of 10 studies (n=83) of IRE for small renal masses. (57) The review included studies

published through 2020. One cohort study (Canvasser 2017, described below) included 41 participants with renal cell carcinoma. The remaining studies were case series including 10 or fewer participants with renal masses. Follow-up was less than 12 months in 7 of the studies (range, 3 to 34 months). The most frequently reported adverse events were transient hematuria and asymptomatic perirenal hematomas. (57)

Randomized Controlled Trials

No published RCTs were identified.

Nonrandomized Studies

The studies of IRE for renal cell cancer are single-arm and the majority have included 10 or fewer participants. (58-67)

Canvasser et al. (2017) reported results of the largest study of IRE for renal masses, including 41 participants with cT1a renal masses treated with IRE in the US between 2013 and 2016. (59) The study was prospective and single center. Mean follow-up was 22 months. No grade II or higher intraoperative or post-operative complications were reported. 2-year local recurrence-free survival was 92%.

Section Summary: Kidney Tumors

Studies of IRE for kidney tumors are single-arm. Only one study has included more than 10 participants. No comparative data are available. Therefore, there is no data to determine how survival or adverse events compare to other methods for locoregional therapy. There are no studies reporting functional or quality of life outcomes.

Lung Tumors

Clinical Context and Therapy Purpose

The American Cancer Society estimates that there will be over 234,000 new cases of lung cancer and over 125,000 lung cancer deaths in 2024. Lung cancer is the second most commonly diagnosed cancer and the leading cause of cancer death in both men and women. (4)

The standard for treatment of stage I non–small cell lung cancer (NSCLC) in operable patients is surgical resection with lobectomy and systematic lymph node evaluation. However, a significant number of patients with stage I lung cancer are considered medically inoperable or high-risk surgical candidates. NCCN guidelines state that local ablative therapy with image-guided thermal ablation includes radiofrequency ablation, microwave ablation, and cryoablation, and may be considered for those patients who are deemed “high risk” (medically inoperable due to comorbidities) and is an option for the management of NSCLC lesions <3 cm. The guidelines also state that in the setting of progression at a limited number of site (oligoprogression), local ablative therapy may extend the duration of benefit of the current line of systemic therapy. (68)

The following PICO was used to select literature to inform this policy.

Populations
Cigarette smoking is the number one risk factor for lung cancer, accounting for 80% to 90% of lung cancer deaths in the US. Other risk factors include radon exposure and radiation therapy to the chest. (69) Black men are approximately 12% more likely to develop lung cancer than White men and Black women are approximately 16% less likely to develop lung cancer than in White women. Women have historically had a lower risk than men, but the gap is closing. (4) The relevant population(s) of interest are patients being treated with local ablation for lung cancer. These patients are generally nonsurgical candidates or those with lesions <3 cm.

Interventions
The therapy being considered is irreversible electroporation. The NanoKnife System is an IRE system cleared in the US for the surgical ablation of soft tissue and prostate tissue ablation.

The NanoKnife System is a software-controlled low-energy direct-current generator that includes single electrode probes and an optional probe spacer. Voltage is applied between pairs of probes in a series of pulses with adjustable waveform. (10)

The IRE procedure is performed under computed tomography guidance and electrocardiography synchronization due to the possibility of muscular spasms caused by high-voltage pulses. (11) IRE is performed under general anesthesia, either percutaneously or open. The physician places 2 to 6 electrodes to bracket the targeted tissue and then applies the series of electrical pulses. (12)

Comparators
NCCN guidelines state that local ablative therapy with image-guided thermal ablation includes radiofrequency ablation, microwave ablation, and cryoablation. (68)

Outcomes
Overall survival, disease-free survival, and recurrence, quality of life, complications and adverse events are outcomes of interest. IRE can cause cardiac arrhythmias and uncontrolled muscle contractions.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials
No published RCTs were identified.

Nonrandomized Studies
Two nonrandomized, prospective, single-arm studies have been published. (61, 70) Thomson et al. (2011) includes a mix of tumor types in 38 participants including lung.

Ricke et al. (2015) reported results of the ALICE single-arm, multicenter (2) trial. (70) The ALICE study was designed to enroll 36 participants with primary and secondary lung malignancies and preserved lung function. However, the study was stopped early (n=23) because the expected efficacy was not met at an interim analysis. Median follow-up was 12 months. 61% (14/23) of participants developed progressive disease. 4% (1/23) of participants had stable disease, 4 (1/23) had partial remission and 30% (7/23) had complete remission. Pneumothoraces occurred in 48% (11/23) of participants with chest tubes required in 8. (70)

Section Summary: Lung Tumors
Studies of IRE for lung tumors are single-arm. The ALICE study was a prospective, single-arm study conducted at two centers that was stopped early (n=23) due to failing to meet expected efficacy at an interim analysis based on high recurrence rates of 61% at a median follow-up of 1 year. No comparative data are available. Therefore, there is no data to determine how survival or adverse events compare to other methods for locoregional therapy. There are no studies reporting functional or quality of life outcomes.

Summary of Evidence
For individuals being treated with locoregional therapy for tumors in the liver who receive irreversible electroporation, the evidence includes primarily single-arm studies. Relevant outcomes are overall survival, disease-specific survival, symptoms, morbid events, functional outcomes, quality of life. Irreversible electroporation may be an option for locoregional therapy that is less damaging to nearby blood vessels, bile ducts, and nerves than thermal ablation therapies. Most studies of IRE for liver tumors lack a comparator arm. One comparative study was identified reporting health outcomes but the study is retrospective and included 18 patients treated with IRE. Therefore, there is insufficient data to determine how survival or adverse events compare to other methods for locoregional therapy. There is a lack of standardization on appropriate use. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with locally advanced pancreatic cancer who receive irreversible electroporation, the evidence includes single-arm studies. Relevant outcomes are overall survival, disease-specific survival, symptoms, morbid events, functional outcomes, quality of life. Thermal ablation therapies are not commonly used to treat pancreatic cancer due to the increased risk of trauma to the adjacent major anatomical structures. IRE may be alternative that does not cause thermal injury to nearby sensitive structures. However, there is a lack of consensus on the optimal IRE treatment protocol. Studies of IRE for pancreatic tumors are single-arm. There is insufficient data to determine whether survival is improved with

chemotherapy followed by IRE compared to chemotherapy alone. 2 RCTs are underway. Prospective, single arm studies suggest a high complication rate. There are no studies reporting functional or quality of life outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals being treated with locoregional therapy for tumors in the kidneys who receive irreversible electroporation, the evidence includes single-arm studies. Relevant outcomes are overall survival, disease-specific survival, symptoms, morbid events, functional outcomes, quality of life. Studies of IRE for kidney tumors are single-arm. Only one study has included more than 10 participants. No comparative data are available. Therefore, there is no data to determine how survival or adverse events compare to other methods for locoregional therapy. There are no studies reporting functional or quality of life outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals being treated with locoregional therapy for tumors in the lungs who receive irreversible electroporation, the evidence includes single-arm studies. Relevant outcomes are overall survival, disease-specific survival, symptoms, morbid events, functional outcomes, quality of life. Irreversible electroporation may be an option for locoregional therapy that is less damaging to nearby bronchovascular structures. Studies of IRE for lung tumors are single-arm. The ALICE study was a prospective, single-arm study conducted at two centers that was stopped early (n=23) due to failing to meet expected efficacy at an interim analysis based on high recurrence rates of 61% at a median follow-up of 1 year. No comparative data are available. Therefore, there is no data to determine how survival or adverse events compare to other methods for locoregional therapy. There are no studies reporting functional or quality of life outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines for Hepatocellular Carcinoma (v2.2025) (6) states that 'Irreversible electroporation (IRE) is an emerging modality for tumor ablation' and that 'Larger studies are needed to determine the effectiveness of IRE for local HCC treatment.'

The National Comprehensive Cancer Network (NCCN) guidelines for Biliary Tract Cancers (v2.2025) (7) states that ablation is a reasonable alternative to surgical resection for intrahepatic CCA, particularly in patients with high-risk disease and 'Options for ablation include radiofrequency ablation, microwave ablation, and irreversible electroporation' for treatment of small, single intrahepatic cholangiocarcinoma tumors (<3cm) amenable to complete ablation, whether recurrent or primary.

The National Comprehensive Cancer Network (NCCN) guidelines for Pancreatic Adenocarcinoma (v2.2025) (29) states that 'Irreversible electroporation (IRE) is an ablative

technique in which electric pulses are used to create nanopores to induce cell death. This technique has been used in patients with locally advanced pancreatic cancer and may be safe and feasible and improve survival. However, due to concerns about complications and technical expertise, the Panel does not currently recommend IRE for treatment of locally advanced pancreatic cancer.'

The National Comprehensive Cancer Network (NCCN) guidelines for Kidney Cancer (v1.2026) (48) do not refer to irreversible electroporation. The guidelines state that 'Percutaneous ablation (e.g., cryosurgery, radiofrequency ablation, microwave ablation) is an option for the management of clinical stage T1 renal lesions. Thermal ablation is suitable for renal masses ≤3 cm. Percutaneous ablation is an option for clinical T1b masses in select patients not eligible for surgery.'

The National Comprehensive Cancer Network (NCCN) guidelines for Non-Small Cell Lung Cancer (v2.2026) (68) do not refer to irreversible electroporation. With respect to ablation therapies, the guidelines state that:

- 'Image-guided thermal ablation (IGTA) therapy (e.g., cryotherapy, microwave, radiofrequency) may be an option for select patients' for initial treatment for stage 1A disease.
- 'IGTA may be considered for those patients who are deemed “high risk”—those with tumors that are for the most part surgically resectable but rendered medically inoperable due to comorbidities. In cases where IGTA is considered for high-risk or borderline operable patients, a multidisciplinary evaluation is recommended.'
- 'IGTA is an option for the management of NSCLC lesions <3 cm. Ablation for NSCLC lesions >3 cm may be associated with higher rates of local recurrence and complications.'
- 'There is evidence on the use of IGTA for selected patients with stage IA NSCLC, those who present with multiple lung cancers, or those who present with locoregional recurrence of symptomatic local thoracic disease.'
- 'In the setting of progression at a limited number of sites on a given line of systemic therapy (oligoprogression), local ablative therapy to the oligoprogressive sites may extend the duration of benefit of the current line of systemic therapy.'

<u>National Institute for Health and Care Excellence (NICE)</u>

In 2019, NICE updated the recommendation for IRE for primary liver cancer (71) stating, “Evidence on the safety of irreversible electroporation for primary liver cancer shows serious but infrequent and well-recognized complications. Evidence on its efficacy is inadequate in quantity and quality” and concluded that the procedure should only be used in the context of research.

The National Institute for Health and Care Excellence (NICE) published an interventional procedures guidance in 2017 on irreversible electroporation for treating pancreatic cancer. (72) The guidance stated that 'Current evidence on the safety and efficacy of irreversible electroporation for treating pancreatic cancer is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research.'

In 2023, NICE updated their 2016 recommendation on IRE for treating prostate cancer (73) which states: "Current evidence on the safety and efficacy of irreversible electroporation for treating prostate cancer is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research. Studies should include randomized controlled trials comparing the procedure with current standards of care. They should report details of patient selection and short- and long-term outcomes, including patient-reported outcomes and the effect on any future prostate surgery."

Ongoing and Unpublished Clinical Trials

Some currently ongoing and/or unpublished trials that might influence this policy are listed in Table 3.

Table 3. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
NCT03899636[a]	A Pivotal Study of Safety and Effectiveness of NanoKnife® IRE for Stage 3 Pancreatic Cancer (DIRECT)	528	Dec 2023
NCT03899649[a]	A Registry Study of NanoKnife IRE for Stage 3 Pancreatic Cancer (DIRECT)	532	Dec 2024
NCT05170802	AHPBA Registry Database (Collection of Clinical Data Related to Pancreatic Cancer & Treatment - Irreversible Electroporation (IRE)	30	Dec 2024
ISRCTN14986389[b]	Investigating the feasibility of a clinical trial to test using irreversible electroporation to treat locally advanced pancreatic cancer following initial chemotherapy (LAP-PIE)	50	Nov 2024

NCT: national clinical trial

[a] Denotes industry-sponsored or cosponsored trial.

[b] ISRCTN registry

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	47384, 55877, 0600T, 0601T

HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
01/01/2026	Document updated. The following change was made to Coverage: 1) Slight rewording of experimental, investigational and/or unproven statement without change to intent. No new references added; others updated.
03/15/2025	Document updated with literature review. The following change was made to Coverage: Added conditional coverage criteria for irreversible electroporation in the treatment of intrahepatic cholangiocarcinoma. Added new references 1-28, 30-32, 34-60, and 62-70; others removed/updated.
03/15/2024	Reviewed. No changes.
07/01/2023	New medical document. Irreversible electroporation (IRE), including use of the NanoKnife, is considered experimental, investigational and/or unproven for all indications, including but not limited to, ablation of soft tissue or solid organs, such as the liver and pancreas.