LOUISIANA BLUE

Irreversible Electroporation and Histotripsy

Policy # 00912
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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.

Investigational or experimental services are not covered. This includes any drug, device, procedure, or service provided under the investigational arm of a clinical trial or clinical study. These services are excluded from coverage under benefits.

Note: Catheter Ablation as Treatment for Atrial Fibrillation is addressed separately in medical policy 00267.

Note: Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy is addressed separately in medical policy 00045.

Note: Microwave Tumor Ablation is addressed separately in medical policy 00569.

Note: Cryosurgical Ablation of Primary or Metastatic Liver Tumors is addressed separately in medical policy 00220.

Note: Radiofrequency Ablation of Primary or Metastatic Liver Tumors is addressed separately in medical policy 00182.

Note: Cryoablation of Tumors Located in the Kidney, Lung, Breast, Pancreas, or Bone is addressed separately in medical policy 00023.

Note: Radiofrequency Ablation of Miscellaneous Solid Tumors Excluding Liver Tumors is addressed separately in medical policy 00175.

Note: Transcatheter Arterial Chemoembolization (TACE) to Treat Primary or Metastatic Liver Malignancies is addressed separately in medical policy 00227.

Note: Radioembolization for Primary and Metastatic Tumors of the Liver is addressed separately in medical policy 00110.

Note: Focal Treatments for Prostate Cancer is addressed separately in medical policy 00484.

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 irreversible electroporation for treatment of primary or metastatic solid tumors including, but not limited to, tumors of the liver, pancreas, kidney, lung, or prostate to be **investigational.***

Based on review of available data, the Company considers histotripsy for treatment of primary or metastatic solid tumors including, but not limited to, tumors of the liver or kidney to be **investigational.***

Policy Guidelines

Pulsed field ablation is a form of irreversible electroporation energy used to treat patients with atrial fibrillation. Pulsed field ablation for atrial fibrillation is discussed in medical policy 00267 Catheter Ablation as Treatment for Atrial Fibrillation.

Background/Overview

Irreversible Electroporation

Electroporation generates high-frequent 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 [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.

Liver Tumors

The National Cancer Institute estimates that there will be over 42,000 new cases of liver and intrahepatic bile duct cancer in 2025. Liver and intrahepatic-bile duct cancer death is the fifth most common cancer related death in males and the seventh most common in females. 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. The prognosis following diagnosis depends on several factors including tumor mass and hepatic reserve.

The main risk factor for HCC in the U.S. is non-alcoholic fatty liver disease, followed by alcoholic liver disease, and hepatitis C virus and hepatitis B virus infections. 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. Mortality rates are higher for Native American people.

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.

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.

Pancreatic Cancer
Pancreatic ductal adenocarcinoma has a poor prognosis. The National Cancer Institute estimates that in 2025, there will be over 67,000 new cases of pancreatic cancer in the U.S. and over 51,000 pancreatic cancer deaths. Pancreatic cancer is the third-leading cause of cancer death in men and women.

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

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.

The NCCN recommended treatment for patients with locally advanced pancreatic adenocarcinoma includes systemic therapy with fluorouracil + leucovorin + irinotecan + oxaliplatin (FOLFIRINOX)-based or gemcitabine-based therapy, potentially with radiation therapy, with the goal of shrinking the tumor enough for surgical resection. Individuals who are unable to undergo surgery may continue systemic therapy. Depending on the kind of cancer and the genetic makeup some individuals may be candidates for immunotherapy or poly adenosine diphosphate-ribose polymerase (PARP) inhibitors. Thermal (radiofrequency and microwave) ablation therapies are not commonly used due to the increased risk of trauma to the adjacent major anatomical structures. 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.

Kidney Tumors
The National Cancer Institute estimates that there will be over 80,000 new cases of kidney cancer and over 14,000 kidney cancer related deaths in 2025. At diagnosis, approximately 65% of disease is localized disease.

Kidney cancer is approximately 2-fold more common in males compared to females. Mortality rates are 2-fold higher for kidney cancers in Native American people compared to White people. 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.

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.

Lung Tumors
The National Cancer Institute estimates that there will be over 226,000 new cases of lung cancer and over 124,000 lung cancer deaths in 2025. Lung cancer is the second most commonly diagnosed cancer and the leading cause of cancer death in both men and women.

Cigarette smoking is the leading 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. 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 White women. Women have historically had a lower risk than men, but the gap is closing.

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 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 sites (oligoprogression), local ablative therapy may extend the duration of benefit of the current line of systemic therapy..

Prostate Cancer
The National Cancer Institute estimates that there will be over 313,000 new cases of prostate cancer and over 35,000 prostate cancer deaths in 2025. The 5-year relative survival rate for prostate cancer is 97.9%. The most common risk factor for developing prostate cancer is increasing age.[24,] Black men are more likely to get prostate cancer compared to men of other races or ethnicities. Black men are also more than twice as likely to die from prostate cancer compared to men of other races. Genetic factors can also be a risk factor for prostate cancer, especially if a first-degree relative has had prostate cancer.

The standard for treatment of low-risk or favorable intermediate-risk prostate cancer includes active surveillance, radiation therapy, or radical prostatectomy. In patients with regional prostate cancer or higher risk groups, androgen deprivation therapy is recommended, generally in combination with

radiation therapy or abiraterone. NCCN guidelines state that ablative therapy (either focal or whole gland ablative therapy) is an experimental and emerging technology for the initial treatment of localized prostate cancer that lacks randomized controlled trial evidence with long-term follow-up showing its superiority or noninferiority to current recommended management strategies. Focal therapy meets the criteria as an alternative therapy, or a non-standard treatment for initial treatment. External beam radiotherapy, brachytherapy, and cryotherapy ablation are currently US Food and Drug Administration (FDA) approved or cleared for initial treatment of prostate cancer, but randomized evidence to the superiority in long-term cancer control and/or quality of life are lacking when delivered as focal rather than whole gland therapy. Other device categories, including IRE, are noted as not currently FDA approved or cleared for the treatment of prostate cancer as focal or whole gland therapy and should only be used in the context of a clinical trial.

NCCN guidelines recommend the use of local therapy as secondary treatment in the case of biopsy-proven recurrence in the prostate after radiation therapy without distant metastatic disease. Local therapy options for patients with recurrence in the prostate include cryotherapy, IRE, high-intensity focused ultrasound, reirradation (ie, brachytherapy, sterotactic body radiotherapy), and prostatectomy plus pelvic lymph node dissection.

Histotripsy
High-intensity focused ultrasound (HIFU) uses thermal effect of long ultrasound bursts with rapid heating and thermal ablation. Histotripsy is a relatively new HIFU-based technology. In contrast to conventional HIFU thermal therapy, histotripsy aims not to heat but to mechanically liquefy targeted tissue into subcellular debris using sequence of short, high-amplitude focused ultrasound pulses causing bubble activity at the focus. As the major mechanism of histotripsy is mechanical, it enables localized tissue disintegration without thermal damage to the overlaying and surrounding tissues.

A high-intensity pulsed ultrasound beam is focused noninvasively to the targeted site. Short pulses with a duration ranging from microseconds to milliseconds are delivered to the focus to generate gas and vapor bubbles. The bubble activity results in mechanical disintegration or liquefaction of tissue. Histotripsy can be monitored in real time using conventional ultrasound due to the presence of bubbles. Connective tissue structures (e.g., blood vessels, biliary structures) are more resistant to mechanical ablation than are cells. The nonthermal mechanism of the approach results in a sharper boundary and higher treatment precision compared with thermal ablation, which is limited by heat sinking and heat diffusion effects. Histotripsy-treated liquefied tissue is reabsorbed by the body over 1–2 months, leaving a millimeter-sized scar tissue. Histotripsy has also been shown to stimulate an immune response and induce abscopal effects in animal models, which may have positive implications for future cancer treatment.

Two major approaches sometimes termed cavitational histotripsy (CH) and boiling histotripsy (BH) have recently been explored. CH relies on initiation of a dense bubble cloud using microsecond-long pulses. By repeatedly expanding and collapsing during each pulse, the cavitation cloud completely homogenizes the tissue. BH uses milliseconds-long pulses containing shock fronts to rapidly heat tissue to boiling temperature and produce a vapor bubble at the focus within each pulse. The

interaction between the rest of the pulse and the vapor cavity results in mechanical fractionation of tissue.

Currently, histotripsy therapy is being evaluated in preclinical studies with small and large animal models for treating cancer, cardiac diseases, thrombosis, hematomas, and abscesses; enhancing tumor-specific immune response; and neurological applications. The first clinical trials using CH for benign prostatic hyperplasia, liver cancer, and renal cancer have been undertaken. Histotripsy is rapidly growing area of research, and many aspects are yet to be studied.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

The NanoKnife System™‡ (Angiodynamics) was originally cleared through the 510(k) process (K102329) in 2011 for the surgical ablation of soft tissue. In 2024, the indication for NanoKnife was expanded to surgical ablation of soft tissue, including prostate tissue. FDA product code: OAB.

In October 2021, the U.S. Food and Drug Administration (FDA) granted HistoSonics, Inc. Breakthrough Device Designation for its new histotripsy platform (HistoSonics, 2021b). In October 2023, the Edison®‡ System (HistoSonics®, Ann Arbor, MI)‡ received de novo marketing clearance from the FDA for the non-invasive non-thermal destruction of liver tumors, including unresectable liver tumors. On February 14, 2024, an updated Edison system was cleared for use in the non-invasive destruction of liver tumors. The authorization was based in part on the 30-day data from two single-arm, non-randomized prospective trials evaluating primary or metastatic liver tumors. Participants will be followed for 5 years post-procedure (NCT04572633, NCT04573881).

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

Irreversible electroporation produces high-frequency electric pulses to create an electric current that permanently damages cell membranes causing cell death due to the inability to maintain homeostasis. Irreversible electroporation produces no thermal effect and appears to preserve vessels, nerves and the extracellular matrix.

Summary of Evidence

For individuals being treated with locoregional therapy for tumors in the liver who receive irreversible electroporation (IRE), the evidence includes primarily single-arm studies. Relevant outcomes are overall survival, disease-specific survival, symptoms, morbid events, functional outcomes, and 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 are 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 IRE, the evidence includes single-arm studies. Relevant outcomes are overall survival, disease-specific survival, symptoms, morbid events, functional outcomes, and 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. Irreversible electroporation may be an 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 are insufficient data to determine whether survival is improved with chemotherapy followed by IRE compared to chemotherapy alone. Two randomized controlled trials 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 IRE, the evidence includes single-arm studies. Relevant outcomes are overall survival, disease-specific survival, symptoms, morbid events, functional outcomes, and 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 are 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 IRE, the evidence includes single-arm studies. Relevant outcomes are overall survival, disease-specific survival, symptoms, morbid events, functional outcomes, and 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 2 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 are 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 prostate who receive IRE, the evidence includes systematic reviews of observational studies and prospective nonrandomized trials. Relevant outcomes are overall survival, disease-specific survival, symptoms, morbid events, functional outcomes, and quality of life. Irreversible electroporation is suggested as an option in clinical guidelines for secondary treatment of biopsy-proven recurrence of prostate cancer after

radiation. Studies included in systematic reviews for IRE as initial therapy were too heterogeneous to conduct any pooled analyses. Across those studies, reports of biopsy-proven recurrence post-IRE ranged from 0% to 38.9%. Similarly, studies included in the systematic review for IRE as salvage therapy were also too dissimilar to conduct meta-analyses. Rates of local oncological control post-IRE varied from 67% to 77%, although the definition of control also varied across studies. In the PRESERVE study, 71% of patients had negative in-field biopsies at 12 months, which aligned with results from observational studies across systematic review. The small sample sizes, heterogeneity across studies and study populations, and observational study designs all preclude conclusions of efficacy compared to other standard treatments. No subgroup analyses have been conducted across various severities of prostate cancer. Additionally, the short follow-up times are insufficient to establish long-term oncological effects. No comparative data with guideline-recommended standard of care are available. 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 liver who receive histotripsy, the evidence includes two human single-arm studies of 8 and 44 patients, a phase I trial (THERESA, NCT03741088) and a multicenter clinical trial (HOPE4LIVER) in the United States (eight sites; NCT04572633) and Europe (six sites; NCT04573881). Relevant outcomes are overall survival, disease-specific survival, symptoms, morbid events, functional outcomes, quality of life. Histotripsy may be an option for locoregional therapy that is less damaging to nearby blood vessels, bile ducts, and nerves than thermal ablation therapies. Published studies of histotripsy for liver tumors lack a comparator arm.

THERESA trial, first-in-human feasibility, phase I, single-arm study (Barcelona, Spain), included eight (8) patients with multifocal liver malignancy (colorectal liver metastasis, breast cancer metastasis, cholangiocarcinoma metastases, and hepatocellular carcinoma), with histotripsy delivered to 11 tumors < 3 cm in diameter using a prototype system (HistoSonics). The primary endpoint was technical success, creating a zone of tissue destruction per MRI one day post-procedure. Safety device-related adverse events through 2 months was a secondary endpoint. The 8 patients had a median age of 60.4 years with an average targeted tumor diameter of 1.4 cm. The primary endpoint was achieved in all procedures. There was one mistargeting as tumor could not be visualized clearly on ultrasound. Remaining 10 tumors were successfully ablated (confirmed by MRI). Nine of the 10 tumors had local tumor regression at a 2-month follow-up (72% volume retraction). Two patients had decline in tumor markers and one patient had off-target tumor shrinkage. The secondary safety profile endpoint identified no device-related adverse events. Trial had several limitations, including small heterogeneous patient population limiting any conclusions regarding long-term effectiveness and the interaction with other therapies. The device used was an investigational prototype device. The trial had a short follow-up period limiting the ability to assess the durability of histotripsy, local recurrence rate, or disease-free survival. Authors concluded that the need for more definitive clinical trials is warranted.

The HOPE4LIVER trials were parallel United States, European Union and England prospective, multicenter, single-arm nonrandomized studies. Up to three tumors smaller than 3 cm in size could be treated. CT or MRI and clinic visits were performed at index-procedure, 36-hours post procedure,

and 30-days post procedure. There were co-primary end points of technical success of tumor treatment (tumor treated volume being greater or equal to targeted volume based on CT or MRI) and absence of procedure-related major complications within 30 days, with performance goals of greater than 70% and less than 25%, respectively. Forty-four participants (21 from the United States, 23 from the European Union or England; 22 female participants, 22 male participants; mean age, 64 years ± 12 [SD]) with 49 tumors were enrolled and treated. Eighteen participants (41%) had hepatocellular carcinoma and 26 (59%) had non-hepatocellular carcinoma liver metastases (primary colon cancer 5, rectum 5, breast 4, pancreas 5, other 7). The maximum pretreatment tumor diameter was 1.5 cm ± 0.6 and the maximum post-histotripsy treatment zone diameter was 3.6 cm ± 1.4. Thirty-nine (39) participants had one tumor, and 5 participants had 2 tumors treated.

Technical success was observed in 42 of 44 treated tumors (95%; 95% CI: 84, 100) with 2 tumors mistargeted. Procedure-related major complications were reported in three of 44 participants (7%; 95% CI: 2, 18). Total 101 adverse events were reported within 30 days; 7 were rated as serious with 3 of them as major adverse events. Two patients had grade 3 event (sepsis related to biliary stent and pleuritic pain), and one patient had grade 5 event with liver failure on day 12 due to extensive liver parenchyma replacement by metastases (patient died 37 days after procedure). Four patients had serious adverse events (splenic hematoma, melena, procedural pain, metastatic colorectal cancer progression). Additional 6 patients had liver damage outside of the expected margin (1 case due to mistargeting and 5 had perfusion changes next to treatment area). A secondary end point was technical efficacy at 30-days (lack of a nodular or mass-like area of enhancement within or along the edge of the treated volume on CT or MRI), reported as 83% and achieved in 30 of 36 lesions (remaining 6 treated lesions did not have imaging, and efficacy could not be assessed in 2 treated lesions). Other clinical outcomes were not reported. Subjects will be evaluated at 6 months and followed annually for up to five years post-index procedure (estimated study completion in 7/2026). Trial had several limitations including short follow-up (long-term follow-up of treatment zones is needed to determine rate of local control), small sample size, and lack of control. Authors concluded that larger trials with longer follow-up in typical candidates for local-regional treatment will provide further outcome data to help define the role of this emerging technology. 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 renal cancer there are no published studies evaluating the use of histotripsy. Two prospective, multi-center, single-arm clinical trials are underway to evaluate the safety and effectiveness of the device in treating renal tumors (NCT05432232, NCT05820087). The preferred treatment of renal cancer is a partial or radical nephrectomy. For individuals with small tumors or for individuals who are not candidates for surgery, ablative therapy, such as RFA, cryoablation or stereotactic ablative body radiation therapy are considered standard alternative therapies (National Cancer Institute (NCI), Renal Cancer Treatment, 2024; NCCN, Kidney cancer V2.2025). Histotripsy is not mentioned as a potential treatment of renal tumors in any current guidelines. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines for hepatocellular carcinoma (HCC) (v1.2025) 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.'

NCCN guidelines for biliary tract cancers (v2.2025) states that ablation is a reasonable alternative to surgical resection for intrahepatic cholangiocarcinoma (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 CCA tumors (<3cm) amenable to complete ablation, whether recurrent or primary.

NCCN guidelines for pancreatic adenocarcinoma (v2.2025) states that '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.'

NCCN guidelines for kidney cancer (v1.2026) do not refer to irreversible electroporation. The guidelines state that 'Percutaneous ablation (eg, cryosurgery, radiofrequency ablation, microwave ablation) is an option for the management of clinical stage T1 renal lesions. Percutaneous ablation is suitable for renal masses ≤3 cm. Percutaneous ablation is an option for clinical T1b masses in select patients not eligible for surgery.'

NCCN guidelines for non-small cell lung cancer (NSCLC) (v8.2025) do not refer to irreversible electroporation. With respect to ablation therapies, the guidelines state that:

- 'Image-guided thermal ablation (IGTA) therapy (eg, 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 1A 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.'

NCCN guidelines for prostate cancer (v.2.2026) recommend the use of local therapy as secondary treatment in the case of biopsy-proven recurrence in the prostate after radiation therapy without distant metastatic disease. Local therapy options for patients with recurrence in the prostate include cryotherapy, IRE, high-intensity focused ultrasound, reirradation (ie, brachytherapy, sterotactic body radiotherapy), and prostatectomy plus pelvic lymph node dissection.

Histotripsy is not recommended as a treatment option in the National Comprehensive Cancer Network (NCCN) guidelines.

National Institute for Health and Care Excellence
The NICE published an interventional procedures guidance in 2017 on IRE for treating pancreatic cancer. 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.'

The NICE published an interventional procedure guidance in 2023 on IRE for treating prostate cancer. The guidance states that "Irreversible electroporation for treating prostate cancer should only be used with special arrangements for clinical governance, consent, and audit or research...Further research should ideally be randomized controlled trials with an appropriate comparator. Further research could also include analysis of registry data or research databases. It should include details of patient selection, details of the procedure (including imaging) and short- and long-term outcomes."

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date

Ongoing			
NCT03899636[a]	A Randomized, Multicenter, Controlled, Unblinded Study to Assess the Safety and Efficacy of the NanoKnife®‡ System for the Ablation of Unresectable Stage 3 Pancreatic Adenocarcinoma	528	Apr 2025
NCT03899649[a]	Registry to Evaluate Effectiveness and Safety of the NanoKnife System for the Ablation of Stage 3 Pancreatic Adenocarcinoma	532	Apr 2025
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
NCT06886321	Evaluation of the Effectiveness of Irreversible Electroporation for the Treatment of Prostate Cancer	10	Jun 2027
NCT06270043	A Prospective Registry and Longitudinal Study of Patients Undergoing Focal Therapy for Localized Prostate Cancer	500	Feb 2034
NCT05513443	Prostate Cancer IRE Study (PRIS) - A Randomized Controlled Trial Comparing Focal to Radical Treatment in Localized Prostate Cancer	184	Sep 2026
NCT05345444	Radiation Therapy and Irreversible Electroporation for Intermediate Risk Prostate Cancer (RTIRE)	48	Apr 2027
NCT02255890	Registry of Irreversible Electroporation for the Ablation of Prostate Cancer With Use of Nanoknife Device; A Multi-Center, International Registry to Evaluate the Treatment of Prostate Cancer in Terms of Recurrence, Functional Outcomes and Safety.	361	Apr 2025

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.
[b] ISRCTN registry

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Policy History

Original Effective Date: 03/01/2025
Current Effective Date: 03/01/2026

02/06/2025	Medical Policy Committee review
02/12/2025	Medical Policy Implementation Committee approval. New policy.
01/1/2026	Coding update
02/05/2026	Medical Policy Committee review
02/11/2026	Medical Policy Implementation Committee approval. Added prostate to the irreversible electroporation investigational statement.
07/01/2026	Coding update

Next Scheduled Review Date: 02/2027

Coding

The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2025 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Louisiana Blue Medical Policy Coverage Guidelines is with Louisiana Blue and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Louisiana Blue Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Louisiana Blue Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

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

Code Type	Code
CPT	0600T, 0601T, 0686T, 0888T, 47384, 55877 Add code effective 07/01/2026: 1037T
HCPCS	N/A
ICD-10 Diagnosis	All related diagnoses

*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. Food and Drug Administration (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 technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

NOTICE: If an authorization for an ongoing course of treatment has been provided to a member and the member changes from one health plan to another health plan (e.g., a member moves from carrier A to Louisiana Blue), Louisiana Blue may honor the previous health plan's authorization for the same service under the same type of in-network benefit for a 90-day transition period. Documentation of the authorization for the ongoing course of treatment from the previous health plan must be provided to us by the member or their provider and the services provided for the course of treatment must otherwise be a covered service under the Louisiana Blue health plan. This provision does not apply to medications covered under the plan's pharmacy benefit.