Irreversible Electroporation and Histotripsy

Medicare Advantage Medical Policy #MA-117
Original Effective Date: 08/01/2025
Current Effective Date: 08/01/2025

Applies to all products administered or underwritten by the Health Plan, unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy is addressed separately in medical policy MA-011.

Note: Focal Treatments for Prostate Cancer is addressed separately in medical policy MA-111.

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

Based on review of available data, the Health Plan 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.

Focal therapy with irreversible electroporation and high-intensity focused ultrasound (HIFU) as a treatment for prostate cancer is addressed separately in medical policy MA-111 Focal Treatments for Prostate Cancer.

Background/Overview

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.

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. NanoKnife has not received clearance for the treatment of any specific disease. 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 federal 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, 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.

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 (v2.2024) 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 (v3.2024) 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 cryoablation, 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 (v3.2024) 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 (v1.2025) do not refer to irreversible electroporation. The guidelines state that 'Thermal ablation (eg, 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. Thermal 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 (v8.2024) 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.'

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

National Institute for Health and Care Excellence
The National Institute for Health and Care Excellence (NICE) published an interventional procedures guidance in 2017 on irreversible electroporation 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.'

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 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

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Policy History

Original Effective Date: 08/01/2025
Current Effective Date: 08/01/2025
05/20/2025 Utilization Management Committee review/approval. New policy.
Next Scheduled Review Date: 05/2026

Coding

The five character codes included in the Health Plan 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 the Health Plan Medical Policy Coverage Guidelines is with the Health Plan 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 the Health Plan 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 the Health Plan 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
HCPCS	No codes
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 Health Plan's 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 Health Plan 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.

Medicare Advantage Members
Established coverage criteria for Medicare Advantage members can be found in Medicare coverage guidelines in statutes, regulations, National Coverage Determinations (NCD)s, and Local Coverage Determinations (LCD)s. To determine if a National or Local Coverage Determination addresses coverage for a specific service, refer to the Medicare Coverage Database at the following link: https://www.cms.gov/medicare-coverage-database/search.aspx. You may wish to review the Guide to the MCD Search here: https://www.cms.gov/medicare-coverage-database/help/mcd-benehelp.aspx.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, internal coverage criteria may be developed. This policy is to serve as the summary of evidence, a list of resources and an explanation of the rationale that supports the adoption of this internal coverage criteria.

InterQual®
Interqual® is utilized as a source of medical evidence to support medical necessity and level of care decisions. InterQual® criteria are intended to be used in connection with the independent professional medical judgment of a qualified health care provider. InterQual® criteria are clinically based on best practice, clinical data, and medical literature. The criteria are updated continually and released annually. InterQual® criteria are a first-level screening tool to assist in determining if the proposed services are clinically indicated and provided in the appropriate level

or whether further evaluation is required. The utilization review staff does the first-level screening. If the criteria are met, the case is approved; if the criteria are not met, the case is referred to the medical director.