MEDICAL POLICY	NanoKnife System: Irreversible Electroporation (IRE)
Effective Date: 7/01/2021  7/1/2021 Medical Officer Date	Medical Policy Number 154 Medical Policy Committee Approved Date: 7/17; 9/18; 11/19; 04/2020; 06/2020; 6/2021

See Policy CPT CODE section below for any prior authorization requirements

SCOPE:

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:

All lines of business

BENEFIT APPLICATION

Medicaid Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

POLICY CRITERIA

Irreversible electroporation (e.g., NanoKnife System) is considered **investigational and is not covered** as a treatment of any condition, including but not limited to:

- Liver tumors (primary and metastatic)
- Pancreatic cancer
- Prostate cancer

Link to Policy Summary

BILLING GUIDELINES

There are specific CPT codes for the use of irreversible electroporation as of July 1, 2020. Unlisted codes are not as specific and would not be the most appropriate to bill for IRE.

CPT CODES

All Lines of Business	
Not Covered	
0600T	Ablation, irreversible electroporation; 1 or more tumors per organ, including imaging guidance, when performed, percutaneous
0601T	Ablation, irreversible electroporation; 1 or more tumors, including fluoroscopic and ultrasound guidance, when performed, open
Unlisted Codes All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then it will be **denied as not covered.**	
32999	Unlisted procedure, lungs and pleura
47399	Unlisted procedure, liver
48999	Unlisted procedure, pancreas
53899	Unlisted procedure, urinary system

DESCRIPTION

Irreversible electroporation (IRE) is a nonthermal tissue ablation technique that permeabilizes cell membranes by delivering pulses of high-voltage, electrical current across cell membranes. This creates permanent pores in the cell membrane, which leads to cell death and tissue necrosis. The process is similar to reversible electroporation, which is used to non-lethally increase the permeability of cells to chemotherapeutic agents, but uses a higher voltage. IRE may be performed percutaneously using imaging guidance or during an open or laparoscopic surgical procedure.

IRE is currently under investigational as a treatment alternative to thermal ablation techniques such as radiofrequency ablation (RFA) and microwave ablation (MWA). However, it is unclear if this alternative to thermal ablation has fewer side effects. Some known side effects specific to IRE include intense but typically transient whole-body muscular contractions and cardiac arrhythmias.

The NanoKnife System (AngioDynamics Inc.) is a device that administers IRE, which is currently available in the United States and several countries worldwide. According to a recent Hayes review, "the NanoKnife System comprises a console with screen; generator; foot pedal; and, single-use, disposable electrode probes; and uses a proprietary algorithm to generate a treatment plan. Electrodes are placed into the tumor under computed tomography (CT) or ultrasonographic guidance. The device generates approximately 90 pulses of 1500 to 3000 volts to the tumor, with an ablation zone of ≤ 2.0 centimeters (cm). Patients are treated under general anesthesia with complete neuromuscular blockade."[1]

REVIEW OF EVIDENCE

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of irreversible electroporation (IRE) as a treatment for any condition. Below is a summary of the available

evidence identified through April of 2021. Due to the large and extensive body of evidence surrounding cancer treatment, the following evidence summary is limited to recent, high-quality, systematic reviews.

Liver Tumors (Primary and Metastatic)

- In 2020, ECRI published a clinical evidence assessment of the NanoKnife System for treating liver cancer.[2] One systematic review and 9 studies, all observational, were included in the assessment. The systematic review by Wu et al consisted on 24 studies, 14 of which were case series on liver cancer, totalling 437 patients.[3] Among the liver cancer studies, they found a complete tumor response in 57% to 87% or patients treated with irreversible electroporation (IRE). They also reported IRE-related morbidity in 7& to 35% of patients at 6 to 36-month follow up. Of the 9 studies,6 reported on overall survival and progression free survival. Two case series found an overall survival rate of 38 months and 26.5 months. Progression free survival was found to be 7 months in one case series, and had a 44% PFS at 12-months in another case series. Overall, the studies and the systematic review were at high risk of bias, due to the following limitations:
    - Small samples sizes
    - Retrospective design
    - Single-center focus
    - Lack of controls, randomization, and blinding
    - Use of surrogate outcomes, rather than objective, patient-centered outcomes.

  ECRI gave the NanoKnife system an 'inconclusive- very low quality' evidence bar rating.

- In 2018 (archived in 2019), Hayes updated their review of the NanoKnife irreversible electroporation (IRE) system as a treatment for liver tumors, including seven small case series (n=34 to 56, four of which were retrospective) and two recent systematic reviews.[4] Hayes archived the assessment in 2019. Overall, the body of evidence was determined to be very low quality. The review reported the following limitations:

    - The individual studies suffered from one or more of the following limitations: lack of sufficient power to detect reported outcomes, inconsistent data reporting, limited data on long-term survival and recurrence, a lack of definitive patient selection criteria, and questionable applicability outside of experienced treatment centers.
    - There was a lack of evidence from well-designed trials and only two studies compared the use of IRE with alternative ablation therapies.
    - IRE might best be delivered within the context of a clinical trial.

  As a result, Hayes rated the NanoKnife System to deliver IRE treatment in patients with unresectable primary or metastatic liver tumors as "**D2**", indicating that substantial uncertainty remains regarding the safety and efficacy of IRE for both primary and metastatic liver tumors, and additional well-designed comparative studies reporting on improved long-term health outcomes such as pain relief are needed.

  Similarly, another recent systematic review reported similar results and also concluded that although IRE treatment shows promise, additional studies are needed to determine the treatment's safety and efficacy in clinical settings.[5]

No additional high-quality systematic reviews comparing IRE to other treatments for primary or metastatic liver tumors were identified after the publication of the systematic reviews above.

Pancreatic Cancer

- In 2020, ECRI published a clinical evidence assessment of NanoKnife for treating pancreatic cancer.[6] Two systematic reviews and 5 additional studies were assessed. The systematic reviews had partial overlap, as did 3 of the individual studies. One systematic review by Moris and colleagues included 18 studies and found a median overall survival of 7 to 27 months in patients treated with IRE and a median progress-free survival of 5 to 15 months. The other systematic review by Tian and colleagues, reviewing 15 studies, reported an overall survival of 33.8% at 24-month follow up. Two retrospective cohort studies with comparator groups reported IRE improved PFS and OS at 2-year followup compared with radiofrequency ablation and radiotherapy. A cohort study comparing IRE plus chemotherapy to chemotherapy alone reported improved PFS and 2 year OS in the IRE group. One historically-controlled study did not find a significant difference in median survival between IRE and patients who received another therapy (radiotherapy, chemotherapy, radiochemotherapy, no treatment, or no reported treatment).

  ECRI noted that the 2 systematic reviews included very-low-quality case series for their analyses, and the comparative studies were at high risk of bias due to too few events per comparison. ECRI rated the NanoKnife system for pancreatic cancer treatment as "Evidence is inconclusive- too few data on outcomes of interest", as randomized trials are needed to determine the efficacy of the treatment in this population.

- In 2018 (archived in 2019), Hayes updated their review of the NanoKnife irreversible electroporation (IRE) system as a treatment for locally advanced pancreatic cancer, including one small nonrandomized comparative study, four case series and two one recent systematic review.[1] Hayes archived the assessment in 2019. Overall, the body of evidence was determined to be very low quality. The review reported the following limitations:

  - The individual studies suffered from one or more of the following: selection bias of healthier patients for IRE treatment, and heterogeneity in terms of adjunctive treatments and patient selection.
  - There was a lack of evidence from well-designed trials and questionable applicability of the procedure outside of experienced centers.
  - The single included comparative study reported improved short-term overall and recurrence-free survival while using IRE as an adjunct compared with chemotherapy or CRT alone. However, by 18 20 months, the differences were no longer statistically significant.
  - IRE might best be delivered within the context of a clinical trial.

  As a result, Hayes rated the NanoKnife System to deliver IRE treatment in patients with locally advanced pancreatic cancer as "**D2**", indicating that definitive criteria for the use of NanoKnife has not been established, and additional well-designed comparative studies reporting on improved long-term health outcomes such as pain relief are needed.

No additional high-quality systematic reviews reporting on the use of IRE to other treatments for locally advanced pancreatic cancer were identified after the publication of the systematic reviews above.

Other Indications

Systematic reviews have also been published on the use of IRE for a number of other indications, including the following:

- Prostate cancer[7-9]
- Mixed indications including kidney, lung, pelvis and lymph node cancers[10]

Also of note, one small noncomparative trial (n ≤ 20) and one small retrospective review (n=20) have also evaluated the use of IRE for renal cell carcinoma.[11,12]

In general, the body of evidence for all indications for which IRE has been evaluated is not of sufficient quality or quantity. Most of the indications are still in the development phase, as evidenced by the majority of studies being noncomparative and retrospective in design. Other limitations reported include heterogenous outcomes, relatively short follow up (6-12 months) and lack of reporting of statistical significance. More robustly designed studies using validated patient reported outcome measures for comparison are needed in order to determine the safety and efficacy of IRE as a treatment for any indication.

CLINICAL PRACTICE GUIDELINES

National Comprehensive Cancer Network (NCCN)

- The NCCN guidelines for pancreatic adenocarcinoma (v.2.2021) state the following regarding irreversible electroporation (IRE):[13]

  "IRE may be safe and feasible and may improve survival outcomes. However, due to concerns about complications and technical expertise, the panel does not currently recommend IRE for locally advanced pancreatic cancer."

- The NCCN guideline for hepatobiliary cancers (v2.2021) states the following regarding IRE:[14]

  "IRE has some advantages over RFA [radiofrequency ablation]. Notably the lack of "heat sink" effect and the ability to treat near vessels, bile ducts, and other critical structures. However, IRE can cause cardiac arrhythmias and uncontrolled muscle contractions. Some small studies have shown that IRE treatment for unresectable HCC is safe and feasible. In a small nonrandomized trial including 30 patients with malignant liver tumors, none of the eight patient with HCC experience a recurrence through 6-month follow-up. Recurrences have been reported following IRE for larger tumors. Larger studies are needed to determine the effectiveness of IRE for local HCC treatment."

National Institute for Health and Care Excellence (NICE)

NICE has published interventional procedures guidance on the use of irreversible electroporation for treating a number of indications, including pancreatic cancer[15], prostate cancer[16], renal cancer[17], primary liver cancer and metastases of the liver[18,19], and primary lung cancer and metastases in the lung[20]. All of these guidance publications came to the same conclusion, stating:

> "Current evidence on the safety and efficacy of irreversible electroporation for treating [cancers indicated above] is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research."

CENTERS FOR MEDICARE & MEDICAID

As of 4/22/2021 no Centers for Medicare & Medicaid (CMS) coverage guidance was identified which addresses irreversible electroporation for any condition.

POLICY SUMMARY

There is insufficient evidence to support the use of irreversible electroporation (IRE) as a treatment for any indication, including but not limited to for treating cancer of the liver, pancreas, prostate, and kidneys. For all indications for which IRE has been proposed as a treatment, there is a paucity of randomized trials comparing IRE to other ablative treatment modalities as well as a lack of data on long-term outcomes. Furthermore, the NanoKnife System, the only IRE device identified, is currently only FDA-approved for soft tissue ablation and not for any specific tumor type. Therefore, the use if this IRE device for any type of cancer treatment is considered off-label. Lastly, clinical practice guidelines do not support the use of IRE for any indication.

INSTRUCTIONS FOR USE

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

REGULATORY STATUS

Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

U.S. Food & Drug Administration (FDA)

The NanoKnife System (AngioDynamics Inc.) is classified as a class II device and received FDA clearance through the 510(k) clearance program in 2011 (K102329).[21]

This FDA clearance is for the surgical ablation of soft tissue. The NanoKnife System has not received clearance for the therapy or treatment of any specific disease or condition. The NanoKnife System has not received approval to market the device as a device for tumor ablation; its use for treating specific types of tumors is considered off-label.[1]

MEDICAL POLICY CROSS REFERENCES

- Liver Tumor Treatment

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