

NanoKnife System: Irreversible Electroporation (IRE)

MEDICAL POLICY NUMBER: 154

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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 Company reserves the right to determine the application of medical policies and make revisions to medical policies at any time. 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. 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.

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”).

PLAN PRODUCT AND BENEFIT APPLICATION

Commercial

Medicaid/OHP*

Medicare**

*Medicaid/OHP 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.

**Medicare Members

Note that investigational services are considered “**not medically necessary**” for Medicare members.

COVERAGE 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

*Investigational services are considered “**not medically necessary**” for **Medicare Plan members**.

Link to [Centers for Medicare and Medicaid Services \(CMS\)](#).

Link to [Evidence Summary](#)

POLICY CROSS REFERENCES

- Liver Tumor Treatment, MPXXX

The full Company portfolio of current Medical Policies is available online and can be [accessed here](#).

POLICY GUIDELINES

BACKGROUND

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.”¹⁻⁴

REGULATORY STATUS

U.S. FOOD AND 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).⁵

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; currently, its use for treating specific types of tumors is considered off-label.¹

The NanoKnife System (AngioDynamics Inc.) is currently undergoing a clinical trial: Pivotal study of the NanoKnife System for the Ablation of Prostate Tissue in an Intermediate-Risk Population.⁶ The study began in March 2022 and expected to conclude in March 2024.

CLINICAL EVIDENCE AND LITERATURE REVIEW

EVIDENCE REVIEW

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 2022. 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 2022, ECRI published a clinical evidence assessment of the NanoKnife System for treating liver cancer.⁷ Two systematic review and meta-analyses and three nonrandomized retrospective studies were included in the assessment. The systematic review and meta-analysis by Gupta et al. consisted of 25 studies and totaled 776 patients.⁸ The pooled overall survival rates at 6, 12, 24, and 36 months for hepatic malignancies was 93.28%. Overall complication rate was high at 23.7%, but most complications were graded as minor with major complications (Society of Interventional radiology classification C-F) occurred in 6.9% of patients. The second systematic review and meta-analysis by Yu et al. consisted of 26 studies with a total of 807 patients.⁹ Among liver cancer patients, there was a complete ablation rate was 86% with irreversible electroporation treatment. Again, the incidence of complications was high at 23%, but most of these complications were minor. Major complications such as fistula development or hemorrhage were rare. One single-center retrospective study, Ma et al., noted that added irreversible electroporation to chemotherapy treatments improved rate of local tumor progression (16.7 % vs. 39.5%) as well as longer overall survival (19.3 months vs. 10.2 months) in patients with unresectable hilar cholangio-carcinoma.¹⁰ Freeman et al. compared irreversible electroporation to radiofrequency ablation in patients with unresectable hepatocellular carcinoma and found that both treatments were comparable in terms of local recurrence-free survival.¹¹ There were no major procedure-related complications or deaths in either group. The final retrospective study by Verloh et al. also found that thermal (microwave ablation/radiofrequency ablation) and non-thermal irreversible electroporation treatments had comparable frequency of complications, duration of hospital/ICU length of stays, and occurrences of a post-ablation syndrome.¹²

Overall, irreversible electroporation works as intended to ablate tissue in the liver. However, its effectiveness for treating malignant liver tumors cannot be determined because reviewed studies pooled outcomes for patients with different cancer types, stages or tumor locations which limited generalization across studies. The studies are also at a high risk of bias due to the following:

- Small sample size
- Single-center design
- Retrospective design
- Lack of control group

ECRI gave the NanoKnife system an ‘inconclusive- very low quality’ evidence bar rating. There are currently three ongoing trials reviewed that may partially address evidence gaps. Two of these studies have estimated completion dates within the next year and the final study has an estimated completion date of January 2030.

- 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.¹³ 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.¹⁴

No additional high-quality systematic reviews comparing IRE to other treatments for primary or metastatic liver tumors were identified after the publication of the 0systematic reviews above.

Pancreatic Cancer

- In 2022, ECRI published a clinical evidence assessment of NanoKnife for treating pancreatic cancer.¹⁵ Four systematic reviews and 4 additional studies were assessed. The systematic reviews all have partial patient overlap as well as three of the four studies also included patient overlap, although report on different comparisons.^{2-4,16-19} One systematic review by Sugumar et al. compared outcomes between multimodal therapy (chemotherapy ± radiotherapy) with or without irreversible electroporation for patients with non-resected locally advanced pancreatic cancer.¹⁶ There was similar overall survival rates between the two groups at 6 and 12 months with a decrease in survival rating at 12% compared to 28% at 24 months. The authors concluded that irreversible electroporation should remain experimental and should be used with caution in this patient population due to the current lack of quality prospective data. Ratnayake et al. analyzed the outcomes following margin accentuation irreversible electroporation pancreatic resection and found that this procedure during pancreatic surgery for stage III pancreatic cancer may result in increased R0 resection rates and improved overall survival with acceptable postoperative morbidity.¹⁷ The third systematic review, Moris et al. concluded that the survival benefits of irreversible electroporation do not currently exist and that there needs to be awareness of the potential morbidity and mortality associated with this treatment option.¹⁸ In the review of outcomes in patients that underwent irreversible electroporation for unresectable locally advanced pancreatic cancer, it was found morbidity at 30% and mortality at 2.2%. For those studies that reported complications according to the Clavien-Dindo classification system, 28.4% experienced grade I-II complications and severe complications (grade III or higher) were reported at 21%. In the final systematic review and meta-analysis by Tian et al., reviewed survival rates and relevant complications for patients with pancreatic cancer after irreversible electroporation.¹⁹ They found a

clear survival benefit for patients receiving this irreversible electroporation, although recommends future safety and effectivity monitoring from more large-scaled studies. One single-center, prospective, historically controlled trial, Månsson et al., did not show obvious gain in survival for the patients that completed the irreversible electroporation treatment (n = 24) compared to the registry group (radiochemotherapy, n = 4; chemotherapy, n = 72; radiotherapy, n = 4; no treatment, n = 4; and no treatment reported, n = 222) for the treatment of unresectable locally advanced pancreatic cancer.²⁰ The median survival after diagnosis for the two groups were 13.3 months and 9.9 months respectively. Six out of the 24 patients in the irreversible electroporation group had a severe complication after treatment. He et al. completed three retrospective studies that evaluated different treatment modalities and survival rates in patients with locally advanced pancreatic cancer.²⁻⁴ One study compared irreversible electroporation to radiofrequency ablation following chemotherapy induction and found that, for tumors 4 cm or smaller, the irreversible electroporation had an increased overall survival at two years (53.5% compared to 27.0%) as well as an improved two year progression-free survival (at 28.4 % vs 6.4%).⁴ For patients with a tumor size larger than 4 cm, the two treatment options resulted in comparable outcomes. A study comparing irreversible electroporation to radiotherapy following chemotherapy induction produced similar results with irreversible electroporation having a 2-year survival rate of 53.5% and 28.4% 2-year progression-free survival compared to radiotherapy at 20.7% and 5.6% respectively.³ The final study by He et al. reviewed chemotherapy with (n= 203) or without (n=3,444) additional irreversible electroporation treatment.² Compared to the chemotherapy without irreversible electroporation group, the combination therapy patients experienced higher survival rates (mean overall survival of 21.6 months vs 7.1 months).

ECRI continues to list irreversible electroporation as inconclusive because the evidence is “too limited in scope and quality to support conclusions”. Additionally, there was a lack of comparative data reported in the reviews. Moris et al. was comparative; however, none of the reviews included randomized trials. The four nonrandomized studies are all at high risk of bias due to the following:

- Small sample size
- Single-center focus
- Retrospective design
- Lack of randomization/blinding
- Lack of control group

Furthermore, three of the four studies used the same small patient population that underwent irreversible electroporation and compared results to registry cohorts for different ablation modalities. One historical control study used patient data that lacked treatment information (such as chemotherapy, radiotherapy, etc.) for 222 of 229 patients. There are currently 11 ongoing trials to be completed in the next 1-2 years that may partially address evidence gaps, 3 of which are multicenter.

- 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.

Prostate Cancer

There were systematic reviews published for the treatment of prostate cancer, frequently evaluating focal treatment options.²¹⁻²⁴ Currently, the body of evidence for irreversible electroporation for prostate cancer do not have sufficient quality or quantity to support this focal treatment option becoming a standard treatment. While treatments were fairly well tolerated, larger studies are needed to evaluate the efficiency and adverse events.

Other Indications

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

- Prostate cancer^{21,23,24}
- Mixed indications including renal, lung, pelvis and lymph node cancers^{25,26}

There have also been theoretical reviews on expanding the use of irreversible electroporation to treat other conditions such as Atrial Fibrillation, although additional research is needed before this treatment option could be explored.^{27,28}

While initial findings indicate that irreversible electroporation may be a safe and feasible treatment option, the body of evidence 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), small sample sizes, 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.1.2022) state the following regarding irreversible electroporation (IRE):

“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.”²⁹

- The NCCN guideline for hepatobiliary cancers (v1.2022) states the following regarding IRE:

“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 patients 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.

Although inconclusive, available evidence suggests that the choice of ablative therapy for patients with early-stage HCC should be based on tumor size and location, underlying liver function, as well as available local radiologist expertise and experience. Ablative therapies are most effective for tumors < 3 cm that are in an appropriate location away from other organs and major vessels/bile ducts, with the best outcomes in tumors < 2 cm.”³⁰

National Institute for Health and Care Excellence (NICE)

NICE has published interventional procedure guidance on the use of irreversible electroporation for treating a number of indications, including pancreatic cancer, prostate cancer^{31,32}, renal cancer, metastases of the liver³³, and primary lung cancer and metastases in the lung. 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. In particular, studies should report the effect of the procedure on local tumour control and patient survival”

NICE has also published interventional procedure guidance on the use of irreversible electroporation for primary liver cancer with the following recommendation: ³⁴

“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. Therefore, this procedure should only be used in the context of research.”

Additionally, patient selection should be multidisciplinary team and the procedure should only be done in specialist centers by clinicians with experience and specific training.

EVIDENCE 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 limitation of randomized trials comparing IRE to other ablative treatment modalities as well as a lack of comparative data between treatment modalities, data on long-term outcomes, multicenter studies, and sufficiently large sample sizes. 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. There is an ongoing FDA-approved trial regarding the use of the NanoKnife System in the treatment of prostate cancer, but it is not expected to conclude until March 2024. Therefore, the use of 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.

MEDICARE ADVANTAGE

Note: The Company policy for *PHA Medicare Medical Policy Development and Application* (MP50) provides details regarding Medicare’s definition of medical necessity and the hierarchy of Medicare references and resources during the development of medical policies, as well as the Plan’s use of evidence-based processes for policy development.

As of April 22, 2022, no specific Medicare coverage policy or guidance (e.g., manual, national coverage determination [NCD], local coverage determination [LCD] article [LCA], etc.) was identified which addresses irreversible electroporation. In the absence of a NCD, LCD, or other Medicare policy, Medicare regulatory guidelines do allow Medicare Advantage Organizations (MAOs) to make their own coverage determinations, as long as the MAO applies an objective, evidence-based process, based on authoritative evidence. (*Medicare Managed Care Manual, Ch. 4, §90.5*) Thus, the Company medical policy criteria may be applied for medical necessity decision-making.

Following an evidence-based assessment of current peer-reviewed medical literature, the Company may consider certain medical services or technologies to be “investigational.” The term “investigational” is

not limited to devices or technologies which have not received the appropriate governmental regulatory approval (e.g., U.S. Food and Drug Administration [FDA]), but rather may also mean the procedure, device, or technology does not meet all of the Company’s technology assessment criteria, as detailed within the Company policy for *Definition: Experimental/Investigational* (MP5). For Medicare, only medically reasonable and necessary services or items which treat illness or injury are eligible for Medicare coverage, as outlined in *Title XVIII of the Social Security Act, §1862(a)(1)(A)*. Thus, services which lack scientific evidence regarding safety and efficacy because they are investigational are “not medically reasonable or necessary” for Medicare Plan members. (*Medicare Claims Processing Manual, Ch. 23, §30 A*)

BILLING GUIDELINES AND CODING

There are specific CPT codes for the use of irreversible electroporation as of April, 2022. Unlisted codes are not as specific and would not be the most appropriate to bill for IRE.

CODES*		
CPT	0600T	Ablation, irreversible electroporation; 1 or more tumors per organ, including imaging guidance, when performed, percutaneous
	0601T	Ablation, irreversible electroporation; 1 or more tumors, including fluoroscopic and ultrasound guidance, when performed, open
	32999	Unlisted procedure, lungs and pleura
	47399	Unlisted procedure, liver
	48999	Unlisted procedure, pancreas
	53899	Unlisted procedure, urinary system
HCPCS	None	

*Coding Notes:

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company [Medical Policy](#), [Reimbursement Policy](#), [Pharmacy Policy](#) and [Provider Information website](#) for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as “medically unlikely edits” (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

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POLICY REVISION HISTORY

DATE	REVISION SUMMARY
4/2023	Interim update (code configuration change only). Converted to new policy template.