PREMERA HMO

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MEDICAL POLICY – 7.01.572

Irreversible Electroporation (NanoKnife System)

Effective Date:	Aug. 1, 2023
Last Revised:	July 24, 2023
Replaces:	N/A

RELATED MEDICAL POLICIES:

7.01.92	Cryosurgical Ablation of Miscellaneous Solid Tumors Other than Liver, Prostate, or Dermatologic Tumors
7.01.95	Radiofrequency Ablation of Miscellaneous Solid Tumors Excluding Liver Tumors
7.01.133	Microwave Tumor Ablation
8.01.61	Focal Treatments for Prostate Cancer
8.01.521	Radioembolization for Primary and Metastatic Tumors of the Liver

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POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

Clicking this icon returns you to the hyperlinks menu above.

Introduction

Irreversible electroporation is a surgical method used to destroy soft tissue (ablation). It is considered a non-thermal type of ablation since it does not produce heat to destroy tissue but uses direct-current electrical fields applied to soft tissue. These direct-current electrical fields create very small holes in the cell membranes of the tissue where it is applied causing the cell to become more porous, which results in the death of the cell. When these electrical fields are delivered for a long enough time and at a high enough energy level, they will permanently damage the tissue. This method of treatment is unproven. More studies are needed to show that it is safe and effective.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Investigational
Irreversible electroporation (NanoKnife System)	**The use of irreversible electroporation (IRE) (i.e., NanoKnife System) is considered investigational for all indications, including, but not limited to, ablation of soft tissue or of solid organs, such as the liver, pancreas, or kidneys.**

Coding

Code	Description
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

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

N/A

Evidence Review

Description

"The NanoKnife System delivers a series of high voltage direct current electrical pulses between two electrodes placed within a target area of tissue."[1] These electrical pulses create nanopore or micropore defects in the cell membrane, increasing the cell's permeability, which results in cell death. Once enough high voltage electrical pulses have been delivered, the cells become

irreversibly damaged. This non-thermal ablation technique is called irreversible electroporation.[2,3]

Background

"The NanoKnife System delivers a series of high voltage direct current electrical pulses between two electrodes placed within a target area of tissue."[1] These electrical pulses create nanopore or micropore defects in the cell membrane, increasing the cell's permeability, which results in cell death. Once enough high voltage electrical pulses have been delivered, the cells become irreversibly damaged. This non-thermal ablation technique is called irreversible electroporation.[2,3]

It is proposed that this technique causes less damage to tissue compared with thermal or radiation procedures. The reported benefit of this type of minimally invasive ablation procedure is that it can be used in areas where precision and preservation of the surrounding tissue, blood vessels, and nerves is paramount. This conservation of critical structures is thought to lead to fewer adverse effects.[4] IRE does require the use of general anesthesia and complete neuromuscular blockade (paralysis) due to the muscle contractions brought about by the strong electric fields created by IRE and the direct stimulation of the neuromuscular junction. It is performed by an interventional radiologist along with an anesthesiologist.[5]

The procedure involves percutaneously placing several electrodes in the form of long needles around the targeted area of soft tissue. It can also be used in open or laparoscopic intraoperative procedures. Imaging such as ultrasound, magnetic resonance or tomography is used to guide the placement of the needles. The needles are then connected to the IRE generator.[6] The NanoKnife System consists of a console with a screen, generator, foot pedal, electrode probe spacer and single-use, disposable electrode probes. The system uses a proprietary algorithm to generate a treatment plan. Depending on the size of the treatment field and the number of electrodes used, the ablation procedure takes place between one and 10 minutes. The electrodes may be repositioned under imaging guidance to extend the targeted treatment area until an entire tumor and appropriate treatment margins have been ablated.[7]

"The NanoKnife System has been cleared by the FDA for the surgical ablation of soft tissue. It has not received clearance for the therapy or treatment of any specific disease or condition."[45] Some of the areas where IRE has been studied is in the ablation of renal masses, liver lesions, pancreatic adenocarcinoma, lung cancer, prostate cancer, uveal melanoma, and thyroid cancer, among others.

The following are considered contraindications by the manufacturer for using the NanoKnife System: ablation of lesions in the presence of any implanted electronic devices such as cardiac pacemakers or defibrillators, ablation of lesions near any implanted metal or electronic device, ablation of lesions of the eye, or use in an individual with a history of epilepsy, cardiac arrhythmia, or myocardial infarction. The manufacturer also notes that some of the adverse effects that have been associated with the use of the NanoKnife system include arrhythmias, muscle contractions, hemorrhage, mechanical perforation, pneumothorax, infection, and damage to vital anatomical structures such as nerves, blood vessels, ducts or glands.[1]

Summary of Evidence

For individuals with primary or metastatic liver tumors or locally advanced pancreatic adenocarcinoma, the evidence includes several non-randomized, retrospective cohort studies, comparative registry studies, retrospective single-arm studies, and prospective single-arm studies, all of which had limitations (Narayanan et al. [2017], Cannon et al. [2013], Dollinger et al. [2015], Niessen et al. [2016], and Martin et al. [2015, 2013, 2012]). All sample sizes were small, none of the studies were randomized prospective comparative studies, and follow-up has been limited to short-term intervals. These studies suggest the irreversible electroporation ablation procedure using the NanoKnife System may be safe, somewhat low-risk, and may enhance survival for small tumors <3 cm, especially for tumors that are located near critical structures that have proven difficult to treat with other ablative methods.

For individuals with prostate cancer, the evidence includes 4 single arm prospective studies (Dong, et al. [2018], Valerio et al. [2017, 2014], Ting [2016]) These studies addressed safety and efficacy and adverse effects. Although IRE in the treatment of localized prostate cancer appears to be safe and has low urogenital toxicity, additional studies are needed to optimize individual selection and treatment parameters. The European Section of Urotechnology (ESUT) position statement (2018) stated that further prospective trials are required to assess medium to long term disease control of different ablative modalities for focal treatment of prostate cancer. There are no randomized trial comparisons to conventional radical prostatectomy or radiotherapy and there is limited oncologic follow-up. Wendler (2017) concluded, "…there is not enough evidence of its effectiveness or adverse effects to justify its use as a definitive treatment option for localized prostate cancer."[36]

For individuals with renal cell carcinoma (RCC), the evidence includes one prospective single arm phase II study, a single arm prospective study, and a retrospective single arm study (Wendler [2018], Canvasser [2017], Trimmer [2015]). IRE appeared to be safe in the treatment of RCC but was found to require substantial procedural effort. There was also a high rate of microscopic

incomplete ablation found after IRE. Larger series, longer follow-up, and comparisons to conventional nephrectomy are needed.

For individuals with unresectable lung malignancies, the evidence includes a single arm prospective phase II trial and case series (Ricke [2015], Usman [2012]). Expected efficacy of the phase II trial was not met and the trial was stopped prematurely. The case series of 2 individuals demonstrated the tumors recurred at 6 months of follow-up.

Additional well-designed, randomized controlled studies are needed to firmly establish the safety and efficacy of IRE. Some of the current identified challenges are the procedure itself has been found to be technically demanding, requiring technical skill and precision for the placement of multiple probes, histologic assessment and imaging of ablation zones following IRE need to be better defined due to the apoptotic cell death versus the coagulation necrosis seen with thermal ablation techniques in order to measure standardized response rates and to best determine local tumor recurrence. Currently, there is only one Investigational Device Exemption in place for the treatment of prostate cancer, so all other investigations into other tissue specific conditions are considered off-label.

Ongoing and Unpublished Clinical Trials

Some ongoing and unpublished trials that might influence this policy are listed in **Table 1**.

Table 1. Summary of Key Trials

NCT No.	Trials Name	Planned Enrollment	Completion Date
Ongoing			
NCT02041936	Evaluation of the Short and Intermediate Term Outcomes of Ablation of Locally Advanced Unresectable Pancreatic Cancer Using the NanoKnife Irreversible Electroporation (IRE) System-A Prospective Study	4	Dec 2024
NCT05345444	Radiation Therapy and Irreversible Electroporation for Intermediate Risk Prostate Cancer (RTIRE)	42	April 2025
NCT04212026	Irreversible Electroporation (IRE) Followed by Nivolumab in Patients with Metastatic Pancreatic Cancer: A Multicenter Single-arm Phase II Trial	15	Dec 2024

NCT No.	Trials Name	Planned Enrollment	Completion Date
NCT03484299	Chemotherapy and Irreversible Electroporation in the Treatment of Advanced Pancreatic Adenocarcinoma	20	July 2024
NCT04972097	Pivotal Study of the NanoKnife System for the Ablation of Prostate Tissue in an Intermediate-Risk Patient Population	118	June 2024
NCT05513443	Prostate Cancer IRE Study (PRIS) - A Randomized Controlled Trial Comparing Focal to Radical Treatment in Localized Prostate Cancer	184	Sept 2025
NCT01835977	Multi-Center Randomized Clinical Two Arm Intervention Study Evaluating Irreversible Electroporation for the Ablation of Localized Prostate Cancer	106	Jan 2025
NCT04212026	Irreversible Electroporation (IRE) Followed by Nivolumab in Patients With Metastatic Pancreatic Cancer: a Multicenter Single-arm Phase II Trial	15	Dec 2024
Unpublished			
NCT03614910	Ablation of Unresectable Locally Advanced Pancreatic Cancer with NanoKnife Irreversible Electroporation (IRE) System: Response and Tolerability	30	May 2023 Completed May 2021
NCT03105921	Irreversible Electroporation (NanoKnife) for the Treatment of Pancreatic Adenocarcinoma	20	June 2022 Completed Apr 2021

NCT: national clinical trial.

Practice Guidelines and Position Statements

National Institute for Health and Care Excellence (NICE)

In 2019, the NICE updated the recommendation for IRE for primary liver cancer stating, " Evidence on the safety of irreversible electroporation for primary liver cancer shows serious but infrequent and well-recognized complications. Evidence on its efficacy is inadequate in quantity and quality" and concluded that the procedure should only be used in the context of research.[19]

The National Institute for Health and Care Excellence (NICE) (2017) recommended that irreversible electroporation (IRE) for treating pancreatic cancer only be used in the context of research. The recommendation stated: "current evidence on the safety and efficacy of IRE for

treating pancreatic cancer is inadequate in quantity and quality."[27] They noted that further research in the form of randomized controlled trials is needed.

In 2016, the NICE recommendation stated, "the current evidence on the safety and efficacy of IRE for treating prostate cancer is inadequate in quantity and quality,." indicating that the procedure should only be used in the context of research. Recommendations were made that RCTs comparing the procedure with current standards of care be performed.[30]

In 2013, the NICE recommendation stated, "current evidence on the safety and efficacy of irreversible electroporation for treating renal cancer is inadequate in quantity and quality," indicating that the procedure should only be used in the context of research. In the same year, they made the same recommendation for IRE for treating liver metastases, primary liver cancer, and for treating primary lung cancer and metastases in the lung.

National Comprehensive Cancer Network

National Comprehensive Cancer Network (NCCN) clinical practice guideline (Version 1.2022) on "Pancreatic Adenocarcinoma" states that IRE has been used in individuals with locally advanced pancreatic cancer and may be considered safe and extend survival. "However, due to concerns about complications and technical expertise, the panel does not currently recommend IRE for treatment of locally advanced pancreatic cancer."[38]

The NCCN clinical practice guideline (Version 1.2023) for hepatocellular carcinoma states "some small studies have shown that IRE for unresectable hepatocellular carcinoma (HCC) is safe and feasible…In a small nonrandomized trial including 30 patients with malignant liver tumors, none of the eight patients with HCC experienced 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."[55]

Medicare National Coverage

There is no national coverage determination.

Regulatory Status

In 2011 NanoKnife System (Angiodynamics, Inc.) was cleared through the 510(k) process (K102329) as a class II device. It is described as a low energy direct current non-thermal ablation device and substantially equivalent to its predecessors, the Oncobionic System with 6 Probe Output (K080202) and the Oncobionic System (K080376). It is intended for the surgical ablation of soft tissue and classified as an electrosurgical cutting and coagulation device.[45]

In May 2011, the FDA granted Investigational Device Exemption (IDE) approval for a clinical trial of the NanoKnife for the ablation of low-risk, localized prostate cancer.

Product Code: OAB

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History

Date	Comments
10/01/19	New policy, approved September 10, 2019, effective January 3, 2020. Add to Surgery section. The use of irreversible electroporation (IRE) (i.e., NanoKnife System) is considered investigational for all indications.
07/01/20	Coding update. Added codes 0600T and 0601T. Removed 32999, 47399, 48999, and 53899.
10/01/20	Annual Review, approved September 1, 2020. Policy updated with literature review. References added. Policy statement unchanged.
11/01/21	Annual Review, approved October 5, 2021. Policy reviewed. References added. Policy statement unchanged.
10/01/22	Annual Review, approved September 26, 2022. Policy updated with literature review. References added. Policy statement unchanged. Changed the wording from "patient" to "individual" throughout the policy for standardization.
08/01/23	Annual Review, approved July 24, 2023.Policy updated with literature review. References updated. No references added. Policy statement unchanged.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

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Language Assistance

ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al 844-722-4661 (TTY: 711).

注意：如果您使用繁體中文，您可以免費獲得語言援助服務。請致電 844-722-4661（TTY：711）。

CHÚ Ý: Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 844-722-4661 (TTY: 711).

주의: 한국어를 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다. 844-722-4661 (TTY: 711) 번으로 전화해 주십시오.

ВНИМАНИЕ: Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода. Звоните 844-722-4661 (телетайп: 711).

PAUNAWA: Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nang walang bayad. Tumawag sa 844-722-4661 (TTY: 711).

УВАГА! Якщо ви розмовляєте українською мовою, ви можете звернутися до безкоштовної служби мовної підтримки. Телефонуйте за номером 844-722-4661 (телетайп: 711).

ប្រយ័ត្ន៖ បើសិនជាអ្នកនិយាយ ភាសាខ្មែរ, សេវាជំនួយផ្នែកភាសា ដោយមិនគិតឈ្នួល គឺអាចមានសំរាប់បំរើអ្នក។ ចូរ ទូរស័ព្ទ 844-722-4661 (TTY: 711)។

注意事項：日本語を話される場合、無料の言語支援をご利用いただけます。844-722-4661（TTY:711）まで、お電話にてご連絡ください。

ማስታወሻ: የሚናገሩት ቋንቋ አማርኛ ከሆነ የትርጉም እርዳታ ድርጅቶች፣ በነጻ ሊያግዝዎት ተዘጋጀተዋል፡ ወደ ሚከተለው ቁጥር ይደውሉ 844-722-4661 (መስማት ለተሳናቸው: 711).

XIYYEEFFANNAA: Afaan dubbattu Oroomiffa, tajaajila gargaarsa afaanii, kanfaltiidhaan ala, ni argama. Bilbilaa 844-722-4661 (TTY: 711).

ملحوظة: إذا كنت تتحدث اذكر اللغة، فإن خدمات المساعدة اللغوية تتوافر لك بالمجان. اتصل برقم 844-722-4661 (رقم هاتف الصم والبكم: 711).

ਧਿਆਨ ਦਿਓ: ਜੇ ਤੁਸੀਂ ਪੰਜਾਬੀ ਬੋਲਦੇ ਹੋ, ਤਾਂ ਭਾਸ਼ਾ ਵਿੱਚ ਸਹਾਇਤਾ ਸੇਵਾ ਤੁਹਾਡੇ ਲਈ ਮੁਫਤ ਉਪਲਬਧ ਹੈ। 844-722-4661 (TTY: 711) 'ਤੇ ਕਾਲ ਕਰੋ।

ACHTUNG: Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zur Verfügung. Rufnummer: 844-722-4661 (TTY: 711).

ໂປດຊາບ: ຖ້າວ່າ ທ່ານເວົ້າພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ, ໂດຍບໍ່ເສັງຄ່າ, ແມ່ນມີພ້ອມໃຫ້ທ່ານ. ໂທຣ 844-722-4661 (TTY: 711).

ATANSYON: Si w pale Kreyòl Ayisyen, gen sèvis èd pou lang ki disponib gratis pou ou. Rele 844-722-4661 (TTY: 711).

ATTENTION : Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 844-722-4661 (ATS : 711).

UWAGA: Jeżeli mówisz po polsku, możesz skorzystać z bezpłatnej pomocy językowej. Zadzwoń pod numer 844-722-4661 (TTY: 711).

ATENÇÃO: Se fala português, encontram-se disponíveis serviços linguísticos, grátis. Ligue para 844-722-4661 (TTY: 711).

ATTENZIONE: In caso la lingua parlata sia l'italiano, sono disponibili servizi di assistenza linguistica gratuiti. Chiamare il numero 844-722-4661 (TTY: 711).

توجه: اگر به زبان فارسی گفتگو می کنید، تسهیلات زبانی بصورت رایگان برای شما فراهم می باشد. با 844-722-4661 (TTY: 711) تماس بگیرید.