MEDICAL POLICY

Medical Policy Title	**Tumor-Treatment Fields Therapy**
Policy Number	**6.01.45**
Current Effective Date	September 16, 2025
Next Review Date	May 2026

Our medical policies are based on the assessment of evidence based, peer-reviewed literature, and professional guidelines. Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract. (Link to Product Disclaimer)

POLICY STATEMENT(S)

I. Alternating electrical field therapy (tumor-treatment field (TTF) therapy) using Optune (Novocure, Portsmouth, New Hampshire) for treatment of recurrent supratentorial glioblastoma multiforme (GBM) is considered **medically appropriate**, when **ALL** the following criteria have been met:

   A. The patient has had a first or second recurrence of GBM;

   B. The patient has a Karnofsky Performance Status (KPS) of 60 or greater;

   C. The patient has not received prior treatment with Bevacizumab;

   D. The device is to be used as monotherapy after failure of standard medical therapy (e.g., chemotherapy, surgery, and/or radiation therapy);

   E. The patient is 22 years or older; **and**

   F. Documentation includes the following:

      1. There is documented evidence that the patient is compliant with the TTF device during a (1) month trial period. Compliance is defined as use of the device for 18 hours or more per day during the one (1) month trial period.

      2. The patient has histologically confirmed GBM (documentation of pathology required);

      3. The Optune (Novocure) will be initially allowed for up to six (6) months if the patient is compliant (18 hours or more per day) with the regimen;

      4. Continued use after six (6) months will require:

         a. Documentation that patient has been compliant (18 hours or more per day); **and**

         b. Documentation that there has been no progression of tumor.

II. TTF therapy using Optune for treatment of newly diagnosed supratentorial GBM is considered **medically appropriate** when **ALL** the following criteria have been met:

   A. The device is to be used as an adjunct with the chemotherapy drug temozolomide (TMZ);

   B. The therapy follows standard treatments that include maximal debulking surgery and completion of radiation therapy, together with concomitant standard of care chemotherapy;

   C. The patient is 22 years or older; **and**

D. Documentation includes the following:

1. There is documented evidence that the patient is compliant with the TTF device during a (1) month trial period. Compliance is defined as use of the device for 18 hours or more per day during the one (1) month trial period;
2. The patient has histologically confirmed GBM (documentation of pathology required);
3. The Optune (Novocure) will be initially allowed for up to six (6) months if the patient is compliant (18 hours or more per day) with the regimen;
4. Continued use after six (6) months will require:
    a. Documentation that patient has been compliant (18 hours or more per day); **and**
    b. Documentation that there has been no progression of tumor.

III. TTF therapy is considered **investigational** for all other indications, including but not limited to:

A. Mesothelioma;

B. Metastatic non-small cell lung cancer (mNSCLC).

IV. Device Repair

A. Repair of a medically necessary [device] or components not under warranty will be considered **medically appropriate** when the following criteria are met:

1. Physician documentation includes **ALL** the following:
    a. date of device implantation/initiation;
    b. manufacturer warranty information, if applicable;
    c. attestation that the patient has been compliant with the use of device and will continue to benefit from the use of device;
2. The device is no longer functioning adequately; and **BOTH** of the following criteria are met:
    a. inadequate function interferes with activities of daily living; **and**
    b. repair is expected to make the equipment fully functional (as defined by manufacturer).

B. Repair of equipment damaged due to patient neglect, theft, abuse, or when another available coverage source is an option (e.g., homeowners, rental, auto, liability insurance, etc.) is **ineligible for coverage**.

V. Device Replacement

A. Replacement of a medically necessary [device] or components not under warranty will be considered **medically appropriate** when **EITHER** of the following criteria are met:

1. The device is no longer functioning adequately and has been determined to be non-repairable or the cost of the repair is in excess of the replacement cost; **or**

2. There is documentation that a change in the patient's condition makes the present unit non-functional and improvement is expected with a replacement unit.

B. The replacement of a properly functioning [device], its components or accessories is considered **not medically necessary**. This includes, but is not limited to, replacement desired due to advanced technology or in order to make the device more aesthetically pleasing;

C. The replacement of equipment damaged or lost due to patient neglect, theft, abuse, or when another available coverage source is an option (e.g., homeowners, rental, auto, liability insurance, etc.) is **ineligible for coverage**.

VI. Accessories or components for [device] that are considered not medically necessary or investigational by peer-reviewed literature will also be considered as **not medically necessary or investigational** by the Health Plan.

RELATED POLICIES

Corporate Medical Policy

11.01.03 Experimental or Investigational Services

POLICY GUIDELINE(S)

Not Applicable

DESCRIPTION

Glioblastoma multiforme (GBM), is the most common and aggressive primary intracranial tumor, with approximately 33% of patients surviving one year and less than 5% surviving more than five (5) years. Median survival with optimal therapy has been reported to be 10-to-15 months, with most tumors recurring within seven-to-nine months, despite multimodal treatment (e.g., repeat surgery, re-irradiation, and chemotherapy). Choice of chemotherapy for treatment in the case of recurrence varies, but may include alkylating agents (e.g., lomustine, carmustine, procarbazine), re-treatment with temozolomide, and, more recently, bevacizumab either alone or in combination with other agents. Overall survival after recurrence is relatively short, even with optimal therapy. New or novel treatments, such as TTF therapy, are being investigated to improve survival in patients with GBM.

TTF therapy is delivered via the Optune, which is a battery-powered, portable device that generates alternating low-intensity, intermediate electrical fields (100-300 kHz) by four (4) disposable electrode arrays (replaced one (1) to two (2) times per week) that are non-invasively attached to the patient's shaved scalp, placed in such a way as to encompass the tumor. The alternating low intensity electrical field is thought to disrupt cell division of the cancer cells, so that either cell division does not occur, or it is ineffective, resulting in death of the cancer cells without harming the normal healthy cells. The device is used by the patient at home on a continuous basis (18 hours per day) for the duration of treatment, which can last for several months. Patients can carry the device in a backpack or shoulder pack while conducting activities of daily living.

SUPPORTIVE LITERATURE

The United States Food and Drug Administration (FDA) approval of the Optune NovoTTF-100A system, was based on a phase three (3), multi-national, prospective, randomized, controlled trial (RCT) (Stupp et al., 2012). Participating in the study were 237 patients with relapsed or progressive GBM, despite conventional radiotherapy, who were randomized in a 1:1 ratio to receive TTF therapy (delivered by the NovoTTF-100A System) only (n=120) or the best standard of care chemotherapy (active control) (n=117). Patient characteristics were balanced in both groups, with median age of 54 years and median Karnofsky Performance Status (KPS) score of 80%. More than 80% of participants had failed two or more prior chemotherapy regimens, and 20% had failed bevacizumab prior to study enrollment. Ninety-seven percent (116) of the 120 participants in the TTF group started treatment, and 93 participants (78%) completed one (1) cycle (four weeks) of therapy. Discontinuation of TTF therapy occurred in 27 participants (22%), due to noncompliance or the inability to manage the device. For each TTF treatment month, the median compliance was 86% (range, 41%-98%), which equaled a mean use of 20.6 hours per day. In the active control group, 113 (97%) of the 117 assigned participants received chemotherapy, and all but one individual completed a full treatment course. Twenty-one participants (18%) in the active control group did not return to the treating site, and details on disease progression and toxicity were not available. This RCT did not reach its primary end point of improved survival compared with active chemotherapy. With a median follow-up of 39 months, 220 participants (93%) had died. Median survival was 6.6 months in the TTF group, compared with 6.0 months in the active control group (hazard ratio, 0.86; 95% confidence interval [CI], 0.66 to 1.12; p=0.27). For both groups, one-year survival was 20%. The survival rates for two- and three-year survival were 8% and 4%, respectively, for the TTF group versus 5% and 1%, respectively, for the active control group. Progression Free Survival (PFS) rate at six months was 21.4% in the TTF group, compared with 15.1% in the active control group (p=0.13). Limitations of the trial included a somewhat heterogeneous patient population, with participants included after progression of one or several lines of chemotherapy, as well as the use of different chemotherapy regimens in the control group. Another limitation was the absence of a placebo/supportive care arm. In the setting of advanced disease, the supportive care arm would have been useful to gauge the safety and efficacy of treatment for both groups of patients. Treatments used in the active control arm (best standard of care chemotherapy) in the recurrent disease setting have previously demonstrated limited efficacy, thus limiting the ability to determine the true treatment effect of TTF. Data from a trial of TTF versus placebo, or TTF plus standard chemotherapy, versus standard chemotherapy alone, would, therefore, provide a better assessment of treatment efficacy.

A subgroup analysis of patient data of this phase 3 trial (Wong et al., 2014) evaluated the different characteristics of responders and nonresponders in the TTF group, compared to the active control group. More patients in the TTF arm were considered responders (14 of 120, versus seven (7) of 117 in the chemotherapy arm). Median response time was longer for those in the TTF arm than the chemotherapy arm (7.3 months versus 5.6 months, p<0.001), and there was a strong correlation (Pearson's r) between response and overall survival in the TTF arm (p<0.001), but not in the chemotherapy arm (p=0.29). Compared with the chemotherapy arm, a higher proportion of responders in the TTF arm had a prior low-grade histology (36% vs 0%). These differences in

treatment responder groups suggest that TTF therapy may differentially benefit certain types of GBM; however, the small numbers of responders in both groups limits generalizations that can be drawn from this analysis.

An analysis of the NovoTTF-100A Patient Registry Dataset (PRiDe) of 457 patients with recurrent GBM who were treated with NovoTTF therapy in the United States between October 2011 and November 2013, and a comparison to patient data in the Phase 3 trial, were performed (Mrugula et al., 2014) to provide a larger data set of patients with recurrent GBM treated with TTF therapy. No new adverse events in the PRiDe group of patients were reported, compared to the Phase 3 trial group. However, median overall survival was longer in the TTF group in the PriDe group (9.6 months), compared to the TTF group in the Phase 3 trial (6.6 months) or to the active chemotherapy group in the Phase 3 trial (6.0 months). Median treatment time was almost double for the TTF PriDe group, compared to either the TTF or chemotherapy group in the Phase 3 trial. Favorable prognostic factors in the PriDe group included 75% or more daily compliance with the device, treatment with TTF at first recurrence, no prior treatment with bevacizumab, and Karnofsky Performance Score (KPS) 90 or greater. The authors suggested that there are subsets of patients who derive significant benefit from TTF therapy and that TTF therapy using the NovoTTF-100A device is safe and efficacious to treat recurrent GBM.

The FDA approval of the Optune device (formerly called the NovoTTF-100A system) for newly diagnosed GBM was based on the results from a clinical trial involving 695 patients who were newly diagnosed with GBM. The study compared those who used the device with temozolomide (TMZ) to those receiving TMZ alone (Stupp, 2015). Patients who used the device along with TMZ lived, on average, about seven (7) months with no disease progression, compared to four (4) months for those who had the drug alone. The device plus TMZ group survived for an average of 19.4 months after starting treatment, compared to 16.6 months for those who were treated with TMZ alone.

In 2019, through the humanitarian device exemption (HDE) process, the FDA approved the Optune Lua system (formerly called the NovoTTF-100L) for treatment of adult patients with unresectable, locally advanced or malignant pleural mesothelioma (MPM), to be used concurrently with pemetrexed and platinum-based chemotherapy (the current gold-standard of treatment). The decision was based on the results of the industry-designed and sponsored STELLAR trial (NCT02397928), which was summarized by Ceresoli et al. This was a prospective, single-arm, multi-center study of 80 participants treated between 2015 and 2018, who had inoperable, previously untreated MPM. The primary endpoint of the trial was overall survival, which was measured from time of diagnosis until date of death. Fifty patients (63%) were treated with a carboplatin and pemetrexed combination with TTF, and 30 patients (37%) received cisplatin and pemetrexed with TTF. Median overall survival was 18.2 months (95% CI 12.1-25.8) and comparable to other recent study results for median overall survival of chemotherapies for treatment of MPM. Even though the median overall survival, objective responses, and progression-free survival results did not appear to be impacted with TTF therapy, the similar outcomes reported in this study were achieved without an increase in systemic toxicity. Thirty-two patients did have severe adverse events during the trial period, which is also consistent with other trials of pemetrexed (anemia, neutropenia, and skin reaction being the most common). The majority of patients did have mild medical device reactions at the site of array adherence on the skin. This study's small sample size, lack of a control group, and lack of quality-of-life assessment did not

provide enough information to draw conclusions on the efficacy of this therapy versus standard medical treatment. Further randomized clinical trials are needed.

Leal et al. (2023), reported on a pivotal phase 3, open-label, randomized study (LUNAR). The study aimed to compare the addition of TTF therapy to standard systemic therapy with standard systemic therapy alone in patients with metastatic non-small-cell lung cancer. Between February 2017 and November 2021, 276 patients were enrolled and randomly assigned to receive TTFields therapy with standard therapy (n=137) or standard therapy alone (n=139). Their median age was 64 years, 178 (64%) were male and 98 (36%) were female, and 232 (84%) were current or former smokers. At baseline, the majority (156 [57%]) had non-squamous histology, 43 (16%) had liver metastasis, and ten (4%) had an ECOG performance score of 2. TTFields therapy (150 kHz) was delivered continuously to the thoracic region with the recommendation to achieve an average usage of at least 75% of each day (18 h/day) with the NovoTTF device system (device manufactured by Novocure). The primary endpoint was overall survival in patients receiving TTFields therapy with standard therapy compared with standard therapy alone. Key secondary endpoints were overall survival in subgroups receiving either docetaxel or an immune checkpoint inhibitor. Other secondary endpoints (reported here) were progression-free survival and overall response rate (both per radiological assessment); overall survival by squamous and non-squamous histology; measurement of patient-reported, health-related quality-of-life scores; and adverse events. Secondary endpoints of overall survival and progression-free survival in TTFields therapy-treated subgroups with average monthly device usage of more than 75% and 75% or less; progression free survival by squamous and non-squamous histology; overall survival and progression-free survival in subgroups who received nivolumab, pembrolizumab, or atezolizumab; and overall survival of patients who received TTFields therapy with docetaxel compared with patients treated with an immune checkpoint inhibitor alone will be reported elsewhere as part of more extensive analyses. Over the entire course of the study, a monthly average device usage of at least 18 h/day (75% of each day) was reached by 13 (19%) of 67 patients in the immune checkpoint inhibitor subgroup and 17 (26%) of 66 patients in the docetaxel subgroup. Overall survival was significantly longer with TTFields therapy and standard therapy versus standard therapy alone. Median overall survival was 13.2 months with TTFields therapy and standard therapy compared with 9.9 months with standard therapy alone, yielding an HR of 0.74 in favor of TTFields therapy. The one-year overall survival rate was 53% with TTFields therapy and standard therapy, and 42% with standard therapy alone. The overall response rate with TTFields therapy and standard therapy was 20.4% versus 17.3% with standard therapy alone. All complete responses (n=5) occurred in patients receiving an immune checkpoint inhibitor (four with TTFields therapy, one with immune checkpoint inhibitor alone). Study limitations include the open-label design and study being industry sponsored. Other limitations are that the study enrolled a low number of patients with brain metastases, potentially affecting the generalizability of these findings to that population. LUNAR was also initiated before the advent of standard genetic profiling by next-generation sequencing in non-small cell lung cancer, and thus little information about the relationship between TTFields therapy efficacy and tumor genetic subtype is available. Authors concluded that data from this study suggests that TTFields therapy is efficacious in metastatic non-small-cell lung cancer and should be considered as a treatment option to manage the disease. Additional studies

are warranted to validate the benefit of TTFields therapy with standard systemic therapies in non-small-cell lung cancer.

PROFESSIONAL GUIDELINE(S)

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Central Nervous System Cancers V.4.2024 states that due to lack of clear efficacy data, the panel is divided about recommending alternating electric field therapy for the treatment and re-irradiation of recurrent glioblastoma. Concurrent treatment with adjuvant TMZ and alternating electric fields is a category 1 recommendation for newly diagnosed glioblastoma patients ≤70 years of age who have a good PS. This is also considered a reasonable treatment option for patients >70 years of age with good PS and newly diagnosed glioblastoma who are treated with standard focal brain radiation and concurrent daily TMZ.

The NCCN Clinical Practice Guidelines for Malignant Pleural Mesothelioma V.2.2025 do not reference TTF therapy as a treatment for this indication.

The NCCN Clinical Practice Guidelines for Non-Small Cell Lung Cancer do not reference TTF therapy as a treatment for this indication.

In addition to malignant pleural mesothelioma, TTF is being investigated in non-small cell lung cancer, brain metastases from non-small cell lung cancer, pancreatic cancer, ovarian cancer, hepatocellular carcinoma and gastric adenocarcinoma. Future studies are warranted to determine the impact of TTF on the net health outcome.

REGULATORY STATUS

In April 2011, the NovoTTF-100A System (Novocure; assigned the generic name of TTF) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process. The FDA approved label reads as follows: "The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."

In September 2014, FDA approved Novocure's request for a product name change from NovoTTF-110A System to Optune.

In October 2015, FDA expanded the indication for Optune in combination with temozolomide to include newly diagnosed GBM.

The device was granted priority review status in May 2015 because there was no legally marketed alternative device available for the treatment of newly diagnosed GBM, a life-threatening condition.

In July 2016, a smaller, lighter version of the Optune device, called the Optune System (NovoTTF-200A System), received FDA approval.

The FDA-approved label for newly diagnosed GBM reads as follows: "This device is indicated as treatment for adult patients (22 years of age or older) with histologically confirmed glioblastoma

multiforme (GBM). Optune with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy."

In May 2019, the FDA approved a modified version of the Optune System (NovoTTF-100A System), which is now called the Optune Lua System (NovoTTF™-100L System), for "treatment of adult patients with unresectable, locally advanced or metastatic, malignant pleural mesothelioma (MPM) to be used concurrently with pemetrexed and platinum-based chemotherapy. The indication was modified from that granted for the Humanitarian Device Exemption designation to more clearly identify the patient population the device is intended to treat and in which the safety and probable benefit of the device is supported by the available clinical data."

In September 2021, the FDA granted breakthrough designation to the NovoTTF-200T System for use together with atezolizumab and bevacizumab for the first-line treatment of patients with unresectable or metastatic liver cancer.

To date, all of the existing tumor treating fields products fall under the brand name Optune. In March 2020, the manufacturer of Optune products announced a plan to include a suffix after the brand name for newly approved indications to further delineate specific indications for individual products (e.g., Optune Lua). Optune was renamed Optune Gio in 2023.

In October 2024, the FDA approved Optune Lua as a device to be used together with PD-1/PD-L1 inhibitors or docetaxel. It is indicated for adult patients with metastatic non-small cell lung cancer (mNSCLC) who have progressed on or after a platinum-based regimen.

CODE(S)

- Codes may not be covered under all circumstances.
- Code list may not be all inclusive (AMA and CMS code updates may occur more frequently than policy updates).
- (E/I)=Experimental/Investigational
- (NMN)=Not medically necessary/appropriate

CPT Codes

Code	Description
	There are no specific CPT codes for tumor treatment field therapy

HCPCS Codes

Code	Description
A4555	Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only

Code	Description
E0766	Electrical stimulation device used for cancer treatment, includes all accessories, any type

ICD10 Codes

Code	Description
C45.0-C45.9	Mesothelioma (code range)
C71.0-C71.9	Malignant neoplasm of brain (code range)

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SEARCH TERMS

Electric field therapy

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

LCD - Tumor Treatment Field Therapy (TTFT) (LCD L34823) [accessed 25 Jan 27]

PRODUCT DISCLAIMER

- Services are contract dependent; if a product does not cover a service, medical policy criteria do not apply.
- If a commercial product (including an Essential Plan or Child Health Plus product) covers a specific service, medical policy criteria apply to the benefit.
- If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.
- If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.
- If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.

POLICY HISTORY/REVISION

Committee Approval Dates

08/18/16, 08/17/17, 04/19/18, 03/21/19, 03/19/20, 03/18/21, 03/24/22, 03/23/23, 03/21/24, 05/22/25

Date	Summary of Changes
05/22/25	• PS III.B added as a new investigational stance. Previous policy guidelines moved into policy criteria. DME repair/replacement canned statements added. Supportive Literature, Professional Guidelines, Regulatory Status and Reference sections updated.
01/01/25	• Summary of changes tracking implemented.
05/28/15	• Original effective date