KAISER PERMANENTE®

Review Criteria

Georgia Region

DEPARTMENT **QUALITY RESOURCE MANAGEMENT**	CRITERIA NUMBER	03-47
SECTION **UTILIZATION MANAGEMENT**	EFFECTIVE DATE	4/20/2018
TITLE **Electronic Tumor Treatment Fields for GBM (Novacure and Novo TTF 100A)**	REVIEW DATES REVISION DATE	2/24/2019 9/21/2018 2/7/2019 1/3/2020 1/21/2021 1/10/2022 2/21/2023
POLICY TYPE **New Reviewed Revised-X**	PAGE NUMBER	1 OF 3

Purpose:
This policy provides the indications and contraindications necessary for the Quality Resource Management staff to make the most appropriate decision related to the medical necessity of the procedure listed.

DIAGNOSIS/CONDITION:
CPT-4/ HCPCS CODE AND DESCRIPTION: INDICATORS: These electronic tumor treatment field devices create an electric field over the scalp which disrupts rapid cell division in cancer cells. The electrodes are placed on shaved head and device is worn continuously. (There are no assigned CPT codes at this time)

1.0 INDICATIONS- Use of Electric Tumor Treatment Fields:

- Adult patients (22 years of age or older) with
- histologically-confirmed glioblastoma multiforme (GBM), (WHO grade IV astrocytoma), and high grade gliomas following histologically- or radiologically-confirmed recurrence in the supra-tentorial region of the brain after receiving chemotherapy.

- The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted

- In combination with temozolomide as adjunctive treatment of newly-diagnosed histologically confirmed supratentorial glioblastoma following standard treatments that include surgery, chemotherapy, and radiation therapy

Initial Approval: 3 months
Subsequent approval(s) for continuation of electric TTF is based on:

☐ Evidence of no documented disease progression by magnetic resonance imaging (MRI) done at a minimum of every 2-4 months. This includes a completed MRI scan with report submitted as part of any request for continuation of electric TTF treatment; and
☐ KPS score of >60; and
☐ Documentation that the individual and/or caregiver have been applying the device daily; and
☐ Documentation that the patient has been wearing the device at least 18 hours daily.

Note: Use of the treatment planning software (NovoTAL transducer array layout system) for use with tumor treatment fields is considered experimental or investigational and not covered.
Computer software used for therapeutic radiology clinical treatment planning in conjunction with electric tumor treatment field (TTF) therapy is unproven and not medically necessary.
There is insufficient evidence to establish the efficacy of these products in the long-term outcomes of patients receiving electric TTF therapy.

2.0 **CONTRAINDICATIONS:** Devices generating ETTF for other malignancies is considered experimental and not covered. This is includes breast, lung, melanoma, ovarian, pancreas and sold tumor with brain mets.

3.0 **VIEWS OF THE SOUTHEAST PERMANENTE MEDICAL GROUP-**

4.0 **VERSIONS:** Tumor treatment fields for patients meeting above indications and recommended by neuro oncologist may be approved on a case by case basis.

- The following are previous review/revision of this review criteria: N/A
- The following is most recent review/revision: 2/7/2019, 1/3/2020, 1/21/2021, 1/10/2022

- **5.0 REFERENCES:**

1.1 INTC 4/27/2020 **Tumor Treating Fields (TTF) Therapy (Optune Systems (NovoTTF-100A/200A), Novocure) for Newly Diagnosed or Recurrent Glioblastoma Multiforme (GBM)**

The existing evidence on the effectiveness and safety of Tumor Treating Fields (TTF) Therapy (Optune) is of insufficient quantity and quality patients with newly diagnosed or recurrent Glioblastoma Multiforme (GBM).

Based on evidence reviewed in a recent Hayes, Inc. report, there is low-quality evidence that Tumor Treating Fields (TTF) may increase the survival while minimizing adverse events of patients with newly diagnosed and/or recurrent GBM.

- UpToDate: Management of Recurrent High-Grade Gliomas 12/2020

ALTERNATING ELECTRIC FIELDS — A portable medical device that generates low-intensity alternating electric fields (tumor treating fields [TTFields]) is also available for treatment of recurrent glioblastoma. Clinicians must be trained and certified to prescribe the device. The device is applied to a shaved scalp, with four transducer arrays connected to a portable battery or power supply operated device; continuous treatment is recommended. The device is an alternative to other salvage therapies for interested patients.

Approval in the United States, Europe, and elsewhere was based on results of a clinical trial that randomly assigned 237 patients with recurrent glioblastoma to TTFields or clinician's choice chemotherapy [97]. The majority of patients were enrolled at the time of second or greater recurrence and approximately 20 percent had received prior bevacizumab. Median progression-free and overall survival were similar in those treated with TTFields versus chemotherapy (2.2 versus 2.1 months and 6.6 versus 6 months, respectively). The objective response rate was nonsignificantly higher in patients treated with TTFields compared with chemotherapy (14 versus 10 percent). Quality-of-life data available in only 27 percent of patients were similar between groups. Mild to moderate scalp dermatitis related to transducer arrays was the most common device-related side effect (16 percent). Hematologic and gastrointestinal adverse events, primarily mild or moderate, occurred in 20 percent of those treated with chemotherapy and less than 3 percent of device-treated patients.

A subsequent open-label randomized trial in patients with newly diagnosed glioblastoma showed prolonged progression-free and overall survival in the group assigned to TTFields when used in combination with postradiation temozolomide [98]. (See "Initial postoperative therapy for glioblastoma and anaplastic astrocytoma", section on 'Alternating electric fields'.)

Consensus-based guidelines published by the National Comprehensive Cancer Network (NCCN) include alternating electric field therapy as a treatment option for patients with recurrent glioblastoma based on the trial data reviewed above as well as postmarketing analysis of >450 patients treated commercially in the United States [22,99].

Hayes Technology Rating: December 2021 – C

Quality of the Evidence
The body of evidence regarding TTF therapy for the treatment of patients with GBM was small in size. The overall quality of the body of evidence pertaining to TTF for treatment of recurrent GBM was considered to be of low quality primarily because of the small quantity of data and lack of concurrent control or comparator groups in most studies. The body of evidence pertaining to TTF for treatment of newly diagnosed GBM was considered to be of low quality because of the small quantity of data for this indication. Overall quality was based on the balance of benefits and harms and was assessed taking into consideration the quality of individual studies; the precision, directness, and consistency of data; and the applicability of the data to general practice.
Conclusion
A low-quality body of evidence suggests that TTF results in OS and PFS at least as effective as chemotherapy for prolonging OS and PFS in patients with recurrent GBM. A low-quality body of evidence suggests that TTF plus TMZ may increase OS and PFS compared with TMZ alone in patients with newly diagnosed GBM. Data from 2 studies suggest that QOL was similar between groups, with the only statistically significant difference being itchy skin in the TTF groups compared with the chemotherapy groups. No serious adverse events related to TTF treatment occurred. The most common complication reported was mild-to-moderate dermatitis under the transducer arrays.
Insights
- The device manufacturer recommends that the device be worn for at least 18 hours per day for each 4-week treatment cycle. However, there are sparse data available in the reviewed literature of the impact of TTF treatment on QOL and functional measures.
- Compliance with the TTF device appears to be a factor associated with favorable treatment outcomes. Future studies should assess compliance in individual patients over the course of treatment.

ECRI: January 2019

The Optune® Treatment Kit provides tumor treating fields (TTFs) therapy and is intended for use as a monotherapy for recurrent glioblastoma (GBM) after patients receive chemotherapy and exhaust surgical and radiation options. TTFs are low-intensity, intermediate-frequency, alternating electric fields that disrupt division in proliferating cells. The kit includes the electric field generator, insulated electrode transducer arrays, power supply, battery charger and rack, battery, connection cables, and case. To apply TTF therapy, the clinician places four insulated transducer arrays on the patient's shaved scalp according to the tumor's location for 20 to 24 hours per day.

Conclusions: Evidence from one high-quality randomized controlled trial (RCT) indicates TTF plus TMZ increases overall survival and progression-free survival in patients with newly diagnosed glioblastoma compared to TMZ alone. Quality of life (QOL) and systemic adverse events (AEs) did not differ statistically between the two groups. Independent RCTs comparing TTF plus TMZ with TMZ alone would be informative to confirm these findings. Ongoing TTF trials are addressing other issues. Moderate-strength evidence indicates TTF results in fewer adverse events (AEs) than chemotherapy (i.e., serious hematologic AEs, diarrhea, nausea, infection, anorexia, muscle weakness). However, moderate-strength evidence shows no difference in median overall survival between TTF and best standard care (BSC) chemotherapy. Low-strength evidence indicates TTF results in more skin-site reactions and falls than BSC. Studies comparing TTF with BSC reported on too few patients to permit conclusions for quality of life. None of the 6 small ongoing trials will address key evidence gaps.

- **Aetna CPB Electronic Tumor Treatment Fields 11/24/2021**
  Aetna considers devices to generate electric tumor treatment fields (ETTF) medically necessary as monotherapy for persons with histologically confirmed glioblastoma (World Health Organization grade IV astrocytoma), after histologically or radiologically confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy.

- Aetna considers combination of devices to generate ETTF and temozolomide medically necessary as adjunctive treatment of newly-diagnosed histologically confirmed supratentorial glioblastoma following standard treatments that include surgery, chemotherapy, and radiation therapy.

- Aetna considers devices to generate ETTF experimental and investigational for the treatment of other malignant tumors (e.g., breast, lung, melanoma, ovarian cancer, pancreatic cancer, and solid tumor brain metastases; not an all-inclusive list) and for all other indications because their effectiveness has not been established.

Cigna – *Omnibus Codes*
"…Cigna covers TTF therapy (i.e., Optune) as **medically necessary** for individual 22 years of age or older with presence of histologically-confirmed glioblastoma multiforme (GBM) when EITHER of the following criteria are met:
• with confirmed recurrence after receiving chemotherapy and the device is being used as a monotherapy
• for adjuvant therapy with temozolomide…
Cigna does not cover the use of treatment planning software (i.e., NovoTAL) (CPT code 64999) for use

with tumor treatment fields for any indication because it is considered **experimental, investigational or unproven**…"

Regence Group – *Tumor Treating Fields Therapy for Glioblastoma*

I. "…Tumor treating fields (TTF) to treat primary supratentorial glioblastoma multiforme (GBM) may be considered **medically necessary** when all of the following are met:

NovoTAL System (Novocure) for the Treatment of Glioblastoma

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4/9/2018

A. Patient is 18 years of age or older; and
B. Documentation of histologically-confirmed primary supratentorial GBM; and
C. Following radiation and chemotherapy; and
D. Concurrent treatment with temozolomide (TMZ), unless TMZ has been ineffective, not tolerated, or is contraindicated.

II. The use of mapping software to optimize TTF therapy may be considered **medically necessary** for GBM when patients meet criterion I. above.

III. The use of TTF and/or TTF-associated mapping software is considered **investigational** when the above criterion I. is not met…"

- **UnitedHealthcare –** *Electric Tumor Treatment Field Therapy- November 2017*
- "…The use of U.S. Food and Drug Administration (FDA) approved devices to generate electric tumor
- treatment fields (TTF) to treat histologically-confirmed supratentorial glioblastoma (known also as
- glioblastoma multiforme [GBM] or World Health Organization [WHO] grade IV astrocytoma) is proven and
- medically necessary as adjunctive therapy when used according to FDA labeled indications,
- contraindications, warnings and precautions, and when ALL of the following criteria are met:
- Initial treatment with debulking surgery or biopsy followed by chemoradiation with concomitant
- temozolomide and radiotherapy has been completed; and
- • Individual has Karnofsky Performance Status (KPS) score of >60; and
- • Individual or caregiver has been trained and is willing and able to apply the device daily; and
- • Individual is willing to wear the device at least 18 hours daily…

- Computer software used for therapeutic radiology clinical treatment planning in conjunction with electric
- tumor treatment field therapy is **unproven** and **not medically necessary**. There is insufficient evidence
- to establish the efficacy of these products in the long-term outcomes of patients receiving electric tumor
- treatment field therapy…

Anthem: June 2017

The use of FDA approved devices to generate electric tumor treatment fields (TTF) to treat histologically-confirmed supratentorial glioblastoma (known also as glioblastoma multiforme [GBM] or World Health Organization [WHO] grade IV astrocytoma) is considered **medically necessary as adjunctive treatment** when **all** of the following criteria below are met:

A. Initial treatment with debulking surgery or biopsy followed by chemoradiation with concomitant temozolomide and radiotherapy has been completed with no documented tumor progression*; **and**

B. TTF is used in combination with temozolomide; **and**

C. TTF is initiated within 7 weeks from final dose of temozolomide and radiotherapy; **and**

D. Individual has Karnofsky Performance Status score of 70 or higher **or** Eastern Cooperative Oncology Group (ECOG) performance status 0-1; **and**

E. Individual or caregiver has been trained and is willing and able to apply and maintain the device at least 18 hours every day.

*Progression is defined as tumor growth greater than 25% compared to smallest measured tumor area **or** the appearance of one or more new GBM lesions in the brain.

Investigational and Not Medically Necessary:

The use of devices to generate electric tumor treatment fields (TTF) is considered **investigational and not medically necessary** when the criteria above are not met and for all other malignant tumors.

Insurers covering NovoTal Software (CPT64999)- Aetna and Regence only

Eastern Cooperative Oncology Group (ECOG) Performance Status: A scale used to determine the individual's level of functioning. This scale may also be referred to as the WHO or Zubrod score which is based on the following scale:

0	Fully active, able to carry on all pre-disease performance without restriction

1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Glioblastoma multiforme: Stage IV glioblastoma, which includes WHO recognized variants, giant cell glioblastoma and

Karnofsky Performance Status Score: A 10-point scale used by healthcare providers to quickly evaluate how an individual is feeling on any given day.

100	Able to work. Normal; No complaints; No evidence of disease.
90	Able to work. Able to carry on normal activity; Minor symptoms.
80	Able to work. Normal activity with effort; Some symptoms.
70	Independent; not able to work. Cares for self; Unable to carry on normal activity.
60	Disabled; dependent. Requires occasional assistance; cares for most needs.
50	Moderately disabled; dependent. Requires considerable assistance and frequent care.
40	Severely disabled; dependent. Requires special care and assistance.
30	Severely disabled. Hospitalized, death not imminent.
20	Very sick. Active supportive treatment needed.
10	Moribund. Fatal processes are rapidly progressing

Approval

_____ 1/30/2017_____

Rhoda Sharp, MD, MBA
Physician Program Director, Quality Resource Management **Date**

_____ _____

Date

Date