Introduction

Tumor treating fields (TTF) is a new treatment being studied for use in certain cancers. The therapy consists of low-level electrical currents that arise from small insulated electrodes placed on the skin surface. TTF is believed to cause cell death during a later stage of development. Currently this therapy is covered as one treatment option for people who have a deadly form of brain cancer called glioblastoma multiforme. People wear a helmet with small electrodes attached to the scalp for at least 18 hours per day during TTF therapy. This treatment requires pre-approval by the plan, and this policy describes when this treatment is covered. TTF is considered investigational for other types of cancer (therefore not covered), as there is not yet enough scientific data that shows it works for other diagnoses.

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.
**Condition**

### Glioblastoma - adjuvant therapy

Tumor treating fields (TTF) therapy to treat glioblastoma is medically necessary when ALL of the following are met:

- The patient has completed debulking surgery or biopsy
- AND
- The patient has completed radiation therapy
- AND
- The patient is being treated with temozolomide
- AND
- TTF therapy is begun within 7 weeks of the final radiation treatment

### Glioblastoma - for advanced or recurrent disease

Tumor treating fields therapy (TTF) to treat advanced or recurrent glioblastoma is considered investigational.

### All other diagnoses

Tumor treating fields (TTF) is considered investigational for all other indications.

**Coding**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A4555</td>
<td>Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only</td>
</tr>
<tr>
<td>E0766</td>
<td>Electrical stimulation device used for cancer treatment, includes all accessories, any type</td>
</tr>
</tbody>
</table>

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Background

*Glioblastome Multiforme*

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults. They comprise approximately 15% of all brain and central nervous system tumors, and more than 50% of all tumors that arise from glial cells.\(^1\) The peak incidence for GBM occurs between the ages of 45 and 70 years. GBMs are grade IV astrocytomas, the most deadly type of glial cell tumor, and are often resistant to standard chemotherapy.\(^1\) According to the National Comprehensive Cancer Network, only a third of patients with GBM survive for 1 year and less than 5% live beyond 5 years.\(^2\)

*Treatment of Glioblastoma Multiforme*

The primary treatment for initial GBM is debulking surgery to remove as much of the tumor as possible. At that time, some patients may undergo implantation of the tumor cavity with a carmustine (bis-chloroethylnitrosourea, or BCNU) impregnated wafer.\(^2\) Depending on the patient’s physical condition, adjuvant radiotherapy and/or chemotherapy (typically temozolomide) are sometimes given. After adjuvant therapy, some patients may undergo maintenance therapy with temozolomide.

No standard treatment exists for recurrent GBM. After these initial treatments, additional debulking surgery may be used if recurrence is localized. Other treatment options for recurrent disease include various forms of systemic medications such as bevacizumab and bevacizumab combined with other chemotherapy such as irinotecan, BCNU/chloroethylnitrosourea (CCNU), or temozolomide. Temozolomide, nitrosourea, PCV (a combination of procarbazine, CCNU, and vincristine), cyclophosphamide, and platinum-based agents have also been used.\(^2\) External beam radiotherapy also may be used. Response rates in recurrent disease are less than 10%, and progression-free survival at 6 months is typically less than 20%.\(^2,3\)
**Tumor Treating Fields Therapy**

TTF therapy is a new, noninvasive technology intended to treat GBM on an outpatient basis using electrical fields. TTF therapy exposes cancer cells to alternating electric fields of low intensity and intermediate frequency, which are purported to both selectively inhibit tumor growth and reduce tumor angiogenesis. TTF are proposed to inhibit rapidly dividing tumor cells by two mechanisms: arrest of cell proliferation and destruction of cells while undergoing division.

The NovoTTF-100A System has received marketing approval from the U.S. Food and Drug Administration to deliver TTF therapy. TTF therapy via the NovoTTF-100A System is delivered by a battery-powered, portable device that generates the fields via disposable electrodes noninvasively attached to the patient’s shaved scalp over the site of the tumor. The device is used by the patient at home on a continuous basis (20-24 h/d) for the duration of treatment, which can last for several months. The device is covered under the DME benefit. Patients can carry the device in a backpack or shoulder pack while carrying out activities of daily living.

**Summary of Evidence**

For individuals who have progressive or recurrent glioblastoma multiforme (GBM) after initial or repeat surgery, radiotherapy, and/or chemotherapy who then receive tumor treatment fields (TTF) therapy as an alternative to standard chemotherapy, the evidence includes a randomized controlled trial (RCT) and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The published RCT reported no differences in outcomes between patients treated with TTF and with standard chemotherapy. This trial had several methodologic limitations. Comparisons that were made only included an active control of questionable efficacy, which might not reflect current standard of care. There was a high dropout rate (>20% of patients in each group were lost to follow-up) and, for the quality of life outcomes, only 25% of enrolled patients had complete data. The 2 nonrandomized studies were small and had limited validity due to differences in the patient populations treated with TTF and standard care. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have newly diagnosed GBM and receive TTF therapy as an adjunct to standard maintenance therapy following their initial treatment with surgery, radiotherapy, and/or chemotherapy, the evidence includes a single RCT. Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The single RCT reported that patients who received TTF treatment plus
temozolomide had longer progression-free survival (3.1 months) and overall survival (4.9 months) than patients who received temozolomide alone. However, the trial had methodologic limitations including the lack of a placebo control, differential dropout between groups, and the possibility of adherence bias for outcomes reported with per-protocol analysis. Further corroboration of these results is needed in high-quality RCTs. Although evidence is limited, NCCN has given this therapy a 2A rating. There are very few treatment options for this disease, and the side effect profile of TTF is much more tolerable to patients.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NCT01894061a</td>
<td>A Prospective Phase II Trial of NovoTTF-100A With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma</td>
<td>40</td>
<td>Dec 2017</td>
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<tr>
<td>NCT01756729a</td>
<td>A Prospective, Non-randomized, Concurrent Control, Open Label, Post-approval Study of NovoTTF-100A in Recurrent GBM Patient</td>
<td>486</td>
<td>Jan 2018</td>
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<tr>
<td>NCT02743078a</td>
<td>Phase II Trial Of Optune® Plus Bevacizumab In Bevacizumab-Refractory Recurrent Glioblastoma</td>
<td>85</td>
<td>Apr 2018</td>
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<tr>
<td>NCT01954576</td>
<td>A Phase II Study of the NovoTTF-100A system, Enhanced by Genomic Analysis to Identify the Genetic Signature of Response in the Treatment of Recurrent Glioblastoma Multiforme</td>
<td>30</td>
<td>May 2018</td>
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<tr>
<td>NCT02663271a</td>
<td>A Phase 2, Multi-center, Single Arm, Histologically Controlled Study Testing the Combination of TTFFields and Pulsed Bevacizumab Treatment in Patients With Bevacizumab-refractory Recurrent Glioblastoma</td>
<td>25</td>
<td>May 2018</td>
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<tr>
<td>NCT02893137a</td>
<td>Phase 1 Enhancing Optune Therapy of Recurrent Glioblastoma Multiforme Using Targeted Surgical Skull Remodeling</td>
<td>15</td>
<td>Oct 2019</td>
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</tbody>
</table>
### NCT No. | Trial Name | Planned Enrollment | Completion Date
--- | --- | --- | ---
NCT01925573\(^a\) | Proposed Pilot Study of Combined Optune+ Bevacizumab, and Hypofractionated Stereotactic Irradiation for Bevacizumab-Naive Recurrent Glioblastoma | 27 | Dec 2021

NCT: national clinical trial. \(^a\) Denotes industry-sponsored or cosponsored trial.

### Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may provide appropriate reviewers who collaborate with and make recommendations during this process, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 3 physician specialty societies (one of which provided 6 responses and 2 of which provided 1 response each) and 1 academic medical center (total of 9 individual responses) while this policy was under review in 2016. There was majority support, but not consensus, for use of tumor treatment fields therapy as an adjunct to maintenance treatment following initial therapy for glioblastoma multiforme. There was mixed support for the use of tumor treatment fields as an alternative to chemotherapy in advanced or recurrent glioblastoma multiforme.

### Practice Guidelines and Position Statements

National Comprehensive Cancer Network guidelines on central nervous system cancers (v.1.2016)\(^2\) include a recommendation for the treatment of glioblastoma. For the initial treatment of patients with glioblastoma with good performance status and either methylated or unmethylated or indeterminate MGMT promotor status, treatment with standard brain radiotherapy plus concurrent temozolomide and adjuvant temozolomide plus alternating electric currents therapy is a category 2A recommendation. Alternating electric currents therapy is only an option for patients with supratentorial disease. Consideration of alternating electric field therapy for recurrent glioblastoma is a 2B recommendation.
Medicare National Coverage

There is no National Coverage Decision (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Regulatory Status

In April 2011, the NovoTTF-100A™ System (Novocure, Haifa, Israel; 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 [glioblastoma multiforme], 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 to change its product name 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 currently available for the treatment of newly diagnosed GBM that represents a life-threatening condition.

The FDA-approved label 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.”

Based on the 2011 approval Optune® is also approved for the treatment of recurrent GBM in the supratentorial region of the brain after receiving chemotherapy. The device is intended for use as a monotherapy, and as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

FDA product code: NZK.


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>10/14/13</td>
<td>New Policy. Policy created with literature search through June 3, 2013; considered investigational.</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>-----------</td>
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<tr>
<td>12/06/13</td>
<td>Update Related Policies. Removed 8.01.31 as it was archived.</td>
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<tr>
<td>09/01/16</td>
<td>Annual Review, approved August 9, 2016. Changed statement to MN when criteria are met.</td>
</tr>
<tr>
<td>03/30/17</td>
<td>Coding correction; updated code descriptions. Minor formatting update.</td>
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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
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Italiano (Italian):
