Tumor-Treatment Fields Therapy for Glioblastoma

Policy Number: 1.01.29
Origination: 12/2013
Last Review: 12/2017
Next Review: 12/2018

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for tumor-treatment fields therapy for glioblastoma. This is considered investigational.

Please note that this is a type of electrical stimulation that is considered a benefit exclusion in many health plan contracts.

When Policy Topic is covered
Not Applicable

When Policy Topic is not covered
Tumor treatment fields therapy to treat glioblastoma is considered investigational, including but not limited to the following situations:

- As an alternative to standard chemotherapy for patients with advanced or recurrent glioblastoma multiforme after initial or repeat treatment with surgery, radiotherapy, and/or chemotherapy.
- As an adjunct to standard maintenance therapy in patients with glioblastoma multiforme following initial treatment with surgery and/or radiotherapy, and/or chemotherapy.

Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Individuals:  
  - With progressive or recurrent glioblastoma multiforme after initial or repeat surgery, radiotherapy, and/or chemotherapy | Interventions of interest are:  
  - Tumor treatment fields therapy as an alternative to standard chemotherapy | Comparators of interest are:  
  - Standard chemotherapy | Relevant outcomes include:  
  - Overall survival  
  - Disease-specific survival  
  - Quality of life  
  - Treatment-related morbidity |
| Individuals:  
  - With glioblastoma multiforme on maintenance therapy after initial treatment | Interventions of interest are:  
  - Tumor treatment fields therapy as an adjunct to | Comparators of interest are:  
  - Standard maintenance therapy alone | Relevant outcomes include:  
  - Overall survival  
  - Disease-specific survival |
Glioblastoma multiforme is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during the course of treatment. Tumor-treatment fields therapy is a new, noninvasive technology that is intended to treat glioblastoma using electrical fields.

For individuals who have advanced or recurrent GBM who receive TTF therapy as an alternative to standard chemotherapy, the evidence includes 1 randomized controlled trial (RCT) and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The single published RCT reported no differences in outcomes between patients treated with TTF and standard chemotherapy. This trial had several methodologic limitations. Comparisons made only included an active control of questionable efficacy, which may not reflect current standard of care. There was high dropout (>20% of patients in each group were lost to follow-up) and, for the quality of life outcomes, only approximately 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 GBM on maintenance therapy after initial treatment with surgery and/or radiotherapy who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes 1 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. The trial had methodologic limitations, including a 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

**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. 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. According to the National Comprehensive Cancer Network, GBM is the “most lethal
brain tumor with only a third of patients surviving for 1 year and less than 5% living beyond 5 years."²

**Treatment**
The primary treatment for patients newly diagnosed with GBM is to resect the tumor, confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. At the time of surgery, some patients may undergo implantation of the tumor cavity with a carmustine (bis-chloroethylNitrosourea)–impregnated wafer.² The cure rate with local treatment is very low; therefore, postsurgical treatment involves adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of the 2 therapies. After adjuvant therapy, some patients may undergo maintenance therapy with temozolomide. Prognostic factors for success of therapy are age, histology, and performance status or physical condition of the patient.

No standard treatment exists for recurrent GBM. In patients with disease that recurs after initial treatment, 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, bevacizumab plus chemotherapy (eg, irinotecan, bis-chloroethylNitrosourea/chloroethylNitrosourea, temozolomide), temozolomide, nitrosourea, procarbazine plus chloroethylNitrosourea and vincristine), cyclophosphamide, and platinum-based agents.²

Fractionated external-beam radiotherapy after surgery is standard adjuvant therapy and may be used to treat recurrent GBM. Response rates in recurrent disease are less than 10%, and progression-free survival rates at 6 months are less than 20%.²,³

Testing for O⁶-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation has been proposed as a method to predict which patients with malignant gliomas may benefit from alkylating agent chemotherapy (eg, temozolomide). Data from randomized controlled trials have shown that MGMT promoter methylation is a predictor to responding to alkylating chemotherapeutic agents. The response and overall survival rates with temozolomide are higher in patients who have MGMT promoter methylation. (See 2.04.113 on Analysis of MGMT promotor methylation in malignant gliomas.)

**Tumor Treatment Fields Therapy**
Tumor treatment fields (TTF) therapy is a noninvasive technology intended to treat GBM on an outpatient basis using electrical fields.³⁻⁵ TTF therapy exposes cancer cells to alternating electric fields of low intensity and intermediate frequency, which are purported selectively both to inhibit tumor growth and reduce tumor angiogenesis. TTF are proposed to inhibit rapidly dividing tumor cells by 2 mechanisms: arrest of cell proliferation and destruction of cells while undergoing division.⁴⁻⁵
Optune, formerly NovoTTF-100A System, is the only legally marketed TTF delivery system available in the United States. Optune is a portable battery or power supply operated device that produces alternating electrical fields within the human body. These fields are called tumor treatment fields and are applied to the patient’s shaved head using electrically insulated surface transducer arrays, such that resistively coupled electric currents are not delivered to the patient. The device is used at home on a continuous basis (20-24 hours a day for the duration of treatment). Patients can carry the device in a backpack or shoulder pack while carrying out activities of daily living.\(^6\)

**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.\(^2\) 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.”\(^2\)

In September 2014, FDA approved Novocure’s request to change its product name from NovoTTF-110A System to Optune®.\(^8\)

In October 2015, FDA expanded the indication for Optune® in combination with temozolomide to include newly diagnosed GBM.\(^6\) 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.

**Rationale**
This evidence review was created in August 2013 and has been updated regularly with searches of the MEDLINE database. The most recent literature review was performed through June 5, 2017.
Re-radiation options are limited for glioblastoma (GBM) patients who have received initial external-beam radiotherapy due to radiation tolerances. The tumors are locally invasive but do not metastasize, therefore, tumor treating fields (TTF) therapy as a locoregional intervention is proposed to treat GBM. For this review, we consider 2 indications: (1) TTF as an alternative to chemotherapy in progressive or recurrent GBM and (2) TTF as an adjunct to maintenance treatment in patients following initial treatment. Comparative trials are essential to determine efficacy in this area, and randomized controlled trials (RCTs) are needed to control for heterogeneity in the patient populations and other confounders of outcome. We include both RCTs and nonrandomized comparative trials. The following is a summary of the key literature.

**TTF Therapy as an Alternative to Chemotherapy for Progressive or Recurrent GBM**

**Randomized Controlled Trials**
The U.S. Food and Drug Administration (FDA) approval of the NovoTTF-100A System was based on a phase 3, multinational prospective RCT (EF-11), results from which were published in 2012 by Stupp et al. The Stupp study, which was supported by the manufacturer of the device (Novocure), compared TTF therapy (delivered by the NovoTTF-100A System) with best physician’s choice (BPC) standard of care chemotherapy (active treatment control). Twenty-eight clinical centers (across 7 countries) enrolled 237 adults with relapsed or progressive GBM, despite conventional radiotherapy. Other prior treatments may have included surgery and/or chemotherapy. Patient characteristics were balanced in both groups, with median age of 54 years old and median Karnofsky Performance Status score of 80%. More than 80% of participants had failed 2 or more prior chemotherapy regimens (≥ second recurrence), and 20% had failed bevacizumab before study enrollment. The performance of additional postrecurrence debulking surgery was 28% in the TFF arm and 25% in the active treatment arm. Prior low-grade glioma progressing to glioblastoma was present in 8% of each trial arm at baseline.

Two hundred thirty-seven patients were randomized in a 1:1 ratio to TTF therapy only (n=120) or active control (n=117). The choice of chemotherapy regimens varied, reflecting local practice at each participating clinical centers. Chemotherapy agents considered as active control during the trial included platinum-based chemotherapy (ie, carboplatin); nitrosoureas; procarbazine; combination of procarbazine, chloroethylnitrosourea, and vincristine; temozolomide; and bevacizumab. For patients assigned to the TTF group, uninterrupted treatment was recommended, although patients were allowed treatment breaks for up to 1 hour, twice a day, for personal needs (eg, shower). In addition, patients assigned to the TTF group were allowed to take 2 to 3 days off treatment at the end of each of 4-week period (which is the minimal required treatment duration for TTF therapy to reverse tumor growth). A period of 28 days of TTF therapy was considered 1 full treatment course.
The study was designed as a superiority trial. The primary end point was overall survival (OS). Secondary end points included progression-free survival (PFS) at 6 months, time to progression, 1-year survival rate, quality of life (QOL), and radiologic response. All end points were evaluated using intention-to-treat analysis. Participants were seen monthly in clinic, and magnetic resonance imaging (MRI) was performed after 2, 4, and 6 months from initiation of treatment, with subsequent MRI performed according to local practice until disease progression. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with participants' caregivers were used to assess mortality rates.

One hundred sixteen (97%) of 120 participants in the TTF group started treatment and 93 (78%) participants completed 1 cycle (4 weeks) of therapy. Discontinuation of TTF therapy occurred in 27 (22%) participants due to noncompliance or inability to handle the device. For each TTF treatment month, 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 except 1 individual completed a full treatment course. Twenty-one (18%) participants in the active control group did not return to the treating site and details on disease progression and toxicity were not available.

We summarize study outcomes in Table 1. The trial did not reach its primary end point of improved survival compared with active chemotherapy. With a median follow-up of 39 months, 220 (93%) participants had died. Median survival was 6.6 months in the TTF group compared with 6.0 months in the active control group (hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.66 to 1.12; p=0.27). For both groups, 1-year survival was 20%. Rates for 2- and 3-year survival were 8% and 4%, respectively, for the TTF group and 5% and 1%, respectively, for the active control group. PFS rate at 6 months was 21.4% in the TTF group compared with 15.1% in the active control group (p=0.13). Objective radiologic responses (partial and complete responses) were noted in 14 participants in the TTF group and in 7 in the active control group, with a calculated response rate of 14.0% (95% CI, 7.9% to 22.4%) versus 9.6% (95% CI, 3.9% to 18.8%), respectively. Sixteen percent of the TTF participants had grade 1 and 2 contact dermatitis on the scalp, which resolved with topical corticosteroids. Active control participants experienced grade 2 to 4 events by organ system related to the pharmacologic activity of chemotherapy agents used; severe (grades 3 and 4) toxicity was observed in 3% of participants.

Longitudinal QOL data were available in 63 (27%) participants. No meaningful differences were observed between groups for the domains of global health and social functioning. However, cognitive, emotional, and role functioning domains favored TTF therapy, whereas physical functioning favored chemotherapy. Symptom scale analysis was in accordance to treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration.
Wong et al (2014) published a subgroup analysis of the Stupp RCT (previously described) to determine characteristics of responders and nonresponders in the active treatment and active treatment control, per BPC groups. Tumor response was assessed using Macdonald criteria. More patients in the TTF arm were considered responders (14/120) than in the chemotherapy arm (7/117). Median response time was longer for those in the TTF arm (7.3 months) than in the chemotherapy arm (5.6 months; p<0.001), and there was a strong correlation (Pearson’s r) between response and OS 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%). Dexamethasone use among responders was also significantly lower than that among nonresponders in both the NovoTTF-100A and BPC cohorts, and responders had a lower daily dexamethasone usage than nonresponders. For the NovoTTF-100A cohort, the respective median and mean daily dexamethasone doses were 1.0 mg and 2.3 mg (95% CI, 0.8 to 3.8 mg) for responders and 5.2 mg and 6.8 mg (95% CI, 5.6 to 8.1 mg) for nonresponders (p=0.002). For the BPC chemotherapy cohort, the respective median and mean daily dexamethasone dose was 1.2 mg and 1.4 mg (95% CI, 0.3 to 2.4 mg) for responders and 6.0 mg and 7.2 mg (95% CI, 6.0 to 8.4 mg) for nonresponders (p=0.004) These differences in treatment responder groups would 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.

### Table 1. Randomized Trial of TTF vs Physicians’ Choice of Chemotherapy in Recurrent Glioblastoma: Principal Efficacy Results From Stupp et al³

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>TTF</th>
<th>Chemotherapy</th>
<th>Measure of Association, Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median overall survival, mo</td>
<td>6.6</td>
<td>6.0</td>
<td>0.86 (95% CI, 0.66 to 1.12)</td>
</tr>
<tr>
<td>Hazard ratio for overall survival</td>
<td></td>
<td></td>
<td>favors TTF</td>
</tr>
<tr>
<td>Radiologic response (not all</td>
<td>14%</td>
<td>9.6%</td>
<td>p=0.19</td>
</tr>
<tr>
<td>patients evaluated)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS, mo</td>
<td>2.2</td>
<td>2.1</td>
<td>0.81 (95% CI, 0.60 to 1.09)</td>
</tr>
<tr>
<td>Hazard ratio for PFS</td>
<td></td>
<td></td>
<td>favors TTF</td>
</tr>
</tbody>
</table>

CI: confidence interval; PFS: progression-free survival; TTF: tumor treatment fields.

A second post hoc analysis (2014) of the EF-11 pivotal trial data was performed to evaluate OS rates among patients who finished at least 1 complete course of TTF or chemotherapy. Investigators analyzed survival in what they referred to as a “modified intention-to-treat” subgroup comprising 93 (78%) of 120 of the original TTF-allocated group and 117 (100%) of 117 of the original chemotherapy allocated group. This exercise revealed median OS of 7.7 months in the TTF-modified intention-to-treat group compared with 5.9 months in the chemotherapy group (HR=0.69; 95% CI, 0.52 to 0.91; p=0.009). They also showed a trend between the proportion of patients with higher TTF compliance and median OS rates (p=0.039). The investigators suggested that TTF therapy provides an OS benefit when used as intended in the FDA-approved label compared with best chemotherapy. This post hoc analysis was limited because it was not prespecified,
included only 78% of the original TTF allocated patients, and it failed to control for noncompliance due to faster clinical deterioration of TTF recipients leading to treatment cessation.

**Nonrandomized Comparative Studies**

Two nonrandomized studies were identified that compared TTF treatment with standard care using historical controls. A study published in late 2014 assessed OS data from 457 patients included in the Patient Registry Dataset (PRiDe), a postmarketing registry of all recurrent GBM patients who received NovoTTF therapy in a real-world, clinical practice setting at 91 centers in the United States between October 2011 and November 2013.\(^1\) Median OS in the PRiDe clinical practice dataset (9.6 months) was reported as significantly superior to that attained in the EF-11 pivotal trial (6.6 months; HR=0.66, 95% CI, 0.05 to 0.86; \(p<0.001\)). One- and 2-year OS rates for TTF in PRiDe were significantly longer than those in the TTF group in the EF-11 trial (44% vs 20% at 1 year; 30% vs 9% at 2 years, respectively). The PRiDe investigators reported no novel or unexpected treatment-related adverse events compared with the EF-11 trial.

Kirson et al (2007) reported findings of a study examining the effects of TTF therapy delivered by the NovoTTF-100A System in 10 patients with recurrent GBM.\(^12\) Median time to progression in these patients was 26.1 weeks, and median OS was 62.2 weeks. The authors noted that these time to progression and OS rates were more than double the medians reported for historical control patients. No device-related serious adverse events were seen after more than 70 months of cumulative treatment in all patients. The only device-related adverse event observed was a mild-to-moderate contact dermatitis beneath the field delivering electrodes. The primary limitation of this study was its use of historical controls, because those patients might not be comparable on major clinical and prognostic features.

**Section Summary: TTF Therapy as an Alternative to Chemotherapy for Progressive or Recurrent GBM**

The single RCT for this indication reported that outcomes following TTF therapy were similar to outcomes following standard chemotherapy. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. There was no placebo control group or supportive care treatment group, and treatments used in the active control arm (best standard of care chemotherapy) have previously demonstrated limited efficacy. Thus, the comparisons made have limited ability to determine the true treatment effect of TTF. Also several methodologic limitations in the study reduce its internal validity. There was heterogeneity in the patient populations and heterogeneity in the chemotherapy regimens for the control group. Furthermore, more patients in the TTF group than in the control group did not complete the treatment course, and patients in the TTF group received more courses of second-line chemotherapy. The number of patients who completed the QOL data was approximately one-quarter of total enrollment, and the self-reported QOL indicators may have been subject to bias due to the lack of blinding.\(^3\) The other published evidence—2 nonrandomized comparative studies—had small sample sizes and was limited by potential differences in patient populations. Thus,
this evidence base does not permit conclusions about the impact of the technology on health outcomes.

**TTF Therapy as an Adjunct to Standard Maintenance Care for GBM**

In 2015, Stupp et al published a planned interim analysis of a multicenter, open-label RCT that evaluated maintenance therapy with TTF for GBM. This trial enrolled patients with GBM who had completed standard treatment consisting of biopsy or surgical resection followed by chemoradiotherapy with temozolomide. A Karnofsky Performance Status score of 70% or higher was an additional inclusion criterion. Patients were randomized in a 2:1 fashion to TTF plus temozolomide or to temozolomide alone. At the time of the interim analysis, 210 patients were randomized to TTF plus temozolomide and 105 patients to temozolomide alone. The primary outcome was PFS analyzed by intention-to-treat; a secondary outcome was OS analyzed by per-protocol analysis.

Patients in the TTF group received continuous TTF therapy delivered mainly in the home setting. Patients were trained on use of the device, including changing the electrodes, and then treatment continued at home. Patients were encouraged to wear the device continuously, with the exception of short breaks to attend to personal needs. All patients were seen monthly for follow-up. Further, MRI was performed every 2 months and QOL measures administered every 3 months. Tumor progression was adjudicated by a central review committee blinded to treatment group.

Planned interim analysis was performed at a median follow-up of 38 months (range, 18-60 months). Median PFS and median OS are summarized in Table 2.

**Table 2. TTF Therapy as an Adjunct to Standard Maintenance Care in Glioblastoma Multiforme**

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Progression-Free Survival (95% CI), mo</th>
<th>Hazard Ratio (98.7% CI)</th>
<th>Overall Survival (95% CI), mo</th>
<th>Hazard Ratio (99.4% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTF + temozolomide</td>
<td>210 (196&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>7.1 (5.9 to 8.2)</td>
<td>0.62 (0.43 to 0.89)</td>
<td>20.5 (16.7 to 25)</td>
<td>0.64 (0.42 to 0.98)</td>
</tr>
<tr>
<td>Temozolomide alone</td>
<td>105 (84&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>4.0 mo (3.3 to 5.2)</td>
<td>15.6 mo (13.3 to 19.1)</td>
<td>\</td>
<td>\</td>
</tr>
</tbody>
</table>

CI: confidence interval; TTF: tumor treatment fields.

<sup>a</sup> Included in per-protocol analysis.

There were 35 (11%) dropouts during the trial—14 (6.7%) of 210 patients in the TTF group and 21 (20%) of 105 in the temozolomide-alone group. Adherence to treatment was defined as wearing the device for at least 18 hours a day, and 157 (75%) of 210 patients met this adherence criterion. The number of treatment cycles with temozolomide differed between groups. The TTF group received a median of 6 cycles compared with a median of 4 cycles for the temozolomide-
alone group. The most common side effect of treatment was local skin irritation, which occurred in 43% of patients treated with TTF.

In October 2014, the trial independent data and safety monitoring committee reviewed the interim analysis, concluding that the trial met its predefined boundaries for success (improvement in PFS and OS) and recommended trial termination. The FDA approved study termination and the trial was closed to recruitment that November after 695 of the planned 700 participants had been randomized. All patients in the control maintenance therapy arm could crossover to receive TTFs. At the time of the Stupp interim analysis, 35 control arm participants had crossed over. FDA considered the results of this analysis for the 2015 expanded approval of Optune.

**Section Summary: TTF Therapy as an Adjunct to Standard Maintenance Care for GBM**

The single RCT for this indication has reported that PFS improved by 3.1 months and OS improved by 4.9 months with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide). Therefore, there may be a survival benefit associated with TTF for this indication, but there is substantial uncertainty around this conclusion. The single RCT has methodologic limitations and the current publication is a planned interim analysis. The lack of a placebo group and the lack of blinding create the possibility of a placebo effect, even with the survival outcomes. There was a moderately high overall dropout rate (11%) and differential dropout between groups (6.7% in the TTF group vs 20% in standard maintenance group). Also, for outcomes evaluated on a per-protocol basis, there is the possibility of an adherence bias, in that patients who completed the treatment protocol may have better outcomes than patients who did not. As a result, conclusions about the efficacy of TTF for this indication lack certainty.

**Summary of Evidence**

For individuals who have progressive or recurrent glioblastoma multiforme (GBM) after initial or repeat surgery, radiotherapy, and/or chemotherapy—who 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 made only included an active control of questionable efficacy, which might not reflect current standard of care. There was high dropout rate (>20% of patients in each group were lost to follow-up) and, for the quality of life outcomes, approximately 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 on maintenance therapy after initial treatment with surgery, radiotherapy, and/or chemotherapy who receive TTF
therapy as an adjunct to standard maintenance therapy, the evidence includes an 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. The trial had methodologic limitations, including a 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Supplemental Information**

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

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, 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 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.

**U.S. Preventive Services Task Force Recommendations**

Not applicable.
Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished or ongoing trials that might influence this review are listed in Table 3.

Table 3. 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>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
</tr>
<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>
</tr>
<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>
</tr>
<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>
</tr>
<tr>
<td>NCT02663271a</td>
<td>A Phase 2, Multi-center, Single Arm, Histologically Controlled Study Testing the Combination of TTFields and Pulsed Bevacizumab Treatment in Patients With Bevacizumab-refractory Recurrent Glioblastoma</td>
<td>25</td>
<td>May 2018</td>
</tr>
<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>
</tr>
<tr>
<td>NCT01925573a</td>
<td>Proposed Pilot Study of Combined Optune+ Bevacizumab, and Hypofractionated Stereotactic Irradiation for Bevacizumab-Naive Recurrent Glioblastoma</td>
<td>27</td>
<td>Dec 2021</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

* Denotes industry-sponsored or cosponsored trial.

References

Billing Coding/Physician Documentation Information

A4555   Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only
E0766   Electrical stimulation device used for cancer treatment, includes all accessories, any type

There are no specific codes for this system or the initial application and instruction on use. The patient re-applies the transducer arrays at home after the initial instruction. Currently the system is reported with the miscellaneous durable medical equipment (DME) code E1399 and the replacement transducer arrays are reported with the miscellaneous DME supply, accessory and/or service code A9900.

ICD-10 Codes
C71.0- C71.9   Malignant neoplasm of brain code range

Additional Policy Key Words
N/A

Policy Implementation/Update Information
12/1/13   New Policy; considered investigational.
12/1/14   No policy statement change
12/1/15   No policy statement changes.
12/1/16   Policy statements rewritten for clarity but tumor treating fields remains
investigational for all indications.

Policy statements rewritten for clarity but tumor treating fields remains investigational for all indications.

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.