I. POLICY

Tumor treating 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
- As an adjunct to standard maintenance therapy in patients with glioblastoma multiforme following initial treatment with surgery and/or radiotherapy.

There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

II. PRODUCT VARIATIONS

This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

**FEP PPO**  **BlueJourney HMO**  **BlueJourney PPO**

*Refer to FEP Medical Policy Manual MP-1.01.29 Tumor Treating Fields Therapy for Glioblastoma. The FEP Medical Policy manual can be found at: [www.fepblue.org](http://www.fepblue.org)

**Refer to Novitas Solutions Local Coverage Determination (LCD) L34823 Tumor Treatment Field Therapy (Ttft)
III. DESCRIPTION/BACKGROUND

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-treating fields therapy (TTF) is a new, noninvasive technology that is intended to treat glioblastoma using electrical fields.

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults, and 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 (NCCN, 2013), GBM is the "deadliest brain tumor with only a third of patients surviving for one year and less than 5% living beyond 5 years."2

The primary treatment for GBM is debulking surgery to remove as much of the tumor as possible. At that time, some patients may undergo implantation with a carmustine (BCNU)-impregnated wafer. Depending on the patient’s physical condition, adjuvant radiation therapy, chemotherapy (typically temozolomide), or a combination of the two are sometimes given. After adjuvant therapy, some patients may undergo maintenance therapy with temozolomide. In patients with disease that recurs after these initial therapies, additional debulking surgery may be used if recurrence is localized. Treatment options for recurrent disease include various forms of systemic medications such as bevacizumab, bevacizumab plus chemotherapy (e.g., irinotecan, BCNU/CCNU, temozolomide), temozolomide, nitrosourea, PCV (procarbazine, CCNU, and vincristine), cyclophosphamide, and platinum-based agents. Response rates in recurrent disease are below 10%, and progression-free survival rates at 6 months are less than 20%.2,3

Tumor-treating fields (TTF) therapy is a new, noninvasive technology that is 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 to both selectively inhibit tumor growth and reduce tumor angiogenesis. Tumor-treating fields are proposed to inhibit rapidly dividing tumor cells by two mechanisms, arrest of cell proliferation and destruction of cells while undergoing division.4,5

The NovoTTF-100A™ System (Novocure Ltd., Haifa, Israel) has been approved by the Food and Drug Administration (FDA) 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 that are 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 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 carrying out activities of daily living.3,4
Regulatory Status
The NovoTTF-100A™ System (assigned the generic name of tumor-treatment fields) was cleared by the Food and Drug Administration (FDA) in April 2011. The FDA-approved indication for use is: “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.”

On September 28, 2014, FDA approved a request for Novocure to change its products name from NovoTTF-110A System to Optune™.

On May 11, 2015, FDA granted a priority review status for Novocure’s premarket approval supplemental applications for the use of Optune in combination with temozolomide for newly diagnosed glioblastoma.

IV. RATIONALE

This evidence review was created in August 2013 and updated periodically through literature reviews, most recently through July 18, 2016. No new studies were identified that would change the conclusions of the evidence review. Following is a summary of the key literature.

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 randomized controlled trial (RCT) (EF11) which was published in 2012 by Stupp et al. The Stupp study, which was sponsored and funded by the manufacturer of the device (Novocure), compared tumor-treatment fields (TTF) therapy (delivered by the NovoTTF-100A System) with the best standard of care chemotherapy (active control). Twenty-eight clinical centers (across 7 countries) enrolled 237 adult participants with relapsed or progressive glioblastoma multiforme (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 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.

Two hundred thirty-seven patients were randomized in a 1:1 ratio to receive TTF therapy only (n=120) or active control (n=117). The choice of chemotherapy regimens varied, reflecting local practice at each of the participating clinical centers. Chemotherapy agents considered as active control during the trial included platinum-based chemotherapy (ie, carboplatin); nitrosoureas; procarbazine; combination of procarbazine, lomustine and vincristine (PCV); temozolomide; and bevacizumab. For patients assigned to the TTF group, uninterrupted treatment was recommended, although patients were allowed to take treatment breaks of up to 1 hour, twice per 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 treatment with TTF was considered 1 full treatment course.

The primary study end point in this RCT was overall survival (OS). Secondary end points included progression-free survival (PFS) at 6 months, TTP, 1-year survival rate, quality of life (QOL), and radiologic response. Participants were seen in clinic monthly, and magnetic resonance imaging (MRI) was performed after 2, 4, and 6 months from initiation of treatment, with subsequent MRI done 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 participant mortality rates.

Ninety-seven percent (116) of 120 participants in the TTF group started treatment and 93 participants (78%) completed 1 cycle (4 weeks) of therapy. Discontinuation of TTF therapy occurred in 27 participants (22%) due to noncompliance or the inability to handle 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 except 1 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.

Outcomes of this study are summarized 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 versus 5% and 1%, respectively, for the active control group. Progression-free survival (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 response) were noted in 14 participants in the TTF group and 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. There were no meaningful differences observed between the groups in the domains of global health and social functioning. However, cognitive, emotional, and role functioning 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 published a subgroup analysis of the previously described RCT to determine characteristics of responders and nonresponders in the treatment and active control groups. Tumor response was assessed by the Macdonald criteria.
More patients in the TTF arm were considered responders (14/120 vs 7/117 in the chemotherapy arm.) Median response time was longer for those in the TTF arm than the chemotherapy arm (7.3 months vs 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%). 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.

A second post hoc analysis of the TTF EF-11 pivotal trial data was performed to evaluate OS rates among patients who completed at least 1 complete course of TTF or chemotherapy.\(^{10}\) These investigators analyzed survival in what they referred to as a “modified ITT [intention-to-treat]” subgroup comprising 93 (78%) of 120 of the original TTF allocated group, versus 117 (100%) of 117 of the original chemotherapy allocated group. This exercise revealed median OS of 7.7 months in the TTF modified ITT 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 relationship between proportion of patients with higher TTF compliance and median OS rates (\( p=0.039 \)). The investigators suggest that TTF provides an OS benefit if used as intended in the FDA-approved label when compared with best chemotherapy. This post hoc analysis is limited as it was not prespecified in the study, includes only 78% of the original TTF allocated patients, and fails 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 to standard care using historical controls. A study published in late 2014 included 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 in 91 centers in the United States between October 2011 and November 2013.\(^{11}\) The median OS rate in the PRiDe clinical practice dataset was reported as significantly superior to that attained in the TTF EF-11 pivotal trial (9.6 months vs 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 the findings of a study examining the effects of TTF therapy delivered by the NovoTTF-100A System in 10 patients with recurrent GBM. Median time to progression (TTP) in these patients was 26.1 weeks, and median OS was 62.2 weeks. The authors noted that these TTP and OS values were more than double the reported medians of historical control patients. No device-related serious adverse events were seen after more than 70 months of cumulative treatment in all of the 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 the use of historical controls, because the patients included may not be comparable on major clinical and prognostic features.

**Section Summary: Alternative to Chemotherapy in Advanced or Recurrent GBM**

The single RCT for this indication reported that outcomes following TTF treatment are similar to outcomes following standard chemotherapy. However, this RCT is not sufficient to allow conclusions on the efficacy of the device. There was no placebo control group or supportive care treatment group, and the 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 there are several methodologic limitations in the study that reduces its internal validity. There was heterogeneity in the patient populations and heterogeneity in the chemotherapy regimens for the control group. Furthermore, there were more patients in the TTF group than in the control group who 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. The other available published evidence, two nonrandomized comparative studies, are small and limited by potential differences in patient populations. This evidence base is limited and does not permit conclusions about the impact of the technology on health outcomes.

**TTF 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 study enrolled patients with GBM who had completed standard treatment consisting of chemoradiotherapy, plus surgery if indicated. Patients were randomized in a 2:1 fashion to receive either TTF plus temozolomide (vs temozolomide alone). At the time of the interim analysis, there were 210 patients randomized to TTF plus temozolomide and 105 patients randomized 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 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. 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>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Progression-Free Survival (95% CI)</th>
<th>Hazard Ratio (98.7% CI)</th>
<th>Overall Survival (95% CI)</th>
<th>Hazard Ratio (99.4% CI)</th>
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<tbody>
<tr>
<td>TTF + temozolomide</td>
<td>210 (196&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>7.1 mo (5.9 to 8.2 mo)</td>
<td>0.62 (0.43 to 0.89)</td>
<td>20.5 mo (16.7 to 25 mo)</td>
<td>0.64 (0.42 to 0.98)</td>
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<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 mo)</td>
<td>15.6 mo (13.3 to 19.1 mo)</td>
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Cl: confidence interval; TTF: tumor treatment fields.
<sup>a</sup> Included in per-protocol analysis.

There were a total of 35 (11%) dropouts during the study, 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 criteria for adherence. The number of cycles of treatment 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.

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

The single RCT for this indication reports that PFS is improved by 3.1 months and OS is improved by 4.9 months after the addition of TTF to standard maintenance therapy. 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 some 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 rate of dropouts overall (11%) and differential dropout between groups (6.7% in the TTF group vs 20% in standard maintenance group). Also, for the outcomes that were evaluated on a per-protocol basis, such as overall survival, there is the possibility of an adherence bias, in that patients who complete the treatment protocol may have better outcomes than patients who do not complete the protocol. As a result of these methodologic limitations, conclusions about the efficacy of TTF for this indication cannot be made with certainty.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 3.
Summary of Evidence
For individuals who have GBM and who receive TTF as an adjunct to maintenance treatment following initial treatment with surgery and/or radiation, the evidence consists of one RCT. Relevant outcomes include overall survival, progression-free survival, quality of life, and treatment-related morbidity. The single RCT on this question reports that patients who receive TTF treatment plus temozolomide have longer progression-free survival (3.1 months) and overall survival (4.9 months) compared to patients receiving temozolomide alone. The trial has methodologic limitations including the lack of placebo control, differential dropout between groups, and the possibility of adherence bias for outcomes reported with per protocol analysis. Further corroboration of these results are needed in high-quality RCTs. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have advanced or recurrent GBM who receive TTF as an alternative to standard chemotherapy, the evidence consists of one RCT and non-randomized comparative studies. Relevant outcomes include overall survival, progression-free survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The single published RCT on this question reported that there is no difference in outcomes between patients treated with TTF and standard chemotherapy. This trial has several methodologic limitations. The comparisons made include only an active control of questionable efficacy and that may not reflect current standard of care. There was high dropout, with >20% of patients in each group lost to follow-up, and for the quality of life outcomes only approximately one-quarter of enrolled patients had complete data. The two non-randomized studies were small and have 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.

Supplemental Information
Clinical Input Received 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 for input on the use of TTF for treatment of GBM in 2016, input was received from 1 academic medical center and 3 physician specialty societies, with a total of 9 individual responses. There was majority support, but not consensus, for use of TTF as an adjunct to maintenance treatment following initial therapy for GBM. There was mixed support for use of TTF as an alternative to chemotherapy in advanced or recurrent GBM.

Practice Guidelines and Position Statements
The National Comprehensive Cancer Network’s Central Nervous System Tumors guidelines (v.1.2015)\(^2\) has updated the recommendation for the treatment of recurrence of glioblastoma, with the option “consider alternating electric field therapy for glioblastomas” from a category 3 recommendation to a 2B recommendation. TTF as an adjunct to maintenance therapy following initial treatment with surgery and/or radiation is listed as an option for patients who have good performance status.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination (NCD).

V. DEFINITIONS

NONE

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of
members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational therefore not covered: When used for Tumor-Treatment Fields Therapy for Glioblastoma

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

IX. REFERENCES


Other Sources:
Durable Medical Equipment Regional Carrier (DME MAC JA) Region JA Noridian Healthcare Solutions, LLC Local Coverage Determination (LCD) L34823 Tumor Treatment Field Therapy. Effective 7/1/16. [Website]: Tumor Treatment Field Therapy. Accessed August 24, 2016. Same indications as CBC Policy therefore no variation above.

X. POLICY HISTORY

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Admin Update 6/1/17 Added Medicare variation L34823 Tumor Treatment Field Therapy.