Tumor Treating Fields Therapy

Policy # 00391
Original Effective Date: 11/20/2013
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Stereotactic Radiosurgery and Stereotactic Body Radiotherapy is addressed separately in medical policy 00045.

Note: Intracavitary Balloon Catheter Brain Brachytherapy for Malignant Gliomas or Metastasis to the Brain is addressed separately in medical policy 00434.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider an initial 6 months of tumor treating fields (TTF) therapy to treat glioblastoma multiforme (GBM) as an adjunct to standard maintenance therapy with temozolomide in patients with newly diagnosed GBM following initial treatment with surgery, radiotherapy, and/or chemotherapy to be **eligible for coverage.**

Patient Selection Criteria
Coverage eligibility will be met for TTF therapy to treat GBM as an adjunct to standard maintenance therapy with temozolomide in patients with newly diagnosed GBM following initial treatment with surgery, radiotherapy, and/or chemotherapy under the following conditions (ALL criteria must be met):

- Adult patients ≥18 years of age; AND
- Supratentorial tumor; AND
- Karnofsky Performance Status (KPS) score ≥70%; AND
- Patient understands device use, including the requirement for a shaved head, and is willing to use Optune for at least 18 hours a day.

Based on review of available data, the Company may consider continuation of TTF therapy to be **eligible for coverage.**

Patient Selection Criteria
Coverage eligibility will be met for continuation of TTF therapy for 3 months if ALL of the following criteria are met:

- 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 report submitted as part of any request for continuation; AND
- KPS score of 70% or greater; AND

- Documentation that the patient has been wearing the device at least 18 hours daily.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers TTF therapy to be **investigational*** in all other conditions, including but not limited to the following situations:

- As an adjunct to standard medical therapy (e.g., bevacizumab, chemotherapy) for patients with progressive or recurrent GBM;
- As an alternative to standard medical therapy for patients with progressive or recurrent GBM;
- For brain metastases;
- For cancer in areas other than the brain.

The use of TTF therapy to treat GBM as an adjunct to standard maintenance therapy with temozolomide in patients with newly diagnosed GBM following initial treatment with surgery, radiotherapy, and/or chemotherapy when patient selection criteria are not met is considered to be **investigational.***

Policy Guidelines

Progression was defined in the EF-14 trial (Stupp et al [2015, 2017]) according to the MacDonald criteria (tumor growth >25% compared with the smallest tumor area measured in the patient during the trial or appearance of 1 or more new tumors in the brain that are diagnosed radiologically as GBM).

The FDA label includes the following notices:

- Patients should use Optune for at least 18 hours a day to get the best response to treatment;
- Patients should finish at least 4 full weeks of therapy to get the best response to treatment. Stopping treatment before 4 weeks lowers the chances of a response to treatment.

Background/Overview

GLIOBLASTOMA MULTIFORME

Glioblastomas, also known as GBM, are the most common form of malignant primary brain tumor in adults. GBMs are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor that is often resistant to standard medical therapy (e.g., bevacizumab, chemotherapy). Together, anaplastic astrocytomas and glioblastomas comprise approximately 38% of all brain and central nervous system tumors. The peak incidence for GBM occurs between the ages of 45 and 70 years, with a median age at diagnosis of 64 years. Glioblastomas have the lowest survival rate of any central nervous system tumor; in one report, about a third of patients survived to 1 year, and the 5-year survival rate was around 5%.

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Clinical Context and Therapy Purpose
The purpose of alternating electrical field therapy, more commonly known as TTF therapy, is to provide a treatment option that is better than existing therapies for GBM. TTF has been investigated as an adjunct to temozolomide for the treatment of newly diagnosed GBM and as an alternative or adjunct to medical therapy for progressive or recurrent GBM.

Treatment of Newly Diagnosed GBM
The primary treatment for patients newly diagnosed with GBM is to resect the tumor to confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. If total resection is not feasible, subtotal resection and open biopsy are options. During surgery, some patients may undergo implantation of the tumor cavity with a carmustine (bis-chloroethylnitrosourea) impregnated wafer. Due to the poor efficacy of local treatment, postsurgical treatment with adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of these 2 therapies is recommended. After adjuvant therapy, patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for 5 days of every 28-day cycle for 6 cycles. Response and overall survival (OS) rates with temozolomide are higher in patients who have O^6-methylguanine-DNA methyltransferase (*MGMT*) gene promoter methylation.

Prognostic factors for therapy success are age, histology, performance status or physical condition of the patient, and extent of resection. National Comprehensive Cancer Network recommendations include patient age and KPS score as important determinants of postsurgical treatment choice (see the Supplemental Information section). For patients with good performance status, the most aggressive treatment (standard radiotherapy [RT] plus temozolomide) is recommended. For patients with poor performance status, only single treatment cycles or even palliative or supportive care are recommended. Hypofractionated RT is indicated for patients with poor performance status because it is better tolerated, and more patients are able to complete RT.

Treatment of GBM is rarely curative, and tumors will recur essentially all patients.

Treatment of Recurrent GBM
When disease recurs, additional debulking surgery may be used if the recurrence is localized. Due to radiation tolerances, re-radiation options for patients with recurrent GBM who have previously received initial external-beam RT are limited. There is no standard adjunctive treatment for recurrent GBM. Treatment options for recurrent disease include various forms of systemic medications such as the antivascular endothelial growth factor drug bevacizumab, alkylating agents such as nitrosoureas (e.g., lomustine, carmustine), or retreatment with temozolomide. Medical therapy is associated with side effects that include hematologic toxicity, headache, loss of appetite, nausea, vomiting, and fatigue. Response rates in recurrent disease are less than 10%, and the progression-free survival (PFS) rate at 6 months is less than 20%. There is a need for new treatments that can improve survival in patients with recurrent GBM or reduce the side effects of treatment while retaining survival benefits.

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The questions addressed in this evidence review are:

- Does TTF, when used as an adjunct to maintenance medical therapy in patients with newly diagnosed GBM, improve the net health outcome?
- Does TTF, when used as an adjunct to medical therapy in patients with recurrent GBM, improve the net health outcome?
- Does TTF, when used as an alternative to medical therapy in patients with recurrent GBM, improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant populations of interest are patients who have newly diagnosed GBM with good performance status or patients with recurrent GBM with good performance status. Newly diagnosed patients would have undergone initial treatment with surgery, RT, and chemotherapy and be receiving maintenance chemotherapy.

Interventions
TTF therapy is a noninvasive technology intended to treat GBM on an outpatient basis and at home using electrical fields. TTF therapy exposes rapidly dividing cancer cells to electric fields of low intensity and intermediate frequency (200 kHz) that alternate in perpendicular orientation. TTF therapy is proposed to inhibit tumor growth by 2 mechanisms: the arrest of cell proliferation by causing microtubule misalignment in the mitotic spindle of rapidly dividing tumor cells and apoptosis due to movement of macromolecules and organelles during telophase. Preclinical studies have indicated that the electric fields may also make the cells more susceptible to chemotherapy.

Optune (formerly NovoTTF-100A System) is the only legally marketed TTF delivery system available in the United States. The portable, battery-powered device is carried in a backpack or shoulder pack while carrying out activities of daily living. For the treatment of glioblastoma, 4 disposable transducer arrays with insulated electrodes are applied to the patient's shaved head. The transducer array layout is typically determined using specialized software. The patient's scalp is re-shaved and the transducer arrays replaced twice a week by the patient, caregiver, or device technician. The device is worn for up to 24 hours a day for the duration of treatment, except for brief periods for personal hygiene and 2 to 3 days at the end of each month. The minimum daily treatment is 18 hours. The minimum duration of treatment is 1 month, with the continuation of treatment available until recurrence.

Comparators
The following practice is currently being used to make decisions about newly diagnosed GBM: maintenance chemotherapy with temozolomide alone.

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The following practices are currently being used to make decisions about recurrent GBM: medical therapy.TTF therapy might also be compared with palliative or supportive care, where survival rarely exceeds 3 to 5 months.

Outcomes
The general outcomes of interest are whether TTF improves survival or quality of life (QOL) during treatment and, because most GBMs recur, the time to tumor recurrence. Measures of cognitive status and QOL measures are also of interest to determine whether TTF alters the decline in cognition and QOL that occur with GBM. Also, adverse events of treatment such as side effects of chemotherapy and the possibility of seizures need to be assessed.

Timing
Due to the rapid progression of GBM, the time of interest for both PFS and OS is months.

Setting
The setting is outpatient care by an oncologist or neuro-oncologist.

FDA or Other Governmental Regulatory Approval

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

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

In October 2015, FDA expanded the indication for Optune in combination with temozolomide to include newly diagnosed GBM. The device was granted priority review status in May 2015 because there was no legally marketed alternative device available for the treatment of newly diagnosed GBM, a life-threatening condition. In July 2016, a smaller, lighter version of the Optune device, called the Optune System (NovoTTF-200A System), received FDA approval.

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

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FDA product code: NZK.

Centers for Medicare and Medicaid Services (CMS)
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.

Rationale/Source

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, QOL, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

For this review, 3 indications are evaluated: (1) TTF as an adjunct to maintenance chemotherapy in newly diagnosed patients following initial treatment with surgery, RT and chemotherapy and (2) TTF as an adjunct or (3) alternative to medical therapy (e.g., bevacizumab, chemotherapy) in progressive or recurrent GBM.

Study Selection
The PICOTS was used to select relevant studies.

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Within each category of study design, studies with larger sample size studies and longer duration were sought.

TTF THERAPY AS AN ADJUNCT TO STANDARD MAINTENANCE CARE FOR NEWLY DIAGNOSED GBM

Randomized Controlled Trials

Stupp et al (2017) published results of the EF-14 multicenter, open-label phase 3 RCT that evaluated maintenance therapy with TTF for newly diagnosed GBM. The trial included 695 patients from 83 sites who had supratentorial GBM and had completed standard treatment consisting of biopsy or surgical resection followed by RT and chemotherapy (see Table 1). A KPS score of 70 or higher was an additional inclusion criterion to ensure independence in activities of daily living, and patients with rapidly progressing GBM following radiochemotherapy were excluded from the trial. Patients were randomized in a 2:1 fashion to TTF plus maintenance temozolomide or maintenance temozolomide alone.

All patients were seen monthly for follow-up. QOL was assessed every 3 months, and MRI was performed every 2 months until tumor progression. Tumor progression on MRI was adjudicated by a central review committee blinded to treatment group. The primary outcome was PFS, and the secondary outcome was OS. The analysis was by intention-to-treat, including 26 patients from the control arm who crossed over to TTF following the planned interim analysis.

In 2014, an independent data and safety monitoring board concluded from the planned interim analysis that the trial met its predefined boundaries for success (improvement in PFS and OS) and recommended trial termination. The FDA approved the trial termination, and the trial was closed to recruitment with 695 of the planned 700 participants randomized. Control arm participants were allowed to cross over to the experimental treatment at this time. The interim analysis, which the FDA considered for the 2015 expanded approval of Optune, was published by Stupp et al (2015). At the time of the interim analysis, data were available for 210 patients randomized to TTF plus temozolomide and 105 patients to temozolomide alone. Follow-up of the remainder of the 695 enrolled patients continued after enrollment was closed.

Table 1. Key Randomized Controlled Trial Characteristics for Newly Diagnosed Glioblastoma

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Stupp et al (2017); EF-14	U.S., E.U., South Korea, Israel	83	2009-2016	• 695 newly diagnosed with GBM and treated by radiochemotherapy • KPS score ≥70	TTF >18 h/d plus maintenance temozolomide (n=466)	Maintenance temozolomide alone (5 d every 28 d for 6 cycles) (n=229)

GBM: glioblastoma multiforme; h/d; hours per day; KPS: Karnofsky Performance Status; TTF: tumor treatment fields.

Results of the final analysis of the EF-14 trial were similar to the interim analysis and are shown in Table 2. Both PFS and OS improved with the addition of TTF therapy to standard maintenance chemotherapy (i.e., temozolomide). PFS increased by 2.7 mo ($p<0.001$) and OS increased by 4.9 mo ($p<0.001$) in the TTF group. The time to a decrease in mental function was 2.5 months longer with TTF therapy ($p<0.01$).

There was a similar percentage of dropouts at the final analysis—with 49 (11%) patients in the TTF group and 27 (12%) patients in the temozolomide alone group. More treatment cycles with temozolomide were administered in the TTF group (median, 6 for TTF group vs 5 for controls), a finding that is consistent with the longer PFS. Rates of adverse events were similar between the groups, including rates of seizures. In secondary analysis of patients who had not progressed, there was no reduction in health-related QOL with TTF compared with temozolomide alone aside from "itchy skin". Interpretation of this result is limited by the low percentage of patients who completed the health-related QOL assessments at follow-up (65.8% of the 655 patients alive at 3 months and 41.7% of the 473 patients alive at 12 months). A mixed-model analysis, which accounts for missing data, confirmed the results of the mean change from baseline analysis.

Table 2. Key Randomized Controlled Trial Results for Newly Diagnosed Glioblastoma

Study	Final N (%)	Median PFS (95% CI), mo	Median OS (95% CI), mo	Systemic Adverse Events, n (%)	Seizures, n (%)	Time to 6-Point Decline in MMSE Score (95% CI), mo
Stupp et al (2017)						
TTF + temozolomide	417 (89)	6.7 (6.1 to 8.1)	20.9 (19.3 to 22.7)	218 (48)	26 (6)	16.7 (14.7 to 19.0)
Temozolomide alone	202 (88)	4.0 (3.8 to 4.4)	16.0 (14.0 to 18.4)	94 (44)	13 (6)	14.2 (12.7 to 17.0)
HR (95% CI)		0.63 (0.52 to 0.76)	0.63 (0.53 to 0.76)			0.79 (0.66 to 0.95)
P value		<0.001	<0.001	0.58		0.01

CI: confidence interval; HR: hazard ratio; MMSE: Mini-Mental State Examination; OS: overall survival; PFS: progression-free survival; TTF: tumor treatment fields.

Tables 3 and 4 display notable gaps identified in this trial, the major limitation is the lack of patient blinding to treatment assignment. However, PFS was assessed by investigators who were blinded to treatment and placebo effects on OS were expected to be minimal. Investigators considered it practically unfeasible (due to the heat and current of the TTF therapy) and ethically unacceptable to submit the control patients to repeated shaving of the head and continuous wear of a sham device over many months.

Table 3. Relevance Gaps

Study; Trial	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Stupp et al (2017); EF-14			3. Possible differences in post-progression treatment affecting overall survival		

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 4. Study Design and Conduct Gaps

Study; Trial	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Stupp et al (2017)[10]; EF-14		1. No sham control and not blinded to treatment assignment				

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

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

The final analysis of the EF-14 trial, which included 695 patients from 83 sites, found a statistically and clinically significant increase of 2.7 months in PFS and an increase of 4.9 months in OS with the addition of TTF therapy to standard maintenance therapy (i.e., temozolomide) in patients with newly diagnosed GBM. There was no sham control, and patients were not blinded to treatment assignment, but PFS was assessed by blinded evaluators, and placebo effects on the objective measure of OS were likely to be minimal. There was no evidence of a negative impact of TTF therapy on health-related QOL, except for itchy skin from the transducers.

TTF THERAPY AS AN ADJUNCT OR ALTERNATIVE TO MEDICAL THERAPY FOR PROGRESSIVE OR RECURRENT GBM

Randomized Controlled Trials

The 2011 FDA approval of the NovoTTF-100A System (now called Optune) was based on a phase 3 multinational RCT (EF-11), results of which were published by Stupp et al (2012). This trial compared TTF therapy alone with physician's choice medical therapy in 237 adults who had relapsed or progressive glioblastoma (see Table 5). Patients had failed conventional treatment with RT, chemotherapy, and/or

surgery, and more than 80% of participants had failed 2 or more prior chemotherapy regimens. In this trial, the term chemotherapy also applied to targeted agents such as bevacizumab. Patient characteristics and performance of additional post-recurrence debulking surgery were similar in the 2 groups.

Table 5. Summary of Key Randomized Controlled Trial Characteristics for Progressive or Recurrent Glioblastoma

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Stupp et al (2012); EF-11	U.S., E.U., Israel	28	1987-2013	• 237 adults with relapsed or progressive supratentorial glioblastoma • KPS score ≥70%	120 patients treated with TTF alone, 93 (78%) completed 1 cycle	117 patients treated with physician's choice of medical therapy[a]

EU: European Union; KPS: Karnofsky Performance Status; TTF: tumor treating fields.
[a] Medical therapy included bevacizumab, irinotecan, nitrosoureas, platinum-based chemotherapy (i.e., carboplatin); temozolomide; or a combination of procarbazine, chloroethyl ether, and vincristine.

Participants were followed monthly, including laboratory tests. MRI images were evaluated at 2, 4, and 6 months from initiation of treatment, with subsequent MRIs performed according to local practice until disease progression. QOL questionnaires were completed every 3 months. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with participants' caregivers were used to assess mortality rates. The primary end point was OS. Secondary end points included PFS, the percentage of patients with PFS at 6 months, time to progression, 1-year survival rate, QOL, and radiologic response. All end points were evaluated using intention-to-treat analysis.

The trial did not reach its primary end point of improved survival compared with active medical therapy (see Table 6). With a median follow-up of 39 months, 93% of patients had died. There was not a statistically significant difference in survival rates at 1, 2, and 3 years between groups. Patients in the TTF group did not, however, suffer the typical systemic side effects of chemotherapy. The most common adverse event in the TTF group was grade 1 and 2 contact dermatitis on the scalp, which resolved with topical corticosteroids and did not require treatment breaks. Control participants experienced grade 2, 3, or 4 events by organ system related to the pharmacologic activity of chemotherapy agents used. Hematologic events of grade 2 or greater were observed in 17% of chemotherapy patients compared with 3% of TTF patients. Gastrointestinal disorders of grade 2 or greater were identified in 17% of chemotherapy patients compared with 4% of TTF patients. Severe (grades 3-4) hematologic and gastrointestinal toxicity was observed in 7% of chemotherapy controls compared with 1% of the TTF group.

Longitudinal QOL data, available in 63 (27%) participants, showed no meaningful differences between groups for the domains of global health and social functioning. However, cognitive and emotional functioning domains favored TTF therapy. Symptom scale analysis was by treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration.

The trial had a number of limitations (see Tables 7 and 8), that included lack of blinding and high loss to follow-up. Discontinuation of TTF therapy occurred in 22% of patients due to noncompliance or inability to handle the device, usually within the first few days. In the control group, 21 (18%) patients did not return to the treatment site, and details on disease progression and toxicity were not available. Longitudinal QOL could be analyzed only for 27% of patients who remained on study therapy for 3 months. The trial was designed as a superiority trial and did not provide adequate evidence of noninferiority.

Table 6. Summary of Key Randomized Controlled Trial Results for Recurrent or Progressive Glioblastoma

Study; Trial	LTFU, n (%)	Median OS, mo	Progression-Free Survival		Overall Survival (95% CI), %		
			Median, mo	Rate at 6 Months (95% CI), %	1 Year	2 Years	3 Years
Stupp et al (2012); EF-11							
TTF	23 (22)	6.6	2.2	21.4 (13.5 to 29.3)	20	8 (4 to 13)	4 (1 to 8)
PCC	12 (18)	6.0	2.1	15.1 (7.8 to 22.3)	20	5 (3 to 10)	1 (0 to 3)
HR (95% CI)		0.86 (0.66 to 1.12)	0.81 (0.60 to 1.09)				
P value		0.27	0.16	0.13			

CI: confidence interval; HR: hazard ratio; LTFU: loss to follow-up; PCC: physician's choice chemotherapy; TTF: tumor treating fields.

Table 7. Relevance Gaps

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Stupp et al (2012); EF-11			2. Physician's choice chemotherapy		

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 8. Study Design and Conduct Gaps

Study; Trial	Allocation[a]	Blinding[b]	Selective Reporting[d]	Data Completeness[e]	Power[d]	Statistical[f]
Stupp et al (2012); EF-11		1. Not blinded to treatment assignment		1. 78% of TTF group completed only 1 cycle of therapy, 18% of control group lost to follow-up 1. Longitudinal QOL data were available for 27% of		1. Not designed as a noninferiority trial

patients

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
QOL: quality of life.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Nonrandomized Comparative Studies

Kesari et al (2017) conducted a post hoc analysis of the EF-14 trial (see Stupp et al [2017] above) to evaluate the efficacy of TTF in patients who had the first recurrence. Some patients in the temozolomide alone group crossed over to receive TTF plus chemotherapy after the first recurrence, resulting in 144 patients who received TTF fields plus chemotherapy and 60 patients who received chemotherapy alone for recurrent GBM (see Table 9). Patient characteristics and second-line treatments were well-balanced between the groups, with bevacizumab the most common second-line therapy. The median OS in patients treated with systemic therapy alone was 9.2 months (see Table 10). In comparison, the group of patients who received TTF therapy in addition to systemic therapy had a median OS of 11.8 months (p=0.043).

A registry study published Mrugala et al (2014) assessed OS data from patients who received NovoTTF therapy in a real-world, clinical practice setting (see Table 9). Concurrent treatment was not captured in the registry, and it is possible that some patients received combination therapy. Median OS in the PRiDe clinical practice dataset (9.6 mo) was reported as superior to that attained in the EF-11 pivotal trial (6.6 mo, p<0.001) (see Table 10). More patients in the PRiDe registry were treated for first recurrence (33% vs 9%), and more had received bevacizumab as prior therapy (55% vs 19%). The PRiDe investigators reported no novel or unexpected treatment-related adverse events compared with the EF-11 trial.

Table 9. Characteristics of Key Nonrandomized Trial Results

Study	Study Type	Country	Dates	Participants	TTF	Controls	FU
Kesari et al (2017)	EF-14 post hoc analysis	U.S., E.U., South Korea, Israel	2009-2016	204 patients with first recurrence in the EF-14 trial	144 patients treated with TTF plus second-line chemotherapy	60 patients treated with second-line chemotherapy	12.6 mo
Mrugala et al (2014)	Registry	U.S. (91 centers)	2011-2013	457 patients with recurrent GBM	Patient Registry Dataset (PRiDe)	EF-11	

FU: follow-up; GBM: glioblastoma; TTF: tumor treating fields.

Table 10. Summary of Key Nonrandomized Trial Results

Study	Median OS, mo	Median OS With Bevacizumab, mo	
Kesari et al (2017); EF-14			
TTF plus chemotherapy	11.8	11.8	
Chemotherapy alone	9.2	9.0	
Hazard ratio (95% CI)	0.70 (0.48 to 1.00)	0.61 (0.37 to 0.99)	
P value	0.049	0.043	
		1-Year OS, %	**2-Year OS, %**
Mrugala et al (2014)			
PRiDe Registry	9.6	44	30
EF-11	6.6	20	9
Hazard ratio (95% CI)	0.66 (0.05 to 0.86)		
P value	<0.001		

CI: confidence interval; OS: overall survival, TTF: tumor treating fields.

Post hoc analyses of the EF-11 pivotal trial have been reported. Wong et al (2014) published a subgroup analysis to determine characteristics of responders and nonresponders in the active treatment and active treatment control. They found that responders had a lower grade of histology and lower daily dexamethasone use than nonresponders. A second post hoc analysis by Kanner et al (2014) of the EF-11 pivotal trial data was performed to evaluate OS among patients who finished at least 1 complete course of TTF or chemotherapy. The investigators reported that median OS was 7.7 months in the TTF group compared with 5.9 months in the chemotherapy group (p=0.009). These post hoc analyses are considered to be hypothesis-generating.

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

The single RCT for TTF as an alternative to chemotherapy 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. The noninferiority of TTF compared with chemotherapy might be considered a sufficient health benefit, if TTF reduced treatment toxicity. However, because the trial was not designed as a noninferiority trial no inferences of noninferiority compared with chemotherapy can be made. Physician's choice therapy during the trial was heterogenous, although analysis indicated that survival was not affected by choice of chemotherapy. More patients in the TTF group than in the control group did not complete the treatment course. The number of patients who contributed QOL data was approximately one-quarter of total enrollment, and the self-reported QOL indicators might have been subject to bias due to the lack of blinding.

A nonrandomized post hoc evaluation of the EF-14 trial suggests that TTF may improve survival when combined with chemotherapy for recurrent GBM. This analysis should be considered hypothesis-generating, and further study in high-quality RCTs is needed.

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SUMMARY OF EVIDENCE

For individuals who have newly diagnosed GBM on maintenance therapy after initial treatment who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes an RCT. Relevant outcomes include OS, disease-specific survival, symptoms, functional outcomes, QOL, and treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in PFS and an increase of 4.9 months in OS with the addition of TTF therapy to standard maintenance therapy (i.e., temozolomide) in patients with newly diagnosed GBM. Although patients were not blinded to treatment assignment, PFS was assessed by blinded evaluators, and the placebo effects on the objective measure of OS are expected to be minimal. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limited. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT and nonrandomized comparative studies. Relevant outcomes are OS, disease-specific survival, QOL, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (OS) compared with physicians' choice chemotherapy. Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, QOL assessment was measured in an insufficient number of patients to reach firm conclusions on differences in QOL between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. A high-quality, prospective RCT is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

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11/07/25013	Medical Policy Committee review
11/20/2013	Medical Policy Implementation Committee approval. New policy.
11/06/2014	Medical Policy Committee review
11/21/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/29/2015	Medical Policy Committee review
11/16/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/09/2018	Medical Policy Committee review
08/15/2018	Medical Policy Implementation Committee approval. This policy was retired on 3/16/2016 and has been returned to active status to adopt BCBSA's policy. Title changed from "Tumor-Treatment Fields Therapy for Glioblastoma" to "Tumor Treating Fields Therapy". Added that an initial 6 months of TTF therapy will be eligible for coverage when criteria are met to treat GBM as an adjunct to standard maintenance therapy with temozolomide in patients with newly diagnosed GBM following initial treatment with surgery, radiotherapy, and/or chemotherapy. Added that continuation of TTF therapy may be eligible for coverage with criteria.

Next Scheduled Review Date: 08/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	A4555, E0766
ICD-10 Diagnosis	C71.0-C71.9

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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