DRAFT

BlueCross BlueShield of Alabama

Name of Policy:

Tumor-Treatment Fields Therapy for Glioblastoma

Policy #: 536
Category: DME

Latest Review Date: April 2018
Policy Grade: C

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *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.*

Description of Procedure or Service:

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

Glioblastome Multiforme

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, 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."

Treatment

The primary treatment for patients newly diagnosed with GBM is to safely resect the tumor, and confirm a diagnosis; meanwhile, debulking the tumor to relieve symptoms of increased intracranial pressure or compression. At that time, some patients may undergo implantation with a carmustine (bischloroethylnitrosourea) (BCNU)-impregnated wafer. The cure rate with local treatment is very low; therefore, postsurgical treatment involves the use of 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 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/chloroethylnitrosourea CCNU, temozolomide), temozolomide, nitrosourea, PCV (procarbazine, CCNU, and vincristine), cyclophosphamide, and platinum-based agents.

Fractionated external-beam radiotherapy after surgery is standard adjuvant therapy and also 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%.

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 the use of alkylating agent chemotherapy, such as temozolomide. Data from randomized controlled trials have shown that MGMT promoter methylation is a predictor to responding to alkylating chemotherapeutic agents such as temozolomide. The response rate and overall survival with the use of temozolomide are higher in patients who have MGMT promoter methylation. *(See Medical Policy #582 on MGMT promotor methylation in malignant gliomas.)*

Tumor Treatment Fields
Tumor-treating fields (TTF) therapy is a noninvasive technology that is intended to treat GBM on an outpatient basis using electrical fields. TTF therapy exposes cancer cells to alternating electric fields of low intensity and intermediate frequency, which are purported to both selectively inhibit tumor growth and reduce tumor angiogenesis. Tumor-treating fields are proposed to inhibit rapidly dividing tumor cells by 2 mechanisms, arrest of cell proliferation and destruction of cells while undergoing division.

Optune®, formerly NovoTTF-100A System (Novocure, Haifa, Israel) 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 by means of electrically insulated surface transducer arrays, such that resistively coupled electric currents are not delivered to the patient. The device is used by the patient 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.

Karnofsky Performance Status (KPS)
KPS is a standard way of measuring the ability of cancer patients to perform ordinary tasks. KPS scores range from 0 to 100; a higher score means a person is better able to carry out daily activities. For example, a KPS of 60 means a person requires occasional assistance, but is able to care for most of their personal needs. KPS may be used to determine a patient's prognosis, to measure changes in a patient's ability to function, or to decide if a patient could be included in a clinical trial.

Supratentorial
Supratentorial refers to the upper portion of the brain comprised of the cerebrum and the diencephalon.

Temozolomide
Temozolomide is an oral alkylating chemotherapy drug used in the treatment of some brain cancers. It is a first-line treatment for glioblastoma.

The FDA has not approved the use of electric TTF devices for indications other than GBM. Further studies are needed to determine the safety and long-term efficacy of electric TTF therapy for other types of cancer.

Policy:

Effective for dates of service on or after 04/26/2018:

Tumor-treating fields (TTF) therapy meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage to treat histologically-confirmed Supratentorial Glioblastoma (known also as glioblastoma multiforme [GBM]) as adjunctive therapy when used according to FDA labeled indications, contraindications, warnings and precautions, and when **ALL of the following criteria are met**:

- Initial treatment with debulking surgery or biopsy followed by chemoradiation with concomitant Temozolomide and radiotherapy have been completed; **and**
- TTF is used in combination with Temozolomide **and**
- Individual has Karnofsky Performance Status (KPS) score of ≥60 (requires occasional assistance, but is able to care for most of their personal needs); **and**
- Individual is age 22 or older **and**
- Individual or caregiver has been trained and is willing and able to apply the device daily; **and**
- Individual is willing to wear the device at least 18 hours daily.

Tumor-treating fields (TTF) therapy meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage to treat **recurrence** of previously histologically confirmed Supratentorial Glioblastoma (known also as glioblastoma multiforme [GBM]) when used according to FDA labeled indications, contraindications, warnings and precautions, and when **ALL of the following criteria are met**:

- There is histologically or radiologically confirmed recurrence of supratentorial glioblastoma following treatment with surgery, chemotherapy, and/or radiation **and**
- TTF is used as monotherapy, **and**
- Individual has Karnofsky Performance Status (KPS) score of ≥60 (requires occasional assistance, but is able to care for most of their personal needs); **and**
- Individual is age 22 or older **and**
- Individual or caregiver has been trained and is willing and able to apply the device daily; **and**
- Individual is willing to wear the device at least 18 hours daily.

Tumor Treatment Fields (TTF) therapy does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage **when the criteria above are not met *and* for all other indications.**

Computer software used for therapeutic radiology clinical treatment planning in conjunction with tumor treatment field (TTF) therapy **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **not medically necessary.**

Effective for dates of service prior to 04/26/2018:

Tumor-treating fields (TTF) therapy for glioblastoma does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** for all indications, 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.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The most recent literature review was through June 5, 2017. Following is a summary of the key literature.

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 a treatment for GBM. Tumor treating fields (TTF) is proposed as a treatment for glioblastoma (GBM). For this review, 2 indications will be considered: (1) TTF as an alternative to chemotherapy in advanced or recurrent GBM and (2) TTF as an adjunct to maintenance treatment in patients following early 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. This review will include both RCTs and nonrandomized comparative trials.

TTF 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 III, multinational prospective RCT which was published in 2012 by Stupp et al. The Stupp et al study, which was sponsored and funded by the manufacturer of the device (NovoCure), compared TTF therapy (delivered by the NovoTTF-100A System) to the best standard of care chemotherapy (active control). Twenty-eight clinical centers (across 7 countries) enrolled 237 adult participants 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 and median Karnofsky performance status (KPS) of 80%. More than 80% of participants had failed 2 or more prior chemotherapy regimens (≥second recurrence), and 20% had failed bevacizumab prior to study

enrollment. The performance of additional post recurrence 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 and 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 (i.e., 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 (e.g., 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.

This study was designed as a superiority trial. The primary study endpoint in this RCT was overall survival (OS). Secondary endpoints included progression-free survival (PFS) at 6 months, time to progression (TTP), 1-year survival rate, quality of life (QOL), and radiological 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 MRIs done according to local practice until disease progression. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with the participants' caregivers were used to assess participant mortality rates.

One hundred sixteen (97%) 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 endpoint of improved survival compared to active chemotherapy. With a median follow-up of 39 months, 220 participants (93%) had died. Median survival was 6.6 months in the TTF group compared to 6.0 months in the active control group (hazard ratio 0.86; 95% confidence interval [95% CI]: 0.66–1.12; p=0.27). For both groups, 1-year survival was 20%. The survival 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 rate at 6 months was 21.4% in the TTF group, compared to 15.1% in the active control group (p=0.13). Objective radiological 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: 7.9–22.4%) compared to 9.6% (95% CI: 3.9– 18.8%), respectively. Sixteen percent of the TTF participants had Grade 1 and 2 contact dermatitis on the scalp, which resolved with topical steroids. Active control

participants experienced Grade 2 to 4 events by organ system related to the pharmacologic activity of chemotherapy agents utilized; severe (Grades 3 and 4) toxicity was observed in 3% of participants.

Longitudinal QOL data were available in 63 participants (27%). There were no meaningful differences observed between the groups in the domains of global health and social functioning. 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 (2014) 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%). Dexamethasone use among responders was also significantly lower than that in nonresponders in both NovoTTF-100A and BPC cohorts, responders had a lower daily dexamethasone usage than nonresponders. For the NovoTTF-100A cohort, the respective median and mean daily dexamethasone dose was 1.0 and 2.3 mg (95% CI, 0.8 to 3.8 mg) for responders and 5.2 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 and 1.4 mg (95% CI, 0.3 to 2.4 mg) mg for responders and 6.0 and 7.2 mg (95% CI, 6.0 to 8.4 mg) mg for nonresponders ($p=0.004$) 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.

Table 1: Randomized Trial of TTF Versus Physicians' Choice Chemotherapy in Recurrent Glioblastoma: Principal Efficacy Results from Stupp et al

Outcomes	TTF	Chemotherapy	Measure of Association, Significance
Median survival, mo	6.6	6.0	
Hazard ratio survival			0.86(95% Cl, 0.66 to 1.12) favors TTF
Radiologic response(not all patients evaluated)	14%	9.6%	p=0.19
Median PFS, mo	2.2	2.1	
Hazard ratio PFS			0.81(95%Cl, 0.60 to 1.09) favors TTF

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

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. 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. 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 one 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), for example, reported the findings of a case study examining the effects of TTF therapy delivered by the NovoTTF-100A System in 10 patients with recurrent glioblastoma multiforme (GBM). Median time to progression (TTP) in these patients was 26.1 weeks and median overall survival (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 (AEs) were seen after more than 70 months of cumulative treatment in all of the patients. The only device-related AE 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, since 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. Overall survival using TTF was noted at 6.6 months versus 6.0 months in the chemotherapy group. 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. There are several methodologic limitations in the study. 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. People who used TTF in a clinical trial self-reported better quality of life with improved cognitive and emotional functioning compared to people who took chemotherapy. The other available published evidence is 2 nonrandomized comparative studies.

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). A Karnofsky Performance Score of 70% or higher was an additional inclusion criterion. 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 2: TTF as an Adjunct to Standard Maintenance Care in GBM

Group	N	Progression-Free Survival (95% Cl)	Hazard Ratio (98.7 Cl)	Overall Survival (95% Cl)	Hazard Ratio (99.4%Cl)
TTF + temozolomide	210(196[a])	7.1 mo (5.9 to 8.2 mo)	0.62 (0.43 to 0.89)	20.5 mo (16.7 to 25 mo)	0.64 (0.42 to 0.98)
Temozolomide alone	105(84[a])	4.0 mo (3.3 to 5.2 mo)		15.6 (13.3 to 19.1 mo)	

CI: confidence interval; TTF: tumor treatment fields

[a] 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.

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 in November 2014 after 695 of the planned 700 participants had been randomized. All patients in the control maintenance therapy arm were

could crossover to receive TTFs. At the time of the Stupp interim analysis, 35 control arm participants had crossed over.

The FDA considered the results of this analysis for the 2015 expanded approval of Optune®.

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. 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.

Summary of Evidence
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 reported overall survival using TTF at 6.6 months versus 6.0 months in the chemotherapy group. This trial has several methodologic limitations, including the comparisons made include only an active control. There was high dropout, with >20% of patients in each group lost to follow-up, and for the quality of life outcomes only approximately 25% of enrolled patients had complete data. The 2 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 sufficient to determine the effects of the technology on health outcomes.

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. The evidence is sufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements
The National Comprehensive Cancer Network guidelines on central nervous system cancers (v.1.2018) 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 1 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.

Key Words:
NovoTTF-100A, NovoTTF, Novocure, TTF, Glioblastoma, GBM, Optune

Approved by Governing Bodies:
The NovoTTF-100A™ System (Novocure, Haifa, Israel; assigned the generic name of TTF) was approved by the FDA in April 2011 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."

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

In October 5, 2015, FDA expanded the indication for Novocure's use of Optune® in combination with temozolomide to include newly diagnosed GBM. The device was granted priority review status on May 8, 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 is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

Benefit Application:
Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply.
FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT:

77299	Unlisted procedure, therapeutic radiology clinical treatment planning

HCPCS Codes:

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

References:

1. Davies AM, Weinberg U, Palti Y. Tumor treating fields: a new frontier in cancer therapy. Ann N Y Acad Sci 2013.
2. De Bonis P, Doglietto F, Anile C et al. Electric fields for the treatment of glioblastoma. Expert Rev Neurother 2012; 12(10):1181-84.
3. Elzinga G, Wong ET. Resolution of cystic enhancement to add-on tumor treating electric fields for recurrent glioblastoma after incomplete response to bevacizumab. Case Rep Neurol. Jan 2014; 6(1):109-115.
4. Kanner AA, Wong ET, Villano JL, et al. Post Hoc analyses of intention-to-treat population in phase III comparison of NovoTTF-100A system versus best physician's choice chemotherapy. Semin Oncol. Oct 2014; 41 Suppl 6:S25-34.
5. Kirson ED, Dbaly V, Tovarys F et al. Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. Proc Natl Acad Sci U S A 2007; 104(24):10152-7.
6. Kirson ED, Schneiderman RS, Dbaly V et al. Chemotherapeutic treatment efficacy and sensitivity are increased by adjuvant alternating electric fields (TTFields). BMC Med Phys 2009; 9:1.
7. Mrugala MM, Engelhard HH, Dinh Tran D, et al. Clinical practice experience with NovoTTF-100A system for glioblastoma: The Patient Registry Dataset (PRiDe). Semin Oncol. Oct 2014; 41 Suppl 6:S4-S13.
8. National Cancer Institute (NCI). Adult Central Nervous System Tumors Treatment (PDQ®)–Health Professional Version. 2017; www.cancer.gov/types/brain/hp/adult-brain-treatment-pdq#cit/section_1.1. Accessed June 5, 2017.
9. National Cancer Institute (NCI) - Adult Brain Tumors Treatment (PDQ®). Last modified May 14, 2013. Available online at: www.cancer.gov/cancertopics/pdq/treatment/adultbrain/HealthProfessional. Accessed May 21, 2015.

10. National Comprehensive Cancer Network (NCCN). Central nervous system cancers. NCCN Clinical Practice Guidelines in Oncology. Version 1.2016. For additional information visit the NCCN website at: www.nccn.org/index.asp.
11. National Comprehensive Cancer Network (NCCN). Anaplastic Gliomas[a]/Glioblastoma. NCCN Clinical Practice Guidelines in Oncology. Version 1.2016. For additional information visit the NCCN website at: www.nccn.org/index.asp.
12. Pharma FW. FDA Grants Priority Review Status for Novocure's PMA Supplement Application of Optune in Newly Diagnosed Glioblastoma. 2015; www.firstwordpharma.com/node/1282764#axzz3bpYYLTNx, June 1, 2015.
13. Pless M, Weinberg U. Tumor treating fields: concept, evidence and future. Expert Opin Investig Drugs 2011; 20(8):1099-106.
14. Ram Z, Gutin PH. Subgroup and quality of life analyses of the phase III clinical trial of NovoTTF- 100A versus best standard chemotherapy for recurrent glioblastoma. Neuro-Oncology 2010; 12:iv48-iv49.
15. Ram Z, Wong ET, Gutin PH. Comparing the effect of novottf to bevacizumab in recurrent GBM: A post-HOC sub-analysis of the phase III trial data. Neuro-Oncology 2011; 13:iii52.
16. Rulseh AM, Keller J, Klener J et al. Long-term survival of patients suffering from glioblastoma multiforme treated with tumor-treating fields. World J Surg Oncol 2012; 10:220.
17. Salzberg M, Kirson E, Palti Y et al. A pilot study with very low-intensity, intermediate-frequency electric fields in patients with locally advanced and/or metastatic solid tumors. Onkologie 2008; 31(7):362-5.
18. Stupp R, Taillibert S, Kanner AA, et al. Maintenance therapy with tumor-treating fields plus temozolomide vs temozolomide alone for glioblastoma: a randomized clinical trial. JAMA. Dec 15 2015; 314(23):2535-2543.
19. Stupp R, Taillibert S, Kanner A, et al. Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma A Randomized Clinical Trial. JAMA. 2017; 318(23):2306–2316. doi:10.1001/jama.2017.18718
20. Stupp R, Wong ET, Kanner AA et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. Eur J Cancer 2012; 48(14):2192-202.
21. Taphoorn MJB, Dirven L, Kanner AA, et al. Influence of Treatment With Tumor-Treating Fields on Health-Related Quality of Life of Patients With Newly Diagnosed Glioblastoma - A Secondary Analysis of a Randomized Clinical Trial. JAMA Oncol. Published online February 01, 2018. doi:10.1001/jamaoncol.2017.5082
22. Turner SG, Gergel T, Wu H, et al. The effect of field strength on glioblastoma multiforme response in patients treated with the NovoTTF-100A system. World J Surg Oncol. 2014; 12(1):162.
23. U.S. Food and Drug Administration (FDA). Tumor treatment fields. NovoTTF-10A System. Summary of safety and effectiveness data (SSED). Premarket Approval Application (PMA) No. P100034. Premarket Notification Database. Rockville, MD: FDA; April 8, 2011. Available online at: www.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=19184.

24. Food and Drug Administration (FDA). Supplemental application for device name change. 2014; www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_template.cfm?id=p100034s010, June 1, 2015.
25. Villano JL, Williams LE, Watson KS et al. Delayed response and survival from NovoTTF-100A in recurrent GBM. Medical Oncology 2013; 30(1):1-3.
26. Wong ET, Lok E, Swanson KD, et al. Response assessment of NovoTTF-100A versus best physician's choice chemotherapy in recurrent glioblastoma. Cancer Med. Jun 2014; 3(3):592-602.

Policy History:

Medical Policy Panel, August 2013
Medical Policy Group, August 2013 **(3)**: New policy; does not meet medical criteria for coverage and therefore considered investigational
Medical Policy Administration Committee, September 2013
Available for comment September 4 through October 19, 2013
Medical Policy Group, December 2013 **(5)**: 2014 Coding Update- added new codes A4555 and E0766 to current coding effective 01/01/2014
Medical Policy Panel, August 2014
Medical Policy Group, August 2014 **(5):** Policy updated with literature review through June 26, 2014. Policy Description, Key Points, and References updated. Policy statement unchanged.
Medical Policy Panel, August 2015
Medical Policy Group, August 2015 **(6):** Updates to Description, Key Points, Approved by Governing Bodies and References; no change to policy statement
Medical Policy Group, May 2016 **(6)**: Added Key Word "Optune"
Medical Policy Panel, August 2016
Medical Policy Group, August 2016 **(6)**: Updates to Policy statement, Key Points, Practice Guidelines and Position Statements, Summary and References. No change in policy intent.
Medical Policy Group, September 2016 (**6**): Update to Practice Guidelines. No change to policy intent; remains investigational.
Medical Policy Panel, July 2017
Medical Policy Group, July 2017 **(6)**: Updates to Description, Key Points, Practice Guidelines, Governing Bodies and References.
Medical Policy Group, April 2018 **(6):** Updates to Policy statement to allow coverage of TTF with criteria, Key Points, Practice Guidelines, Coding and References; full literature review to be completed with annual update.
Medical Policy Administration Committee May 2018
Available for comment May 4 through June 17, 2018