i) [FINAL DRAFT – LOGO TO BE INSERTED UPON FINAL PRODUCTION DATE]

Clinical UM Guideline

Subject:	Electric Tumor Treatment Field (TTF)		
Guideline #:	CG-DME-44	**Publish Date:**	04/24/2019~~06/28/2018~~
Status:	~~New~~Revised	**Last Review Date:**	0~~35~~/21~~03~~/201~~98~~

Description

This document addresses electrical fields known as "tumor treatment fields (TTF)" that are created by low-intensity, intermediate frequency (100–200 kilohertz [kHz]) electric currents delivered to the malignant tumor site by insulated electrodes placed on the skin surface. TTF are felt to cause tumor cell death (apoptosis) by disrupting the assembly of microtubules during later stages of cell division.

Clinical Indications

Medically Necessary:

The use of FDA approved devices to generate electric tumor treatment fields (TTF) to treat histologically-confirmed supratentorial glioblastoma (known also as glioblastoma multiforme [GBM] or World Health Organization [WHO] grade IV astrocytoma) is considered **medically necessary as adjunctive treatment** when **all** of the following criteria below are met:

A. Initial treatment with debulking surgery or biopsy followed by chemoradiation with concomitant temozolomide and radiotherapy has been completed with no documented tumor progression*; **and**
B. TTF is used in combination with temozolomide; **and**
C. TTF is initiated within 7 weeks from final dose of temozolomide and radiotherapy; **and**
D. Individual has Karnofsky Performance Status score of 70 or higher **or** Eastern Cooperative Oncology Group (ECOG) performance status 0-1; **and**

This Clinical UM Guideline is intended to provide assistance in interpreting Healthy Blue's standard Medicaid benefit plan. When evaluating insurance coverage for the provision of medical care, federal, state and/or contractual requirements must be referenced, since these may limit or differ from the standard benefit plan. In the event of a conflict, the federal, state and/or contractual requirements for the applicable benefit plan coverage will govern. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Clinical UM Guideline is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

E. Individual or caregiver has been trained and is willing and able to apply and maintain the device at least 18 hours every day.

*Progression is defined as tumor growth greater than 25% compared to smallest measured tumor area **or** the appearance of one or more new GBM lesions in the brain.

Not Medically Necessary:

The use of devices to generate electric tumor treatment fields (TTF) is considered **not medically necessary** when the criteria above are not met and for all other malignant tumors.

The use of enhanced computer treatment planning software (such as NovoTal) is considered **not medically necessary** in all cases.

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT

77299	Unlisted procedure, therapeutic radiology clinical treatment planning [when specified as plan for using an electrical stimulation device for TTF; -Note: when specified as enhanced computer software considered not medically necessary]

HCPCS

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

This Clinical UM Guideline is intended to provide assistance in interpreting Healthy Blue's standard Medicaid benefit plan. When evaluating insurance coverage for the provision of medical care, federal, state and/or contractual requirements must be referenced, since these may limit or differ from the standard benefit plan. In the event of a conflict, the federal, state and/or contractual requirements for the applicable benefit plan coverage will govern. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Clinical UM Guideline is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

ICD-10 Diagnosis	
C71.0-C71.9	Malignant neoplasm of brain
Z85.841	Personal history of malignant neoplasm of brain

Discussion/General Information

According to the NCI (2018), glioblastoma (WHO grade IV astrocytoma) is also known as GBM. The peak incidence for GBM occurs between the ages of 45 and 70 years. Glioblastoma is highly invasive and is the most frequently occurring brain tumor accounting for approximately 12% to 15% of all brain tumors and 50% to 60% of all astrocytic tumors. Giant cell glioblastoma and gliosarcoma are two histologic variants of glioblastoma multiforme. According to the NCCN (2018) GBM is the "deadliest brain tumor with only a third of patients surviving for one year and less than 5% living beyond 5 years."

The U.S. Food and Drug Administration (FDA) approved the premarket approval application (PMA) for NovoTTF™-100A System (NovoCure™ Ltd., Portsmouth, NH; Haifa, Israel) in 2011. The device is now marketed as Optune™ (NovoCure Ltd., Portsmouth, NH, Haifa, Israel). ~~The~~ Optune, a portable, non-invasive device designed for the delivery of TTF to the head, ~~(formerly NovoTTF-100A System) was approved by the FDA in April 2011, as~~was originally approved as a novel device to treat adults age 22 years or older with GBM that recurs or progresses after receiving chemotherapy and radiation therapy. On October 5, 2015, the FDA approved the use of Optune in combination with temozolomide for the treatment of adults with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and radiation therapy. TTF technology is also being studied as a treatment for other solid tumors such as non-small cell lung cancer and melanoma. There are published data from TTF use to treat tumors in pre-clinical trials and from small case series. However, the published evidence does not support that long term safety and efficacy of TTF has been established when used as a treatment of tumors other than GBM. On October 5, 2015 the FDA granted approval for use of Optune in combination with temozolomide to treat adults age 22 years or older with newly diagnosed, supratentorial GBM after maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.

This Clinical UM Guideline is intended to provide assistance in interpreting Healthy Blue's standard Medicaid benefit plan. When evaluating insurance coverage for the provision of medical care, federal, state and/or contractual requirements must be referenced, since these may limit or differ from the standard benefit plan. In the event of a conflict, the federal, state and/or contractual requirements for the applicable benefit plan coverage will govern. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Clinical UM Guideline is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

The use of electric fields and the corresponding effects upon living tissue has been studied in the laboratory and clinical settings. At very low frequencies alternating electric fields (below 1 kHz) cause membrane depolarization which stimulates excitable tissue (Kirson 2004, 2007, 2009; Salzberg, 2008). Electric fields in the tens of kHz to megahertz (intermediate frequency) alternate too fast to stimulate tissue and results in minute heating. Kirson and colleagues (2004) demonstrated targeted inhibitory effects on dividing cells with the application of alternating electric fields of very low intensity (less than 2 V/centimeter [cm]) and intermediate frequency, called TTF. Utilizing time-lapse microphotography of mouse melanoma cell cultures, unique cellular processes as a result of TTF exposure were identified. Prolongation of mitosis in TTF-treated cells was statistically significant, and one-quarter of the treated cells were destroyed. Cellular destruction was observed only in mitotic cells, and cells at rest (quiescent) remained intact, both functionally and morphologically. Nuclear rotation was also observed in TTF-treated cell cultures. Microtubules, in the form of spatially organized mitotic spindles in dividing cells, have very large electric dipole moments that may be disoriented by TTF forces. In the control cell cultures, 95% of the mitotic spindles were intact and exhibited normal features in cells undergoing mitosis compared to 50% of abnormal cell activity in TTF-treated cultures. The use of TTF was then applied in vivo, to two animal tumor models (adenocarcinoma and malignant melanoma cells). TTF-treated tumors were significantly smaller compared to the control tumor size, and the surrounding normal tissue was spared from injury. The encouraging preclinical data led to studies of electric TTF treatment in humans based on the principle that TTF results in disruption of the cell membrane and programmed cell death of cancer cells.

***Newly diagnosed* Glioblastoma Multiforme (GBM)**

The current standard of treatment for newly diagnosed GBM consists of tumor resection followed by daily low-dose temozolomide administered concurrently with external beam radiotherapy followed by adjuvant temozolomide with alternating electric field therapy (NCCN, 2018). Radiochemotherapy is followed by adjuvant temozolomide given for 6 to 12 months. The prognosis for individuals with GBM is poor, with a 1-year survival rate of less than 40%.

~~The U.S. Food and Drug Administration (FDA) approved the premarket approval application (PMA) for NovoTTF™ 100A System (NovoCure™ Ltd., Portsmouth, NH; Haifa, Israel) in 2011. The device is now marketed as Optune™ (NovoCure Ltd., Portsmouth, NH, Haifa, Israel). Optune is a portable, non-invasive device that is designed for the delivery of TTF to the head. The device is considered to be an alternative to standard medical~~
This Clinical UM Guideline is intended to provide assistance in interpreting Healthy Blue's standard Medicaid benefit plan. When evaluating insurance coverage for the provision of medical care, federal, state and/or contractual requirements must be referenced, since these may limit or differ from the standard benefit plan. In the event of a conflict, the federal, state and/or contractual requirements for the applicable benefit plan coverage will govern. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Clinical UM Guideline is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

~~therapy for GBM after surgical and radiation treatment options are exhausted. Initially, Optune (NovoTTF) was approved as a solitary treatment for adults (22 years of age or older) with histologically-confirmed, recurrent GBM in the supratentorial region of the brain after receiving chemotherapy. On October 5, 2015, the FDA approved the use of Optune in combination with temozolomide for the treatment of adults with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and radiation therapy.~~

Stupp and colleagues (2015) evaluated the safety and efficacy of TTF in individuals with newly diagnosed GBM following chemoradiation therapy. In a multi-center clinical trial, 695 individuals were randomized (2:1) to either TTF with temozolomide or temozolomide alone. The primary endpoint was identified as progression-free survival (PFS) in the intent-to-treat (ITT) population (significant threshold, $p \leq 0.01$). An interim analysis was designed into the study to be conducted on the first 315 participants who had completed at least 18 months of follow-up. At interim analysis, the median PFS in the TTF plus temozolomide group was 7.1 months (95% confidence interval [CI], 5.9-8.2 months) compared to 4.0 months (95% CI, 3.3-5.2 months) in the temozolomide group (Hazard Ratio [HR] 0.62; 98.7% CI, 0.43-0.89; stratified log-rank, p=0.001). The secondary endpoint, the overall survival (OS) in the per-protocol population also showed significant improvement in the treatment group versus control. Median overall survival in the per-protocol population in the TTF plus temozolomide group versus the temozolomide alone group was 20.5 months (95% CI, 16.7-25.0 months) and 15.6 months (95% CI, 13.3-19.1 months) respectively (HR, 0.64; 99.4% CI, 0.42-0.98; p=0.004). Based on the interim analysis results, the study was terminated and individuals in the control group were offered TTF in addition to temozolomide. A total of 11 individuals crossed over and began using TTF. With the exception of a higher incidence of localized skin reactions in the TTF plus temozolomide group, the incidence, distribution, and severity of adverse events were similar across both treatment groups. This trial does contain a few limitations. As enrollment was not initiated until following radiochemotherapy, this initial phase of treatment is subject to variability. Participants were excluded from participation for progression during early radiotherapy; therefore, those with a very poor prognosis were not included in the sample population. In addition, as TTF was continued beyond tumor progression, there was additional data on this group, increasing the potential for reporting bias. The final analysis of the data was consistent with the interim analysis results (Stupp, 2017).

~~In 2018, NCCN added a category 1 recommendation for adjuvant alternating electric field therapy when used as an initial therapy along with temozolomide for individuals with anaplastic gliomas/ glioblastoma with good performance status following standard radiotherapy and concurrent temozolomide.~~

This Clinical UM Guideline is intended to provide assistance in interpreting Healthy Blue's standard Medicaid benefit plan. When evaluating insurance coverage for the provision of medical care, federal, state and/or contractual requirements must be referenced, since these may limit or differ from the standard benefit plan. In the event of a conflict, the federal, state and/or contractual requirements for the applicable benefit plan coverage will govern. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Clinical UM Guideline is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Results from an industry-sponsored pilot study of TTF alone and TTF in combination with chemotherapy for individuals with diagnosed GBM were reported (Kirson, 2009b). In this single arm study, the first group included 10 individuals with recurrent GBM after failure of maintenance temozolomide, and 10 individuals with newly diagnosed GBM treated with TTF combined with temozolomide were in the second cohort. All 20 individuals were treated for an average of 1 year (range 2.5-24 months) continuously. The first group was compared to a matched group of 18 concurrent controls who received salvage chemotherapy for relapsed/recurrent GBM. The TTF-chemotherapy group was compared to a matched group of 32 concurrent controls who received temozolomide alone. In addition, OS for both cohorts was compared to matched historical control data. Data for the first group were reported by Kirson and colleagues in 2007. For the group of 10 individuals with newly diagnosed GBM, PFS was significantly different (HR 3.32; 95% CI, 1.9-5.9; p=0.0002) between the TTF-chemotherapy group compared to the matched concurrent and historical controls. The difference in OS was also significant (p=0.0018). The authors concluded TTF may also be an effective sensitizer when used concurrently with chemotherapeutic agents.

In 2018, NCCN added a category 1 recommendation for adjuvant alternating electric field therapy when used as an initial therapy along with temozolomide for individuals with anaplastic gliomas/ glioblastoma with good performance status following standard radiotherapy and concurrent temozolomide.

Recurrent or Progressive GBM

Stupp and associates (2012) conducted a phase III, multinational, randomized controlled pivotal clinical trial upon which the initial PMA was based. Between September 2006 and May 2009, 28 clinical centers enrolled 237 adult participants with relapsed or progressive GBM despite conventional therapy (e.g., surgery and chemo-radiotherapy followed by chemotherapy). A total of 120 participants were randomized in a 1:1 ratio to receive monotherapy with NovoTTF treatment and 117 participants were randomized to the group treated with available best standard care (BSC) chemotherapies as practiced at each of the participating clinical centers. Chemotherapy agents considered as BSC during the trial included platinum-based chemotherapy (i.e., carboplatin); nitrosureas (BCNU); procarbazine; combination of procarbazine, lomustine and vincristine (PCV); temozolomide; and bevacizumab. A period of 28 days of treatment with NovoTTF was considered 1 full treatment course. Participants treated with NovoTTF were allowed to take breaks from treatment up to an hour, twice per day for personal needs such as

showers. The primary endpoint of the study was OS. Secondary endpoints included PFS at 6 months (PFS6), 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 and subsequent MRIs were 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.

Of the 237 enrollees, 8 participants (4 in each group) did not receive the assigned therapy. A total of 97% (116) of 120 enrollees in the NovoTTF group started treatment and 93 participants (78%) completed 1 cycle (4 weeks) of therapy. Discontinuation of TTF occurred in 27 participants 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 BSC (active control) group, 113 (97%) of the 117 assigned participants received chemotherapy and all completed 1 full treatment course with the exception of 1 individual. In the BSC cohort, 21 participants did not return to the site and details on disease progression and toxicity were not available. Stupp and colleagues (2012) noted the median survival of 6.6 months in the TTF group was marginally higher than 6 months in the BSC group (HR 0.86, 95% CI, 0.66–1.12; p=0.27). For both groups, 1-year survival was 20%. The survival rates for 2 and 3 years were 8% (95% CI: 4, 13) and 4% (95% CI: 1, 8) versus 5% (95% CI: 3, 10) and 1% (95% CI: 0, 3) for the TTF cohort compared to the BSC cohort, respectively. With a median follow-up of 39 months, 93% (220 participants) had died. Objective radiological responses (partial response [PR] and complete response [CR]) were noted in 14 participants in the TTF group and 7 in the BSC 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. BSC participants experienced grade 2-4 events by organ system related to the pharmacologic activity of chemotherapy agents utilized. QOL data were available in 63 participants (27%). Based on the Quality of Life Questionnaire-Core 30 (QLQ C-30) and Brain Cancer Module (BN-20) questionnaires, 5 out of 6 general scales and 7 of 9 symptom scales including nausea, vomiting, diarrhea, constipation and pain, QOL was consistently higher in NovoTTF than in the control group. There were no meaningful differences observed between the domains of global health and social functioning. The BSC cohort had a larger decrease in the negative effects of seizures than the TTF cohort. The self-reporting of QOL indicators may be influenced by bias for the treatment group (FDA Label, 2011; Stupp, 2012). Although the NovoTTF-100A device has received FDA approval, the pivotal trial did not achieve the primary endpoint of the study, which was improved survival with NovoTTF treatment in

comparison to chemotherapy. The study was not sufficiently powered to evaluate for a non-inferiority determination.

In an industry-sponsored study, Kirson and colleagues (2007) reported results of TTF treatment on various tumor cell lines and animal tumor models and noted "Optimal frequencies differed between cancer cell types." Additionally, the effects of a total of 280 weeks of TTF treatment on 10 individuals with recurrent GBM were reported in the pilot study. TTF treatment resulted in a median TTP of 26.1 weeks (range, 3-124 weeks) and the PFS6 of 50% (23-77% CI). The median OS was 62.2 weeks (range, 20.3-124.0 weeks). One individual achieved a CR and is free from tumor 10 months after stopping treatment, and 1 participant achieved and continues to maintain a PR 7 months after stopping treatment. The authors concluded TTF treatment is encouraging when compared to historical average PFS6 of 15.3 ± 3.8% and average historical TTP of 9.5 ± 1.6 weeks and an average OS 29.3 ± 6 weeks. Mild to moderate contact dermatitis was reported in 9 out of 10 participants.

~~Results from an industry-sponsored pilot study of TTF alone and TTF in combination with chemotherapy for individuals with diagnosed GBM were reported (Kirson, 2009b). In this single arm study, the first group included 10 individuals with recurrent GBM after failure of maintenance temozolomide, and 10 individuals with newly diagnosed GBM treated with TTF combined with temozolomide were in the second cohort. All 20 individuals were treated for an average of 1 year (range 2.5-24 months) continuously. The first group was compared to a matched group of 18 concurrent controls who received salvage chemotherapy for relapsed/recurrent GBM. The TTF-chemotherapy group was compared to a matched group of 32 concurrent controls who received temozolomide alone. In addition, OS for both cohorts was compared to matched historical control data. Data for the first group were reported by Kirson and colleagues in 2007. For the group of 10 individuals with newly diagnosed GBM, PFS was significantly different (HR 3.32; 95% CI, 1.9-5.9; p=0.0002) between the TTF-chemotherapy group compared to the matched concurrent and historical controls. The difference in OS was also significant (p=0.0018). The authors concluded TTF may also be an effective sensitizer when used concurrently with chemotherapeutic agents.~~

Vymazal and colleagues (2015) analyzed the response patterns in individuals with recurrent GBM who exhibited an objective response in two previous studies in order to evaluate the baseline characteristics of those individuals who responded and to evaluate the relationship between compliance with use and efficacy outcomes. The analysis was completed on one pilot study (n=10) and a phase III trial (n=237) in which TTF was compared to standard chemotherapy. Between both studies, TTF was administered as monotherapy in 130 individuals. Across both

trials, there was a 15% response rate (16/110 with a 4% CR rate). There were no significant differences in baseline characteristics between the responder and non-responder groups. In those in which a response was noted, there was frequently a delayed response; the tumor would initially continue to grow before responding to treatment. Analysis supported that an increase in compliance was associated with better treatment response and longer OS. The extent of treatment response in those who exhibited a response was dependent on compliance ($p<0.001$).

Treatment recommendations for brain tumors published by the National Comprehensive Cancer Network® (NCCN, 2018) and the National Cancer Institute (NCI, 20187) include surgical resection, radiation therapy and/or chemotherapy as treatment options. In 2014, the NCCN clinical practice guideline for CNS Tumors was updated and the consideration for alternating electric field therapy for individuals with recurrent, diffuse or multiple GBM was changed to a category 3 from the previous 2B level of evidence. This, revision denoteding a major disagreement on the appropriateness of the intervention, with NCCN members noting similar survival in both arms of the RCT trial. In May 2015, the NCCN clinical practice guideline was again revised to change the recommendation to consider alternating electric field therapy for glioblastoma from a category 3 back to a category 2B for recurrent disease. In 2018, NCCN added a category 1 recommendation for adjuvant alternating electric field therapy when used as an initial therapy along with temozolomide for individuals with anaplastic gliomas/ glioblastoma with good performance status following standard radiotherapy and concurrent temozolomide. The NCI Adult Brain Tumors Treatment (PDQ®) (2018) does not include TTF treatment for recurrent GBM.

The evidence does not support that TTF is effective in the treatment of recurrent GBM. The evidence is limited to a RCT, a retrospective review and small prospective studies (Kirson, 2009b; Mrugala, 2014; Rulseh, 2012; Stupp, 2012). The RCT did not meet its primary endpoint of demonstrating an improvement in survival in this population.

Other Solid Tumors

In addition to TTF treatment for brain tumors, this therapy has been studied in other types of malignancies, including breast cancer, non-small cell lung cancer (NSCLC) and pancreatic carcinoma. However, at this time, there are no studies which support that the use of tumor treating fields for conditions other than GBM. The NCCN clinical practice guidelines do not include any recommendations regarding the use of electric TTF treatment for any condition other than GBM.

This Clinical UM Guideline is intended to provide assistance in interpreting Healthy Blue's standard Medicaid benefit plan. When evaluating insurance coverage for the provision of medical care, federal, state and/or contractual requirements must be referenced, since these may limit or differ from the standard benefit plan. In the event of a conflict, the federal, state and/or contractual requirements for the applicable benefit plan coverage will govern. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Clinical UM Guideline is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Treatment Planning Software

In 2013, the FDA approved NovoTal through a PreMarket Approval (PMA) supplement. NovoTal is an algorithmic software package which allows treating physicians, who have completed a certification program, to create individualized treatment maps. The standard treatment plan developed by the manufacturer uses post-contrast MRI sequences to develop a treatment plan. Treating physicians using NovoTal are able to incorporate additional imaging data and other clinical considerations into TTF treatment planning (Connelly, 2016). There is a paucity of literature reporting on planning approaches in TTF treatment and their effect on clinical outcomes. Connelly and colleagues (2016) reported on the use of NovoTal in a case series of eight individuals with grades 2-4 glioblastomas. In addition to contrast enhancing MRI imaging, other clinical considerations, such as the heterogeneity in contrast enhancement in tumors, were taken into account during the planning process. The authors discuss the use of alternative MRI sequences during the planning stage of treatment, but do not report on clinical outcomes, noting:

> this case series demonstrates that treatment planning beyond the extent of contrast enhancement is clinically feasible and should be prospectively compared to standard treatment planning in a clinical trial setting, in order to determine the impact on patient outcomes.

Chaudhry and associates (2015) compared physician performance using the NovoTal system to conduct transducer array layout mapping to the mapping laid out by the Novocure in-house clinical team. Neuro-oncologists, medical oncologists and neurosurgeons (n=14) evaluated 5 cases of recurrent glioblastoma and developed treatment plans. While the study demonstrated a high level of concordance in transducer array layout planning between NovoTal certified physicians and the Novocure in-house clinical team, the study did not address whether clinical outcomes were affected. ~~At this time,~~The evidence does not support ~~confirm~~ that ~~this~~ the use of enhanced treatment planning software is considered effective ~~results in improved clinical outcomes when compared with standard treatment plans~~in the use of TTF treatment.

Definitions

This Clinical UM Guideline is intended to provide assistance in interpreting Healthy Blue's standard Medicaid benefit plan. When evaluating insurance coverage for the provision of medical care, federal, state and/or contractual requirements must be referenced, since these may limit or differ from the standard benefit plan. In the event of a conflict, the federal, state and/or contractual requirements for the applicable benefit plan coverage will govern. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Clinical UM Guideline is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Cytokinesis: The cytoplasmic changes accompanying mitosis. The cleavage of the cytoplasm into daughter cells following nuclear division.

Eastern Cooperative Oncology Group (ECOG) Performance Status: A scale used to determine the individual's level of functioning. This scale may also be referred to as the WHO or Zubrod score which is based on the following scale:

0 Fully active, able to carry on all pre-disease performance without restriction
1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3 Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5 Dead

Glioblastoma multiforme: Stage IV glioblastoma, which includes WHO recognized variants, giant cell glioblastoma and gliosarcoma.

Karnofsky Performance Status Score: A 10 point scale used by healthcare providers to quickly evaluate how an individual is feeling on any given day.

100 Able to work. Normal; No complaints; No evidence of disease.
90 Able to work. Able to carry on normal activity; Minor symptoms.
80 Able to work. Normal activity with effort; Some symptoms.
70 Independent; not able to work. Cares for self; Unable to carry on normal activity.
60 Disabled; dependent. Requires occasional assistance; cares for most needs.
50 Moderately disabled; dependent. Requires considerable assistance and frequent care.
40 Severely disabled; dependent. Requires special care and assistance.
30 Severely disabled. Hospitalized, death not imminent.
20 Very sick. Active supportive treatment needed.
10 Moribund. Fatal processes are rapidly progressing

This Clinical UM Guideline is intended to provide assistance in interpreting Healthy Blue's standard Medicaid benefit plan. When evaluating insurance coverage for the provision of medical care, federal, state and/or contractual requirements must be referenced, since these may limit or differ from the standard benefit plan. In the event of a conflict, the federal, state and/or contractual requirements for the applicable benefit plan coverage will govern. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Clinical UM Guideline is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Mitosis: The process by which a single parent cell divides to make two new daughter cells. Each daughter cell receives a complete set of chromosomes from the parent cell, allowing the body to grow and replace cells.

Progressive disease: Disease that is growing, spreading or getting worse.

Recurrent disease: Disease that has recurred (come back), usually after a period of time during which the disease could not be detected. In the case of cancer, the disease may come back to the same place as the original (primary) tumor or to another place in the body: also called recurrence.

References

Peer Reviewed Publications:

1. Burri SH, Gondi V, Brown PD, Mehta MP. The Evolving Role of Tumor Treating Fields in Managing Glioblastoma: Guide for Oncologists. Am J Clin Oncol. 2018; 41(2):191-196.
2. Chaudhry A, Benson L, Varshaver M, et al. NovoTTF™ - 100A System (Tumor Treating Fields) transducer array layout planning for glioblastoma: a NovoTAL ™ System user study. World J Surg Oncol. 2015; 13:316.
3. Connelly J, Hormigo A, Mohilie N, et al. Planning TTFields treatment using the NovoTAL system-clinical case series beyond the use of MRI contrast enhancement. BMC Cancer. 2016; 16(1):842.
4. Domingo-Musibay E, Galanis E. What next for newly diagnosed glioblastoma? Future Oncol. 2015; 11(24):3273-3283.
1. ~~Domingo-Musibay E, Galanis E. What next for newly diagnosed glioblastoma? Future Oncol. 2015; 11(24):3273-3283.~~
5. Kanner AA, Wong ET, Villano JL, Ram Z.; EF-11 Investigators. Post hoc analysis of intention-to-treat population in phase 3 comparison of NovoTTF-100A™ System versus best physician's choice chemotherapy. Semin Oncol. 2014; 41(Suppl 6):S25-S34.
2. ~~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.~~

~~3. Kanner AA, Wong ET, Villano JL, Ram Z.; EF-11 Investigators. Post hoc analysis of intention-to-treat population in phase 3 comparison of NovoTTF-100A™ System versus best physician's choice chemotherapy. Semin Oncol. 2014; 41(Suppl 6):S25-S34.~~

~~4.~~6. 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 USA. 2007; 104(24):10152-10157.

~~5.~~7. Kirson ED, Giladi M, Gurvich Z, et al. Alternating electric fields (TTFields) inhibit metastatic spread of solid tumors to the lungs. Clin Exp Metastasis. 2009a; 26(7):633-640.

~~6.~~8. Kirson ED, Gurvich Z, Schneiderman R, et al. Disruption of cancer cell replication by alternating electric fields. Cancer Res. 2004; 64(9):3288-3295.

~~7.~~9. Kirson ED, Schneiderman RS, Dbalý V, et al. Chemotherapeutic treatment efficacy and sensitivity are increased by adjuvant alternating electric fields (TTFields). BMC Med Phys. 2009b; 9:1.

~~8.~~10. Mehta M, Wen P, Nishikawa R, et al. Critical review of the addition of tumor treating fields (TTFields) to the existing standard of care for newly diagnosed glioblastoma patients. Crit Rev Oncol Hematol. 2017; 111:60-65.

~~9.~~11. 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. 2014; 41 (Suppl 6):S4-S13.

~~10.~~12. Pless M, Droege C, von Moos R, et al. A phase I/II trial of Tumor Treating Fields (TTFields) therapy in combination with pemetrexed for advanced non-small cell lung cancer. Lung Cancer. 2013; 81(3):445-450.

~~11.~~13. 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.

~~12.~~14. Salzberg M, Kirson E, Palti Y, Rochlitz C. 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):362-365.

~~13.~~15. Sampson JH. Alternating electric fields for the treatment of glioblastoma. JAMA. 2015; 314(23):2511-2513.

16. 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. 2015; 314(23):2535-2543.

~~14.~~17. 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.

This Clinical UM Guideline is intended to provide assistance in interpreting Healthy Blue's standard Medicaid benefit plan. When evaluating insurance coverage for the provision of medical care, federal, state and/or contractual requirements must be referenced, since these may limit or differ from the standard benefit plan. In the event of a conflict, the federal, state and/or contractual requirements for the applicable benefit plan coverage will govern. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Clinical UM Guideline is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

18. 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):2192-2202.
~~15.~~19. Trusheim J, Dunbar E, Battiste J, et al. A state-of-the-art review and guidelines for tumor treating fields treatment planning and patient follow-up in glioblastoma. CNS Oncol. 2017; 6(1):29-43.
~~16.~~20. Vymazal J, Wong ET. Response patterns of recurrent glioblastomas treated with tumor-treating fields. Semin Oncol. 2015; 42(3):e44-e55.
~~17.~~21. Wong ET, Lok E, Swanson KD, et al. Response assessment of NovoTTF-100A versus best physician's choice chemotherapy in recurrent glioblastoma. Cancer Med. 2014; 3(3):592-602.

Government Agency, Medical Society, and Other Authoritative Publications:

1. American Urological Association (AUA) / American Society for Radiation Oncology (ASTRO) / Society of Urologic Oncology (SUO). Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline. 2017. Available at: https://www.astro.org/uploadedFiles/_MAIN_SITE/Patient_Care/Clinical_Practice_Statements/Content_Pieces/ClinicallyLocalizedProstateCancer.pdf. Accessed on ~~April~~ February ~~1~~1, 201~~9~~8.
2. Gilbert MR. Establishing the standard of care for patients with newly diagnosed and recurrent glioblastoma. Am Soc Clin Oncol Educ Book. 2012:112-117.
3. National Cancer Institute (NCI). Available at http://www.cancer.gov/. Accessed on ~~April~~ February 1~~0~~, 201~~9~~8.
   - Adult Central Nervous System Tumors Treatment (PDQ®). Last modified ~~January~~ February ~~3~~1, 201~~9~~8.
   - Non-Small Cell Lung Cancer Treatment (PDQ®). Last modified March 20, 2018.
4. NCCN Clinical Practice Guidelines in Oncology®. © 201~~9~~8 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website at: http://www.nccn.org/index.asp. Accessed on ~~April~~ February 1~~0~~, 201~~9~~8.
   - Breast Cancer (V~~3~~1.2018). October~~March~~ 2~~5~~0, 2018.
   - Central Nervous System Cancers (V~~2~~1.2018). ~~March~~ November 2~~6~~0, 2018.
   - Cutaneous Melanoma (V~~1~~2.201~~9~~8). November~~January~~ 1~~9~~, 2018.
   - Non-Small Cell Lung Cancer (V3.201~~9~~8). January~~February~~ ~~2~~18, 201~~9~~8.
   - Pancreatic Adenocarcinoma (V~~1~~3.201~~9~~7). November~~September~~ 8~~11~~, 201~~8~~7.
5. Novocure.

This Clinical UM Guideline is intended to provide assistance in interpreting Healthy Blue's standard Medicaid benefit plan. When evaluating insurance coverage for the provision of medical care, federal, state and/or contractual requirements must be referenced, since these may limit or differ from the standard benefit plan. In the event of a conflict, the federal, state and/or contractual requirements for the applicable benefit plan coverage will govern. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Clinical UM Guideline is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

- Optune Instructions for Use. Issue Date: January 2019. Available at: https://www.optune.com/Content/pdfs/Optune_IFU_8.5x11.pdf. Accessed on February 6, 2019.
- Patient Information and Operation Manual. Issue Date: January 2019. Available at: https://www.optune.com/content/pdfs/Optune_PIOM_8.5x11.pdf. Accessed on February 6, 2019.

5.6. U.S. Food and Drug Administration (FDA). Neurological Devices Panel. ~~March 17, 2011a.~~ Available at: https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/. Accessed on ~~April~~ February 1~~1~~, 2019~~8~~.

6.7. U.S. Food and Drug Administration (FDA) Premarket Notification Database. Tumor Treatment Fields. NovoTTF-10A System. Summary of Safety and Effectiveness Data (SSED). No. P100034. Rockville, MD: FDA. April 8, 2011b. Available at: http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100034b.pdf. Accessed on ~~May~~ February 1~~2~~, 2019~~8~~.

7.8. U.S. Food and Drug Administration (FDA) Premarket Approval (PMA) Database. Premarket Notification Database. Tumor Treatment Fields. Optune™. Summary of Safety and Effectiveness Data (SSED). No. P100034/S013. Rockville, MD: FDA. October 5, 2015. Available at: http://www.accessdata.fda.gov/cdrh_docs/pdf10/p100034s013b.pdf . Accessed on ~~May~~ February 1~~2~~, 2019~~8~~.

Websites for Additional Information

1. American Cancer Society (ACS). Brain and Spinal Cord Tumors in Adults. Available at: https://www.cancer.org/cancer/brain-spinal-cord-tumors-adults/about/what-are-brain-spinal-tumors.html~~http://www.cancer.org~~. Accessed ~~April~~ February 1~~1~~, 2019~~8~~.
2. National Institutes of Health. Brain and Spinal Tumors Information Page~~ClinicalTrials.gov~~. Available at: https://www.ninds.nih.gov/Disorders/All-Disorders/Brain-and-Spinal-Tumors-Information-Page~~http://clinicaltrials.gov/~~. Accessed on ~~April~~ February ~~1~~1, 2019~~8~~.

Index

NovoTTF-100A System
NovoTTF-100L System
Optune

This Clinical UM Guideline is intended to provide assistance in interpreting Healthy Blue's standard Medicaid benefit plan. When evaluating insurance coverage for the provision of medical care, federal, state and/or contractual requirements must be referenced, since these may limit or differ from the standard benefit plan. In the event of a conflict, the federal, state and/or contractual requirements for the applicable benefit plan coverage will govern. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Clinical UM Guideline is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Tumor Treatment Field (TTF)

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
Revised	03/21/2019	Medical Policy & Technology Assessment Committee (MPTAC) review.
Revised	03/20/2019	Hematology/Oncology Subcommittee review. Added a not medically necessary statement for treatment mapping and planning computer software. Updated Discussion and References sections.
New	05/03/2018	~~Medical Policy & Technology Assessment Committee (~~MPTAC~~)~~ review.
New	05/02/2018	Hematology/Oncology Subcommittee review. Initial document development. Moved content of DME.00035 Electric Tumor Treatment Field (TTF) to new clinical utilization management guideline document with the same title.

This Clinical UM Guideline is intended to provide assistance in interpreting Healthy Blue's standard Medicaid benefit plan. When evaluating insurance coverage for the provision of medical care, federal, state and/or contractual requirements must be referenced, since these may limit or differ from the standard benefit plan. In the event of a conflict, the federal, state and/or contractual requirements for the applicable benefit plan coverage will govern. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Clinical UM Guideline is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.