Clinical Policy Title: Tumor treatment fields for glioblastoma

Clinical Policy Number: 05.02.05

Effective Date:	**July 1, 2015**
Initial Review Date:	March 18, 2015
Most Recent Review Date:	May 1, 2018
Next Review Date:	May 2019

Policy contains:

- Alternating electric fields (AEF).
- Tumor treatment fields (TTF).
- Electric tumor treatment fields (ETTF).
- Optune.
- Glioblastoma multiforme.

Related policies:

CP# 05.02.01	Proton beam therapy
CP# 05.02.02	Brachytherapy
CP# 05.02.03	Intensity modulated radiotherapy IMRT

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Coverage policy

AmeriHealth Caritas considers the use of tumor treatment fields for the management of patients with glioblastoma multiform to be investigational and, therefore, not medically necessary (Stupp, 2012; 2017; Zhu 2017).

Limitations:

There is insufficient evidence to demonstrate the use of cranial electrical stimulation for depression. All other uses of tumor treatment fields are not medically necessary.

E0766 - Electrical stimulation device used for cancer treatment, includes all accessories, any type.

NOTE: For Pennsylvania lines of business, Tumor treatment fields will be considered as a program

exception and approved in cases where they are deemed medically necessary.

Alternative covered services:

Chemotherapy and radiotherapy.

Background

Glioblastoma multiform is the most frequently occurring primary brain tumor in the United States, affecting some 17,000 patients each year. The median survival rate for glioblastoma multiform is 14 – 16 months. A few patients may survive five years, representing less than three percent of all glioblastoma multiform patients.

Because of the discouraging prognosis for those suffering from glioblastoma multiform when treated with traditional therapies, there has been a search for alternative treatment modalities that can provide localized treatment without adversely impacting normal brain tissue.

Tumor treatment fields are low-intensity (1 – 2 volts/CM), intermediate frequency (100 – 200 KHz) alternating electrical fields (AEFs) established through insulated electrodes on the skin around the region of a malignant tumor. Tumor cells undergoing mitosis may be destroyed, leaving nondividing cells unaffected.

The use of tumor treatment fields has had modest success in the reduction of growth of glioblastoma multiform in limited series of trials in several single-institution programs.

On September 24, 2014, the U.S. Food and Drug Administration (FDA) cleared Optune® as a class III device, a category of intervention generally reserved for the highest-risk devices and therefore subject to the highest level of regulatory control.

The use of alternating electrical fields has also been utilized for treatment of depression. While there have been a few papers describing successful therapy of this condition, they have generally not been controlled studies, and have been characterized as suboptimal in design and fraught with inconsistent outcomes.

Searches

AmeriHealth Caritas searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality's National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on April 20, 2018. Search terms were “tumor treatment fields” and “alternating electric fields.”

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

Findings

The National Comprehensive Cancer Network (NCCN) guidelines of 2014 include alternating electric field therapy for local recurrence of glioblastoma multiform as a category 3 recommendation, after palliative supportive care, systemic chemotherapy, or reirradiation therapy have been offered to the patient.

The American Academy of Neurological Sciences (AANS, 2014) guidelines recommend treatment of glioblastoma multiform with chemotherapy (i.e., bevacizumab) as it provides improved disease control, as measured by best imaging response and progression-free survival at six months. The AANS also recommends that, for progression of disease despite treatment, the patient be enrolled in a clinical trial.

Rulseh published a study in 2012 of 20 glioblastoma multiform patients treated with tumor treatment fields, of whom only five were long-term survivors (of at least five years).

Hayes Inc.’s review of the literature found very few well-designed studies to weigh as evidence of efficacy of therapy.

In sum, the findings of medical evidence for tumor treatment fields for therapy of glioblastoma multiform are insufficient to confidently support their use.

Policy updates:

In 2017, we found that during the past 18 months, there has been further information published regarding tumor treatment fields for glioblastoma.

In a phase III clinical trial for recurrent glioblastoma (Wong, 2015), tumor treatment fields were shown to have equivalent efficacy when compared to conventional chemotherapies in 37 participants, while lacking the typical side effects associated with chemotherapies. Furthermore, an interim analysis of a recent clinical trial in the upfront setting demonstrated superiority to standard of care cytotoxic chemotherapy, most likely because the subjects' tumors were at an earlier stage of clonal evolution, possessed less tumor-induced immunosuppression, or both. The authors concluded that the efficacy of tumor treatment fields can be increased by combining them with other anti-cancer treatment modalities.

In 2018, we identified one systematic review (Zhu, 2017) which included an analysis of two randomized phase III trials of the efficacy and safety of tumor treatment fields in glioblastoma.

- The first of these is the EF-11 trial, examined in Stupp (2012) which was previously included in this policy's Summary of clinical evidence. Stupp (2012) compares monotherapies of tumor treatment fields (n = 120) versus the chemotherapy of the physician's choice (n = 117) in recurrent glioblastoma. Treatment efficacy of in the two arms was approximately equivalent as measured by overall survival and progression-free survival. The chemotherapy group had more severe adverse events (16% compared to 6% in the tumor treatment fields group), while the tumor treatment fields group had more mild and moderate adverse events (14% and 2% compared to none in the chemotherapy group) (p = 0.022). While physical functioning was reported to be better in the chemotherapy group, cognitive, emotional, and role functioning were better in the tumor treatment field group.
- The second randomized clinical study included in Zhu's (2017) paper is known as EF-14 and is also from Stupp's research group. The final analysis of the data (Stupp, 2017) was published after Zhu's (2017) paper. In the EF-14 trial, 695 participants were randomized to receive combined therapy with temozolomide and tumor treatment fields (n = 466) or monotherapy with temozolomide alone (n = 229). The combination treatment with tumor treatment fields was associated with a median increase from 4.0 to 6.7 months of progression-free survival (Hazard Ratio [HR], 0.63; 95% Confidence Interval [CI], 0.52-0.76; p < 0.001)and a median increase from 16.0 to 20.7 months of overall survival (HR, 0.63; 95% CI, 0.53-0.76; p < 0.001). The frequency of adverse events was similar in the two arms (48% in the tumor treatment fields group compared to 44% in the temozolomide alone group), while 52% of those in the tumor treatment fields group had mild to moderate skin toxicity where the electrical equipment attached to the scalp. Stupp (2017) has been added to this policy's Summary of clinical evidence, as has Taphoorn (2018) which is based on the same dataset.
- Zhu (2017) also describes PRiDe, a third dataset based on a patient registry database that was compared with the EF-11 study and described in Mrugala (2014). The Mrugala paper was previously included in this policy's Summary of clinical evidence. The PRiDe patients have somewhat different treatment characteristics and outcomes than the EF-11 participants, having started treatment with tumor treatment fields earlier and having higher overall survival (1-year overall survival 44% in PRiDe and 20% in EF-11; 2-year overall survival 30% in PRiDe and 9% in EF-11).

Zhu (2017) concludes that the benefits of tumor treatment fields lie in their non-invasive anti-tumor effect, higher efficacy when combined with chemotherapy, and minimal toxicity, and recommends that future studies examine combinations of treatment with chemotherapy, radiation therapy, targeted therapy, and immunotherapy. Burri (2018), discussing the outcomes of EF-11, EF-14, and the PRiDe registry, states that it can be "reasonably argued" that clinicians should discuss tumor treatment fields with all patients with new diagnoses of glioblastoma as a potential part of their initial therapy, noting that "further studies would be useful to refine the population most likely to benefit, and most importantly identify subsets where benefit is miniscule or not present." Similarly, Mittal's (2018) review finds that tumor treating fields are efficacious, and that further research is necessary to optimize patient selection, analyze cost-effectiveness, and measure the full impact on quality of life. We have not identified any randomized clinical trials of tumor treatment fields for pediatric glioblastoma (Green, 2017).

Additionally in 2018, we updated the reference for the National Comprehensive Cancer Network (2017) guideline on central nervous system cancers, which recommends alternating electric field therapy as an optional therapy under the following conditions (evidence category 2b):

- Patients with a diagnosis of glioblastoma, with supratentorial disease, either on or not on carmustine chemotherapy, with good performance status as measured by Karnofsky Performance Status of at least 60, with O^6-methylguanine-DNA methyltransferase (MGMT promoter) status either methylated, unmethylated, or indeterminate, along with standard brain radiation therapy and concurrent temozolomide and adjuvant temozolomide (evidence category 2A).
- Patients with a diagnosis of recurrent glioblastoma, whether diffuse, multiple or local, unresectable or post-resection.

While there appears to be a benefit to the treatment, this has been observed in a small total number of participants, the benefit is relatively short-term, and it is not understood who would most benefit from the treatment. Therefore at this time the treatment remains experimental.

Summary of clinical evidence:

Citation	Content, Methods, Recommendations
Taphoorn (2018) 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	**Key points:** • This paper was published by the same group and analyzes the same sample as Stupp (2017) and Stupp (2012) below. A total of 695 participants were randomized 2:1 to the enhanced group (tumor treatment fields plus temozolomide) or the standard (temozolomide alone). • Of the 695 patients in the study, 639 (91.9%) completed the baseline health related quality of life questionnaire. • Health-related quality of life did not differ significantly between treatment arms except for itchy skin. Deterioration-free survival was significantly longer in the enhanced arm

Citation	Content, Methods, Recommendations
	for the following measures, each at P < 0.01: global health (4.8 vs 3.3 months); physical (5.1 vs 3.7 months) and emotional functioning (5.3 vs 3.9 months); pain (5.6 vs 3.6 months); and leg weakness (5.6 vs 3.9 months), likely related to improved progression-free survival. • Time to deterioration, reflecting the influence of treatment, did not differ significantly except for itchy skin (enhanced arm poorer; 8.2 vs 14.4 months; P < 0.001) and pain (enhanced arm improved; 13.4 vs 12.1 months; P < 0.01). Tumor treatment fields had no effect on role, social, and physical functioning. • Enhanced treatment with tumor treatment fields and temozolomide results in improved survival without a negative impact on health related quality of life with the exception of itchy skin due to the transducer arrays
Stupp (2017) Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: A randomized clinical trial.	**Key points:** • Randomized, non-blinded clinical trial enrolled 695 participants with diagnosis of glioblastoma post-resection or biopsy and post-radiochemotherapy, over July 2009 to 2014, at 83 centers. This publication is based on the final analysis. • Participants were randomized to either tumor treatment fields plus maintenance temozolomide (n = 466) or temozolomide without tumor treatment fields (n = 229). The treatment consisted of of low-intensity, 200 kHz frequency, alternating electric fields delivered (≥ 18 hours/d) by four transducer arrays on the shaved scalp and connected to a portable device. Both arms received temozolomide (150-200 mg/m2) for five days per 28-day cycle (six to 12 cycles). • Median progression-free survival was 6.7 months in the tumor treatment fields group and 4.0 months in the temozolomide-alone group (Hazard Ratio [HR], 0.63; 95% Confidence Interval [CI], 0.52-0.76; p < 0.001). Median overall survival was 20.9 months in the tumor treatment fields group vs 16.0 months in the temozolomide-alone group (HR, 0.63; 95% CI, 0.53-0.76; p < 0.001). Systemic adverse event frequency was 48% in the tumor treatment fields group and 44% in the temozolomide-alone group. Mild to moderate skin toxicity where the transducer arrays attached occurred in 52% of patients who received tumor treatment fields compared to none of those who received temozolomide alone.
Wong (2015) An Evidence-Based Review of Alternating Electric Fields Therapy for Malignant Gliomas	**Key points:** • Phase III clinical trial for recurrent glioblastoma. • Tumor treatment fields showed equivalent efficacy when compared to conventional chemotherapies. • In one trial, tumor treatment fields demonstrated superiority to standard of care cytotoxic chemotherapy. • The authors concluded that the efficacy of tumor treatment fields can be increased by combining them with other anti-cancer treatment modalities.
Wong (2015) Clinical benefit in recurrent glioblastoma from adjuvant NovoTTF-100A and TCCC	**Key points:** • Thirty-seven patients in treatment with tumor treatment fields and standard chemotherapy, but two different regimens. • This is a descriptive study without good randomization**.**

Citation	Content, Methods, Recommendations
Mrugala (2014) Clinical practice experience with NovoTTF-100A™ system for glioblastoma	**Key points:** • Analysis from PRiDe registry data from patients treated with NovoTTF therapy from October 2011 to November 2013. • Four-hundred-and-fifty-seven patients with recurrent glioblastoma multiform, not randomized and included a mix of chemotherapy only, tumor treatment fields only, and both chemotherapy and tumor treatment fields . • Groups with TTF had higher response rates than chemotherapy alone with lower side effects. • This is a descriptive study from a registry and not a controlled trial.
Stupp (2012) NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma	**Key points:** • Phase III clinical trial comparing tumor treatment fields (n = 120) to standard chemotherapy (n = 117). • Median survival was 6.6 months versus 6 months for standard treatment. • No improvement in overall survival was demonstrated; however, efficacy and activity with this chemotherapy-free treatment device appears comparable to chemotherapy regimens commonly used for recurrent glioblastoma multiform. Toxicity and quality of life clearly favored tumor treatment fields.

References

Professional society guidelines/other:

Hayes, Inc. Hayes Medical Technology Directory Report. *Optune® (NovoTTF® 100 A System; Novocure®) for the Treatment of Recurrent Glioblastoma.* Lansdale, Pa: Hayes, Inc.

NCCN Clinical Practice Guidelines in Oncology. Central nervous system cancers. Version 1.2017, National Comprehensive Cancer Network. NCCN.org. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed January 29, 2018.

Olson JJ, Nayak L, Ormond DR, Wen PY, Kalkanis SN, Ryken TC. AANS/CNS Joint Guidelines Committee. The role of targeted therapies in the management of progressive glioblastoma: a systematic review and evidence-based clinical practice guideline. *J Neurooncol*. 2014;118(3):557-599. Doi: 10.1007/s11060-013-1339-4.

Peer-reviewed references:

Barani IJ, Larson DA. Radiation therapy of glioblastoma. *Cancer Treat Res*. 2015;163:49-73. Doi: 10.1007/978-3-319-12048-5_4.

Borm GF, Lemmers O, Fransen J, Donders R. The evidence provided by a single trial is less reliable than its statistical analysis suggests. *J Clin Epidemiol*. 2009;62(7):711-715. Doi:

10.1016/j.jclinepi.2008.09.013.

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. Doi: 10.1097/COC.0000000000000395.

Davies AM, Weinberg U, Palti Y. Tumor treating fields: a new frontier in cancer therapy. *Ann NY Acad Sci*. 2013;1291:86-95. Doi: 10.1111/nyas.12112.

Green AL, Mulcahy Levy JM, Vibhakar R, et al. Tumor treating fields in pediatric high-grade glioma. *Child's Nerv Syst.* 2017;33(7):1043-1045. Doi: 10.1007/s00381-017-3431-0.

Kirson ED, Gurvich Z, Schneiderman R, et al. Disruption of cancer cell replication by alternating electric fields. *Cancer Res*. 2004;64(9):3288-3295. PMID: 15126372.

Miranda PC, Mekonnen A, Salvador R, Basser PJ. Predicting the electric field distribution in the brain for the treatment of glioblastoma. *Phys Med Biol*. 2014;59(15):4137-4147. Doi: 10.1088/0031-9155/59/15/4137.

Mittal S, Klinger NV, Michelhaugh SK, Barger GR, Pannullo SC, Juhasz C. Alternating electric tumor treating fields for treatment of glioblastoma: Rationale, preclinical, and clinical studies. *J Neurosurg.* 2018;128(2):414-421.

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. Doi: 10.1053/j.seminoncol.2014.09.010.

Rehman AA, Elmore KB, Mattei TA. The effects of alternating electric fields in glioblastoma: current evidence on therapeutic mechanisms and clinical outcomes. *Neurosurg Focus*. 2015;38(3):E14. (abstract only). Doi: 10.3171/2015.1.FOCUS14742.

Ruffini G, Wendling F, Merlet I, Molaee-Ardekani B, Mekonnen A, Salvador R, Soria-Frisch A, Grau C, Dunne S, Miranda PC. Transcranial current brain stimulation (tCS): models and technologies. *IEEE Trans Neural Syst Rehabil Eng*. 2013;21(3):333-345. Doi: 10.1109/TNSRE.2012.2200046

Rulseh AM, Keller J, Klener J, Sroubek J, Dbalý V, Syrůček M, Tovaryš F, Vymazal J. Long-term survival of patients suffering from glioblastoma multiforme treated with tumor-treating fields. *World J Surg Oncol*. 2012;10:220. Doi: 10.1186/1477-7819-10-220.

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. Doi: 10.1159/000137713.

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.

Stupp R, Wong ET, Kanner AA, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomized phase III trial of a novel treatment modality. *Eur J Cancer*. 2012;48(14):2192-2202. Doi: 10.1016/j.ejca.2012.04.011.

Taphoorn MB, 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.* 2018;4(4):495-504. Doi: 10.1001/jamaoncol.2017.5082.

Wong ET, Lok E, Swanson KD. An evidence-based review of alternating electric fields therapy for malignant gliomas. *Curr Treat Options Oncol*. 2015;16(8):40. Doi: 10.1007/s11864-015-0353-5.

Wong ET, Lok E, Swanson KD. Clinical benefit in recurrent glioblastoma from adjuvant NovoTTF-100A and TCCC after temozolomide and bevacizumab failure: a preliminary observation. *Cancer Med*. 2015; 4(3): 383-91. Doi: 10.1002/cam4.421.

Zhu P, Zhu JJ. Tumor treating fields: a novel and effective therapy for glioblastoma: mechanism, efficacy, safety and future perspectives. *Chin Clin Oncol.* 2017;6(4):41. Doi: 10.21037/cco.2017.06.29.

CMS National Coverage Determination (NCDs):

No NCDs identified as of the writing of this policy.

Local Coverage Determinations (LCDs):

L34823 TUMOR TREATMENT FIELD Therapy (TTFT). CMS Medicare Coverage Database website. Revision effective date January 1, 2017. https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34823&ver=10&articleId=52711&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=tumor+treatment+field&KeyWordLookUp=Title&KeyWordSearchType=And&bc=gAAAABAAEAAAAA%3d%3d&. Accessed January 29, 2018.

Commonly submitted codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

CPT Code	Description	Comments
N/A	Not Applicable	

ICD-10 Code	Description	Comments
C71.0	Malignant neoplasm cerebrum except lobes and ventricles	
C71.1	Malignant neoplasm of frontal lobe	
C71.2	Malignant neoplasm of temporal lobe	
C71.3	Malignant neoplasm of parietal lobe	
C71.4	Malignant neoplasm of occipital lobe	
C71.5	Malignant neoplasm of cerebral ventricle	
C71.6	Malignant neoplasm of cerebellum	
C71.7	Malignant neoplasm of brain stem	
C71.8	Malignant neoplasm of overlapping sites of brain	
C71.9	Malignant neoplasm of brain, unspecified	

HCPCS Level II Code	Description	Comments
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	