## Plan: Aetna Better Health

| Policy Number: 0827 | Effective Date: | Revision Date: 11/27/2018 |

### Policy Name:
- Electric Tumor Treatment Fields

### Type of Submission – Check all that apply:
- [ ] New Policy
- [x] Revised Policy*
- [ ] Annual Review – NoRevisions
- [ ] Statewide PDL

*All revisions to the policy must be highlighted using track changes throughout the document.

Please provide any clarifying information for the policy below:

**CPB 0827 Electric Tumor Treatment Fields**

Clinical content was last revised on 11/27/2018. No additional non-clinical updates were made by Corporate since the last PARP submission.

### Name of Authorized Individual (Please type or print):
- **Dr. Bernard Lewin, M.D.**

### Signature of Authorized Individual:
- [Signature]

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Revised July 22, 2019
Electric Tumor Treatment Fields

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

Aetna considers devices to generate electric tumor treatment fields (ETTF) and temozolomide medically necessary for persons with histologically confirmed glioblastoma (World Health Organization grade IV astrocytoma), after histologically or radiologically confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy. (Note: For recurrent glioblastoma, treatment until disease progression is considered medically necessary).

Aetna considers combination of devices to generate ETTF and temozolomide medically necessary as adjunctive treatment of newly-diagnosed histologically confirmed supratentorial glioblastoma following standard treatments that include surgery, chemotherapy, and radiation therapy. (Note: for newly diagnosed glioblastoma, treatment until disease progression for up to 24 months is considered medically necessary.)

Aetna considers devices to generate ETTF experimental and investigational for the treatment of other malignant tumors (e.g., breast, lung, melanoma, ovarian cancer, pancreatic cancer, salivary gland tumors (e.g., parotid adenoid cystic carcinoma), and solid tumor brain metastases; not an all-inclusive list) and for all other indications because their effectiveness has not been established.

Aetna considers combined ETTF therapy and chemo-immuno-therapy other than temozolomide (e.g., 6-thioguanine, bevacizumab, capecitabine, celecoxib, cisplatin, cyclophosphamide, dacarbazine, doxorubicin, lomustine, paclitaxel, and pemetrexed; not an all-
inclusive list) for the treatment of other malignant tumors experimental and investigational because the effectiveness of this approach has not been established.

Background

Alternating electric fields, generated by insulated electrodes, have been reported to exhibit inhibitory effect on the growth rate of a variety of human and rodent tumor cell lines as well as malignant tumors in animals. This non-thermal effect selectively affects dividing cells while quiescent cells are left intact. There are 2 modes of action for these anti-tumoric effects: (i) arrest of cell proliferation, and (ii) destruction of cells while undergoing division. Both effects were observed when such fields were applied for 24 hours to cells undergoing mitosis that is oriented along the field direction. The 1st mode of action is manifested by interference with the proper formation of the mitotic spindle, while the 2nd mode of action results in rapid disintegration of the dividing cells. Both effects are consistent with the computed directional forces exerted by these specific fields on charges and dipoles within the dividing cells. In-vivo treatment of tumors in C57BL/6 and BALB/c mice resulted in significant slowing of tumor growth and extensive destruction of tumor cells within 3 to 6 days. These findings showed the potential applicability of alternating electric fields as a novel therapeutic modality for malignant tumors (Kirson et al, 2004).

Electric tumor treating fields (ETTF), also known as alternating electrical field therapy, are low-intensity (1 to 2 V/cm), intermediate-frequency (100 to 200 kHz), alternating electric fields employed for the treatment of malignant tumors. ETTFs are delivered to a malignant tumor site via insulated electrodes placed around the region of the body containing the tumor. This novel treatment modality has shown promise in pilot clinical trials in patients with advanced stage solid tumors including glioblastoma (GBM).

Kirson et al (2007) reported the findings of a pilot clinical trial examining the effects of ETTF in 10 patients with recurrent 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 authors concluded that ETTF are a safe and effective new treatment modality that effectively slows down tumor growth in-vitro, in-vivo, as well as in human cancer patients.
In a pilot study, Salzberg and colleagues (2008) evaluated the safety, tolerability, and effectiveness of ETTF treatment in patients with locally advanced or metastatic solid tumors using the NovoTTF-100A device. A total of 6 patients were heavily pre-treated with several lines of therapy; no additional standard treatment option was available to them. Electric tumor treating fields treatment using continuous NovoTTF-100A lasted a minimum of 14 days and was well-tolerated. No related serious AEs occurred. Outcomes showed 1 partial response of a treated skin metastasis from a primary breast cancer, 3 cases where tumor growth was arrested during treatment, and 1 case of disease progression. One mesothelioma patient experienced lesion regression near ETTF with simultaneous tumor stability or progression in distal areas. The authors concluded that although the number of patients in this study was small, the lack of therapy toxicity and the effectiveness observed in data gathered to date indicate the potential of ETTF as a new treatment modality for solid tumors, thus, warranting further investigation.

Recent reviews indicated the ETTF is a promising approach for the treatment of GBM and non-small cell lung cancer. Stupp and Weller (2010) noted that novel treatment approaches in recurrent GBM include anti-angiogenic agents (e.g., bevacizumab and cilengitide) as well as ETTF (NovoTTF). Furthermore, Pless and Weinberg (2011) reviewed in-vitro and in-vivo pre-clinical studies, showing the activity of ETTF both as a monotherapy as well as in combination with several cytotoxic agents. They also summarized the clinical experience with ETTF, mainly in 2 indications: (i) recurrent GBM: in a prospective randomized phase III trial, ETTF was compared with best standard care (BSC, including chemotherapy): ETTF significantly improved median OS compared with standard therapy (7.8 versus 6.1 months) for the patients treated per protocol (Stupp et al, 2010; published as an abstract). Importantly, quality-of-life was also better in the ETTF group (Ram et al, 2010); (ii) a phase II study of second-line treatment of non-small cell lung cancer, where ETTF was administered concomitantly with pemetrexed. This combination resulted in an excellent median OS of 13.8 months (Pless et al, 2010; published as an abstract). Interestingly, the progression-free survival (PFS) within the area of the ETTF was 28 weeks; however, outside the ETTF the PFS was only 22 weeks. This is an important finding because it can be assumed that in the same patient the higher tumor control within the tumor-treating fields (TTFields) area was a specific effect of TTFields. Median OS was 13.8 months and 1-year survival was 57 %; 6 patients (14.6 %) had a radiological partial remission and 16 patients had stable disease (39 %). The authors stated that these results are promising and compare well with matched historical controls treated with pemetrexed alone in second-line treatment. The authors stated that the proof of concept of ETTF has been demonstrated in the pre-clinical setting, and the clinical data seem promising in various tumor types. The side effects of ETTF were minimal and in general consisted of skin reaction to the electrodes. The authors said that there are are a number of ways in which ETTF could be further evaluated, for example, in combination with chemotherapy, as a maintenance
treatment, or as a salvage therapy if radiotherapy or surgery is not possible. The authors concluded that while more clinical data are clearly needed, ETTF is an emerging and promising novel treatment concept (Pless and Weinberg, 2011).

On April 15, 2011, the Food and Drug Administration (FDA) approved the NovoTTF-100A System (Novocure, Portsmouth, NH) for the treatment of adults with GBM that recurs or progresses after receiving chemotherapy and radiation therapy. The NovoTTF-100A System is not intended to be used in combination with other cancer treatments. It should only be used after other treatments have failed. The FDA-approved indication for use is: "The NovoTTF-100A System is intended as treatment for adult patients (22 years of age or older) with histologically confirmed glioblastoma multiforme (GBM), following histologically or radiologically confirmed recurrence in the supra-tentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted."

The approval was based on data presented to the FDA from a multi-national, randomized, controlled study. The expedited pre-market approval (PMA) includes a requirement for a post-market non-randomized, unblinded, concurrent control study of NovoTTF-100A in patients with recurrent GBM. The primary question to be addressed by the study (FDA, 2011): "Is the overall survival of patients treated with NovoTTF-100A non-inferior to the survival of patients treated with the best standard of care (chemotherapy)"?

The first randomized clinical study of ETTF did not reach its primary end-point of improved survival compared to active chemotherapy (Stupp et al, 2012; Novocure, 2012). This study was funded and sponsored by the device manufacturer, Novocure, Ltd. Subjects for this study were age 18 years or older with histologically confirmed glioblastoma (World Health Organization grade IV astrocytoma) with radiologically confirmed disease progression. Patients had a Karnofsky performance status greater than or equal to 70 %, and adequate hematologic, renal and hepatic function (absolute neutrophil count greater than or equal to 1,000/mm3, hemoglobin greater than or equal to 100 g/L, platelet count greater than or equal to 100,000/mm3, serum creatinine level less than or equal to 1.7 mg/dL, total serum bilirubin less than or equal to the upper limit of normal, and liver function values less than 3 times the upper limit of normal. Prior therapy must have included radiotherapy (with and without concomitant and/or adjuvant temozolomide). Patients with infra-tentorial tumor location were excluded, as were patients with implanted electronic medical devices (e.g. pacemaker, programmable ventriculo-peritoneal shunt). Patients were randomized in a 1:1 ratio to receive either NovoTTF-100A without chemotherapy or the physician's choice of active chemotherapy (active control). Chemotherapy agents considered as best standard of care (BSC) during the study included platinum-based chemotherapy (i.e., carboplatin); nitrosoureas; procarbazine; combination of procarbazine,
lomustine and vincristine; temozolomide; and bevacizumab. For patients assigned to Novo-TTF, 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 Novo-TTF were allowed to take 2 to 3 days off treatment at the end of each of 4 week (which is the minimal required treatment duration for TTF therapy to reverse tumor growth). A period of 28 days of treatment with ETTF was considered 1 full treatment course. The primary end-point of the study was OS. Secondary end-points included PFS rates at 6-months; median time to progression (TTP), 1-year survival rate; quality-of-life; and radiological response. Subjects 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 subjects’ caregivers were used to evaluate subject mortality rates. A total of 28 clinical centers enrolled 237 adult subjects with 120 subjects randomized to the NovoTTF treatment group and 117 subjects randomized to the BSC group. A total of 30 subjects never started on trial (4 in the treatment group and 26 in the BSC group); 207 subjects started on trial, with 79 % discontinuation rate (n = 47 deaths; n = 49 deterioration of condition; and n = 68 study requirements of 2 additional clinic visits after disease progression were completed). Consent was withdrawn before completing 2 months of post-progression follow-up in 20 subjects. Adverse events led to 20 additional subject withdrawals. Non-compliance with follow-up was attributed to 3 subjects. The proportions were similar between the NovoTTF-100A group and the BSC group of subjects who did not complete the protocol-defined follow-up due to withdrawal of consent, non-compliance, or AEs. An average of 4.2 months of TTF treatment per subject was completed for the 116 subjects in the active treatment cohort. Complete vital statistics were known for 93 % (221 subjects) at the end of the study. There were 202 known deaths and 19 subjects (ETTF = 9; BSC = 10) were still alive 6 months after the last subject was randomized; 16 (7 %) subjects were lost to follow-up.

The trial did not reach its primary end-point of improved survival compared to active chemotherapy (Stupp et al, 2011; Novocure, 2012). In addition, differences in response rates, PFS at 6 months, and reduction in risk of death were not statistically significant. Quality of life analyses favored ETTF therapy in most domains. The differences in median OS between patients in the NovoTTF-100A group and the BSC group were not statistically significant. According to the FDA, the median OS is 6.3 months (95 % confidence interval [CI]: 5.6 to 7.8) in the NovoTTF-100A group and 6.4 months (95 % CI: 5.2 to 7.4) in the BSC group (log rank p = 0.98; Wilcoxon p = 0.72). The hazard ratio (HR) is 1.0 (95 % CI: 0.76 to 1.32) (test for proportional hazards p = 0.45). In the active chemotherapy control arm of the trial, survival was not significantly affected by the choice of chemotherapy. The Kaplan-Meier survival curve for the 2 treatment groups appeared to be very similar during the first 12 months of follow-up. Between 12 and 24 months, the survival curves separated slightly in favor of the BSC control.
group. There were no statistically significant differences in secondary end-points of 1-year survival, PFS, radiologic response rates, and median TTP. Mild-to-moderate (grade 1 and 2) contact dermatitis on the scalp beneath the transducer arrays occurred in 16% of ETTF patients. Patients receiving active control chemotherapy experienced toxicity related to pharmacologic mechanism of the agents used: gastrointestinal (30% versus 8%), hematological (19% versus 4%) and infectious (12% versus 4%). Longitudinal Quality of Life (QOL) was available in only 27% of subjects (63 patients) who remained on study therapy for 3 months and for whom QOL data were available. In the domains of global health and social functioning, no meaningful differences between chemotherapy and ETTF were observed. However, cognitive, emotional, and role functioning favored ETTF, whereas physical functioning favored chemotherapy. Symptom scale analysis is in accordance to treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea and vomiting were directly related to the chemotherapy administration. Increased pain and fatigue was reported in the chemotherapy-treated patients and not in the ETTF treatment group.

Commenting on the trial by Stupp et al, Debonis et al (2012) stated that the study was designed for superiority; although well conducted, it might not have shown it for a limited compliance in the ETTF group. Debonis et al (2012) stated that, even with this limitation, the trial by Stupp et al has shown at least equivalence of ETTF to chemotherapy, with a decreased toxicity and increased quality of life favoring ETTF.

The manufacturer initiated a subsequent randomized clinical trial enrolling newly diagnosed glioblastoma patients after completion of standard radiochemotherapy, parallel to starting the adjuvant or maintenance temozolomide chemotherapy (Stupp et al, 2012). Patients randomized to the experimental arm received ETTF in addition to maintenance temozolomide. In an abstract, Stupp et al (2014) reported on an interim analysis of this international, multi-center, prospective, randomized phase III trial in newly diagnosed GBM patients. After completion of radiotherapy (RT) with concomitant temozolomide (TMZ), patients were randomized (2:1) to adjuvant TMZ with NovoTTF or adjuvant TMZ alone. The primary end-point was PFS, with OS an important secondary end-point. Analysis was by intention-to-treat. The investigators reported on a pre-specified interim analysis of the first 315 patients randomized, after a minimum follow-up of 18 months (range of 18 to 60 months). Investigators randomized 210 patients NovoTTF/TMZ and 105 to TMZ alone. Patient characteristics were balanced: median age of 57 and 58 years, tumor resection in 89 and 90%, KPS 90%, for the NovoTTF and the control arms, respectively. MGMT promoter methylation status was assessable centrally in 60% of patients; of these 39% and 41% were methylated. Adverse events (AE) were comparable between treatment arms. The most common device-related AE was skin irritation in 45% of patients (all grades, severe 2%). Severe seizures were observed at a frequency of 7% in both arms. Median PFS was 7.1 months [mo] (95% CI: 5.9 to 8.2) and 4.0 mo (CI: 3.0 to 4.3; HR 0.63, p =
both favoring NovoTTF. This translated into a 24-mo survival rate of 43 % (CI: 36 to 50 %) and 29 % (CI: 21 to 39 %) for the NovoTTF/TMZ and the TMZ alone arm, respectively. The investigators stated that the trial met its primary and main secondary end-points, and was closed to accrual after this interim analysis. The investigators concluded that adjuvant TMZ chemotherapy and NovoTTF provided a clinically and statistically significant improvement in PFS and OS, and should become the new standard of care against GBM.

The National Comprehensive Cancer Network (NCCN, 2013) had a Category 2B recommendation to consider the use of ETTF for persons with local, diffuse or multiple recurrences of glioblastoma. This was changed to a Category 3 recommendation in 2014 (NCCN, 2014). NCCN guidelines explain that approval of tumor treating fields (TTF) for recurrent glioblastoma was based on results of a clinical trial that randomized 237 patients to TTF or chemotherapy. Similar survival was observed in the 2 arms, and TTF therapy was associated with lower toxicity and improved quality of life. Due to the lack of efficacy, not all NCCN panelists recommended the treatment. This was subsequently changed to a category 2B recommendation in 2015 (NCCN, 2015).

Medicare Durable Medical Equipment Medicare Administrative Contractor (DME MAC) considers tumor treatment field therapy not reasonable and necessary for Medicare beneficiaries (NHIC, 2014).

On October 5, 2015, the FDA approved an expanded indication for the Optune device (using alternating electrical fields called “tumor treatment fields” [TTFields]) to treat patients with newly-diagnosed GBM. It is administered along with temozolomide (TMZ) following standard treatments that include surgery, chemotherapy, and radiation therapy. In the clinical study used to support the expanded indication, patients treated with the device and TMZ lived on average 3 months longer than those treated with the drug alone. Optune was initially approved in 2011 to treat patients with GBM that recurred or progressed after chemotherapy. With this expanded indication, Optune can be used as part of a standard treatment for GBM before the disease progresses. For newly diagnosed GBM, Optune is not intended to be used as a substitute for standard treatments, but rather as an adjunct therapy. The device is portable and can be powered with batteries or plugged into an electrical outlet. Patients can use the device at home or work, allowing them to continue their normal daily activities.

The FDA based its approval of the expanded indication of the Optune device on results from a clinical trial involving 695 patients newly diagnosed with GBM that compared those who used Optune with TMZ to those receiving TMZ alone. Patients who used the device along with TMZ lived, on average, about 7 months with no disease progression compared to 4 months for those
who had the drug alone. The Optune plus TMZ group survived for an average of 19.4 months after diagnosis compared to 16.6 months for those who were treated with only TMZ. The most common side effect experienced with Optune was skin irritation. Clinical trial participants also experienced a slightly higher incidence of neurological side effects, including convulsions and headaches, compared to subjects receiving TMZ alone. Patients should not use the Optune system if they have an active implanted medical device or a skull defect, have an underlying skin condition involving the scalp or have a known sensitivity to conductive hydrogels, such as those used on electrocardiogram stickers.

Electric tumor treating fields technology is also being studied as a treatment for other solid tumors (e.g., melanoma and non-small cell lung cancer). However, there is a paucity of published evidence from randomized controlled trials examining the long-term safety and effectiveness of ETTF as a treatment of tumors.

Davis et al (2013) stated that TTFields therapy has been demonstrated in multiple cell lines when the appropriate frequency was utilized. A phase III trial of TTFields monotherapy compared to active chemotherapy in recurrent glioblastoma patients established that TTFields therapy is associated with minimal toxicity, better quality of life, and comparable efficacy to chemotherapy. Ongoing and future trials will evaluate TTFields in newly diagnosed glioblastoma, solid tumor brain metastases, non-small cell lung cancer, and ovarian and pancreatic cancers.

The NovoTAL System is a workstation-based software tool that uses MRI head morphology, tumor size and location measurements, and tissue di-electric properties to optimize TTFields distribution and intensity within the brain tumor. This system is part of the NovoTTF electronic tumor treatment fields treatments used for the treatment of GBM.

Melanoma

Li and colleagues (2016) proposed a method of using electrical stimulation for treatment of malignant melanoma through directly spray-printing liquid metal on skin as soft electrodes to deliver low intensity, intermediate frequency electric fields. With patterned conductive liquid metal components on mice skin and under assistance of a signal generator, a sine wave electrical power with voltage of 5 V and 300 kHz could be administrated on treating malignant melanoma tumor. The experiments demonstrated that tumor volume was significantly reduced compared with that of the control group. Under the designed parameters (signal: sine wave, signal amplitude Vpp: 5 V and Vpp: 4 V, frequency: 300 kHz) of Tumor treating fields (TTFields) with the sprayed liquid metal electrode, 4 mice tumor groups became diminishing after 1 week of treatment. The only device-related side effect as seen was a mild-to-moderate contact dermatitis underneath the field delivering electrodes. The scanning electron microscope (SEM) images
pathological analysis demonstrated the targeted treating behavior of the malignant melanoma tumor. Further, thermal infrared imaging experiments indicated that there was no evidence of heating effects in the course of treatment. Besides, the liquid metal was easy to remove through medical alcohol. The authors concluded that tumor treating fields through liquid metal electrode could offer a safe, straightforward and effective treatment modality that slowed down tumor growth in vivo. They stated that these promising results also raised the possibility of applying spray-printing TTFields as an easy going physical way for future cancer therapy.

Combination of ETTF and Chemo-Immuno-Therapy for Other Malignant Tumors

In a pilot, in-vitro and in-vivo, clinical trial, Kirson et al (2009) examined the effectiveness and toxicity of combining TTFields with chemotherapeutic treatment. Cell proliferation in culture was studied in human breast carcinoma (MDA-MB-231) and human glioma (U-118) cell lines, exposed to TTFields, paclitaxel, doxorubicin, cyclophosphamide and dacarbazine (DTIC) separately and in combinations. In addition, these researchers studied the effects of combining chemotherapy with TTFields in an animal tumor model and in a pilot clinical trial in recurrent and newly diagnosed GBM patients. The effectiveness of TTFields-chemotherapy combination in-vitro was found to be additive with a tendency towards synergism for all drugs and cell lines tested (combination index less than or equal to 1). The sensitivity to chemotherapeutic treatment was increased by 1 to 3 orders of magnitude by adjuvant TTFields therapy (dose reduction indexes 23 to 1,316). Similar findings were seen in an animal tumor model. Finally, 20 GBM patients were treated with TTFields for a median duration of 1 year. No TTFields-related systemic toxicity was observed in any of these patients, nor was an increase in temozolomide toxicity seen in patients receiving combined treatment. In newly diagnosed GBM patients, combining TTFields with temozolomide treatment led to a PFS of 155 weeks and OS of 39+ months. The authors concluded that these results indicated that combining chemotherapeutic cancer treatment with TTFields may increase chemotherapeutic effectiveness and sensitivity without increasing treatment related toxicity.

Pless et al (2013) noted that TTFields exhibit anti-mitotic activity in cancer cells, and promising pre-clinical data have led to a single-arm phase I/II clinical trial in patients with non-small cell lung cancer (NSCLC). A total of 42 inoperable stage IIIB (with pleural effusion) and stage IV NSCLC patients who had had tumor progression received intravenous pemetrexed 500 mg/m(2) q3w together with daily TTFields therapy until disease progression. The primary end-point was time to "in-field" progression. Median age for all patients was 63 years, 76 % had stage IV disease, 78 % had adenocarcinoma and 17 % had performance status of 2. The median time to in-field progression was 28 weeks and the median time to systemic progression was 22 weeks. Six patients (14.6 %) had a partial remission (PR) and 20 had stable disease (SD) (48.8 %). Median OS was 13.8 months and 1 year survival rate was 57 %. There were no TTFields-related
serious adverse events. The authors concluded that the combination of TTFields and pemetrexed as a second-line therapy for NSCLC is safe and potentially more effective than pemetrexed alone. They stated that TTFields improved disease control within the treatment field and a phase III study is planned to further investigate its role as a novel treatment in NSCLC.

Giladi et al (2014) stated that NSCLC is one of the leading causes of cancer-related deaths worldwide. Common treatment modalities for NSCLC include surgery, radiotherapy, chemotherapy, and, in recent years, the clinical management paradigm has evolved with the advent of targeted therapies. Despite such advances, the impact of systemic therapies for advanced disease remains modest, and as such, the prognosis for patients with NSCLC remains poor. Standard modalities are not without their respective toxicities and there is a clear need to improve both safety and effectiveness for current management approaches. Tumor-treating fields are low-intensity, intermediate-frequency alternating electric fields that disrupt proper spindle microtubule arrangement, thereby leading to mitotic arrest and ultimately to cell death. These researchers evaluated the effects of combining TTFields with standard chemotherapeutic agents on several NSCLC cell lines, both in-vitro and in-vivo. Frequency titration curves demonstrated that the inhibitory effects of TTFields were maximal at 150 kHz for all NSCLC cell lines tested, and that the addition of TTFields to chemotherapy resulted in enhanced treatment efficacy across all cell lines. They investigated the response of Lewis lung carcinoma and KLN205 squamous cell carcinoma in mice treated with TTFields in combination with pemetrexed, cisplatin, or paclitaxel and compared these to the efficacy observed in mice exposed only to the single agents. Combining TTFields with these therapeutic agents enhanced treatment efficacy in comparison with the respective single agents and control groups in all animal models. The authors concluded that these findings suggested that combining TTFields therapy with chemotherapy may provide an additive efficacy benefit in the management of NSCLC. They stated that further prospective studies to examine the optimal combinations of therapy are needed.

Omar (2014) stated that prior to the approval of the TTF System, the only FDA approved treatment for recurrent GBM (rGBM) was bevacizumab. By blocking the VEGF pathway, bevacizumab can result in a significant radiographic response (pseudo-response), improve PFS and reduce corticosteroid requirements in rGBM patients. Bevacizumab however failed to prolong OS in a recent phase III trial. A pivotal phase III trial (EF-11) demonstrated comparable OS between physicians' choice chemotherapy and TTF Therapy but better quality of life were observed in the TTF arm. There is currently an unmet need to develop novel approaches designed to prolong OS and/or improve quality of life in this unfortunate patient population. One appealing approach would be to combine the 2 currently approved treatment modalities namely bevacizumab and TTF Therapy. These 2 treatments are currently approved as monotherapy, but their combination has never been evaluated in a clinical trial.
Wong et al (2015) treated a series of patients with NovoTTF-100A and bevacizumab alone (n = 34) or in combination with a regimen consisting of 6-thioguanine, lomustine, capecitabine, and celecoxib (TCCC) (n = 3). Compared to the former cohort, the latter cohort exhibited a trend for prolonged OS, median of 4.1 (0.3 to 22.7) months versus 10.3 (7.7 to 13.6) months, respectively (p = 0.0951), with 1 experiencing an objective response with a 50 % reduction in tumor size on MRI despite possessing a larger tumor size at baseline and more severe neurologic dysfunction than the median for either group. These preliminary observations illustrated the possibility of improving survival and achieving a response in patients with end-stage recurrent glioblastoma by biasing the tumor toward anti-tumor immunologic response with a combination of NovoTTF-100A and TCCC, as well as the continuation of bevacizumab in order to limit dexamethasone use due to its global immunosuppressive effect on the patient.

Ovarian Cancer

In a phase-II, single-arm pilot clinical trial (the INNOVATE (EF-22) Study), Vergote and colleagues (2018) examined the safety and efficacy of TTFields (20-kHz) in combination with weekly paclitaxel (weekly for 8 weeks and then on days 1, 8, 15 of each subsequent 28-day cycle; starting dose 80 mg/m2) in 31 patients with recurrent, platinum-resistant ovarian carcinoma. The primary end-point was safety and secondary end-points included OS, PFS and response rate (RR). Median age was 60 years (range of 45 to 77), 24 patients (77 %) had serous histology, 16 patients (52 %) Eastern Cooperative Oncology Group (ECOG) performance score of 0 and 15 (48 %) ECOG 1, the median number of prior chemotherapy lines was 4 (range of 1 to 11). All patients received prior platinum-based chemotherapy and 30 (97 %) received prior taxanes. No serious AEs related to TTFields were reported. There was no increase in grade 3 to 4 AEs compared to the frequency of such events reported in the literature with single agent weekly paclitaxel; 26 patients (84 %) had the expected TTFields-related dermatitis but only 1 patient permanently discontinued TTFields due to dermatitis. The median PFS was 8.9 months, 7 patients (25 %) had PR and the clinical benefit rate was 71 %. The median OS was not reached: the 1-year survival rate was 61 %. The authors concluded that TTFields combined with weekly paclitaxel were safe in platinum-resistant recurrent ovarian cancer and warrants evaluation in a randomized phase-III clinical trial.

CPT Codes / HCPCS Codes / ICD-10 Codes

**Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":**

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>HCPCS codes covered if selection criteria are met:</td>
<td></td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------------------------------------------------------------</td>
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<tr>
<td>A4555</td>
<td>Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only</td>
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<td>J8700</td>
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<tr>
<td>J9328</td>
<td>Injection, temozolomide, 1 mg</td>
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ICD-10 codes covered if selection criteria are met:

- **C71.0 - C71.9**: Malignant neoplasm of brain [supratentorial glioblastomas (WHO grade IV astrocytomas)]

ICD-10 codes not covered for indications listed in the CPB (not all inclusive):

- **C08.0 - C08.9**: Malignant neoplasm of other and unspecified major salivary glands
- **C11.0 - C11.9**: Malignant neoplasm of nasopharynx
- **C15.3 - C15.9**: Malignant neoplasm of esophagus
- **C16.0 - C16.9**: Malignant neoplasm of stomach
- **C18.0 - C18.9**: Malignant neoplasm of colon
- **C19 - C21.8**: Malignant neoplasm of rectosigmoid junction, rectum, anus and anal canal
- **C22.1**: Intrahepatic bile duct carcinoma
- **C23 - C24.9**: Malignant neoplasm of gall bladder and other and unspecified parts of biliary tract
- **C25.0 - C25.9**: Malignant neoplasm of pancreas
- **C31.0 - C31.9**: Malignant neoplasm of accessory sinuses (paranasal)
- **C33 - C34.92**: Malignant neoplasm trachea, bronchus, and lung
- **C37**: Malignant neoplasm of thymus
- **C43.0 - C43.9**: Malignant neoplasm of skin
- **C46.1**: Kaposi's sarcoma of soft tissue
- **C49.0 - C49.9**: Malignant neoplasm of peripheral nerves, autonomic nervous system and other connective and soft tissue
- **C50.011 - C50.929**: Malignant neoplasm of breast
- **C53.0 - C53.9**: Malignant neoplasm of cervix uteri
- **C54.0 - C54.9**: Malignant neoplasm of corpus uteri
- **C56.1 - C56.9**: Malignant neoplasm of ovary
- **C57.00 - C57.02**: Malignant neoplasm of fallopian tube
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<td>C68.0 - C68.9</td>
<td>Malignant neoplasm of kidney and other and unspecified urinary organs</td>
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<tr>
<td>C73</td>
<td>Malignant neoplasm of thyroid gland</td>
</tr>
<tr>
<td>C79.31</td>
<td>Secondary malignant neoplasm of brain [solid tumor brain metastases]</td>
</tr>
<tr>
<td>D00.00 - D09.9</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>D11.0 - D11.9</td>
<td>Benign neoplasm of major salivary glands</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:


28. NHIC, Inc. Local Coverage Determination (LCD) for Tumor Treatment Field Therapy (TTF) (L34730). Durable Medical Equipment Medicare Administrative Contractor (DME MAC) Jurisdiction A. Hingham, MA: NHIC; June 6, 2014.


AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0827
Electric Tumor Treatment Fields

There are no amendments for Medicaid.