Medical Coverage Policy

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Electromagnetic Field and Alternating Electric Field Therapy for Cancer Treatment

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INSTRUCTIONS FOR USE

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must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This Coverage Policy addresses intrabuccal, systemic delivery of amplitude-modulated, radiofrequency electromagnetic fields therapy and alternating electric field therapy (tumor treating fields) for cancer treatment.

Coverage Policy

Alternating Electric Field Therapy/Tumor Treating Fields (TTFields) (HCPCS E0766, CPT® 1025T)

- Tumor treating fields therapy is considered medically necessary for the treatment of newly diagnosed glioblastoma multiforme (GBM) when ALL of the following criteria are met:
  - Individual is 22 years of age or older
  - Histologically confirmed supratentorial glioblastoma multiforme (GBM) (including IDH-mutant grade 4 astrocytoma and gliosarcoma)
  - Karnofsky Performance Score of 60 or greater
  - Device will be used as adjuvant therapy after completion of maximal debulking (if feasible) and radiation therapy
  - Device will be used concomitantly with temozolomide
  - Device will be used for at least 18 hours per day

- Tumor treating fields therapy is considered medically necessary for the treatment of recurrent glioblastoma multiforme (GBM) when ALL of the following criteria are met:
  - Individual is 22 years of age or older
  - Histologically or radiologically confirmed recurrence of glioblastoma multiforme (GBM) (including gliosarcoma) in the supratentorial region of the brain after receiving chemotherapy
  - Device will be used as monotherapy
  - Surgical and radiation therapy options have been exhausted
  - Device will be used for at least 18 hours per day

- Tumor treating fields therapy for ANY other indication is considered not medically necessary.

Amplitude-Modulated Radiofrequency Electromagnetic Fields Therapy (AM RF-EMF) (HCPCS E0767)

- Amplitude-modulated, radiofrequency electromagnetic fields therapy is considered experimental, investigational or unproven.

Coding Information

Notes:

1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare & Medicaid Services (CMS) code updates may occur more frequently than policy updates.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
1025T	Alternating electric fields dosimetry and delivery-simulation modeling, creation and selection of patient-specific array layouts, and placement verification

HCPCS Codes	Description
E0766	Electrical stimulation device used for cancer treatment, includes all accessories, any type

Considered Experimental/Investigational/Unproven:

HCPCS Codes	Description
E0767	Intrabuccal, systemic delivery of amplitude-modulated, radiofrequency electromagnetic field device, for cancer treatment, includes all accessories

General Background

Amplitude-Modulated Radiofrequency Electromagnetic Fields

Low-energy radio frequency electromagnetic fields (EMFs) penetrate cells and can influence multiple cell biological processes via non-thermal effects. It is hypothesized that amplitude-modulation frequencies that alter the behavior of electrically excitable cells may also disrupt the proliferation of cancer cells.

Two existing medical devices provide systemic exposure to low-power Low-Energy Amplitude-Modulated Radiofrequency Electromagnetic Fields (LEAM RF EMFs) with a carrier wave frequency of 27.12 MHz: the P1 (TheraBionic) and the AutEMdev (Autem Therapeutics). These small battery-operated devices emit extremely low-power EMFs, each delivering less than 100 mW into a spoon-shaped stainless-steel antenna that is placed into the individual's mouth. The resulting whole body-specific absorption rate of 1.77 mW/kg lies far below international safety limits and is too low to cause detectable heating. The device power is about 1,000 times lower than that of a mobile phone and 100,000 times lower than that of thermal tumor ablation devices.
Low-Energy Amplitude-Modulated Radiofrequency Electromagnetic Fields (LEAM RF EMF) technology differs from so-called Tumor Treating Fields because it uses different frequency ranges, uses electromagnetic rather than electric fields, and delivers energy systemically rather than locally (Tuszynski, et al., 2022).

U.S. Food and Drug Administration (FDA): The TheraBionic device received Breakthrough Designation in 2019 and Humanitarian Device Exemption (HDE) approval on September 26, 2023 (Thera Bionic P1 – H220001) (TheraBionic Inc., North Carolina). The TheraBionic P1 medical device is intended for the treatment of individuals ≥ 18 years of age with advanced hepatocellular carcinoma (HCC) who fail first- and second-line therapy.

AutEMdev™/AutEMsys™ (Autem Therapeutics, New Hampshire, USA) has not yet received regulatory approval and is not available for commercial distribution.

See Appendix for a list of FDA approved/cleared devices.

Literature Review: There is a paucity of well-designed, published peer-reviewed scientific trials addressing the safety and effectiveness of amplitude-modulated radiofrequency electromagnetic fields (AM RF-EMF) therapy on long-term health outcomes including mortality.

AM RF-EMF for Hepatocellular Carcinoma (HCC)

Costa et al. (2011) assessed the safety and effectiveness of the intrabuccal administration of very low levels of electromagnetic fields amplitude modulated at HCC-specific frequencies in 41 individuals with advanced HCC and limited therapeutic options. The brand or manufacturer of the devices used is not specified.

- Inclusion criteria: eligible for surgical resection or had disease progression after surgical or locoregional therapies or had disease progression after chemotherapy or sorafenib therapy. Individuals with measurable, inoperable HCC were eligible for enrolment. Previous local or systemic treatments were allowed as long as they were discontinued at least 4 weeks before enrolment. Inclusion criteria included Eastern Cooperative Oncology Group performance status of 0, 1, or 2 and biopsy-confirmed HCC. Also allowed were individuals with no pathological confirmation of HCC with a level of *x*-fetoprotein higher than 400 ng ml^{-1} and characteristic imaging findings as assessed by multi-slice computer tomography (CT) scan or intravenous contrast ultrasound (US).
- Exclusion criteria included confirmed or suspected brain metastasis, Child–Pugh C, previous liver transplant, and pregnancy.
- Three-daily 60-min outpatient treatments were administered until disease progression or death. Imaging studies were performed every 8 weeks. The primary efficacy end point was progression-free survival ≥6 months. Secondary efficacy end points were progression-free survival and overall survival.
- The author reported treatment was well tolerated and there was no NCI grade 2, 3 or 4 toxicities. In all, 14 individuals (34.1%) had stable disease for more than 6 months. Median progression-free survival was 4.4 months, and median overall survival was 6.7 months. There were three partial and one near complete responses. Three of the four partial responses were observed in individuals with biopsy-proven HCC.
- The author noted a study limitation is that only 19 of the 41 individuals had biopsy-proven HCC, and the others were diagnosed by clinical criteria.
- The authors concluded that "the encouraging findings from this study warrant a randomized study to determine the impact of AM EMFs on OS and time to symptomatic progression".

Blackstock et al. (2021) reported a study including 18 individuals from multiple centers and 41 individuals from the Costa et al. (2011) study.

- Of the 18 individuals, twelve individuals had Child-Pugh A, four individuals Child-Pugh B, and two individuals had Child-Pugh C liver function. Half of the individuals had serum Alpha-Fetoprotein (AFP) levels greater than 400 ng/mL. Fifteen (83.3%) individuals had

evidence of disease progression and all individuals except for one had received at least one systemic therapy prior to initiation of treatment with the TheraBionic device. Fifty-nine individuals receiving TheraBionic treatment were included in these analyses.
- The median overall survival was 6.72 months. Only grade 1 mucositis and fatigue were reported by individuals using the device, even among Child-Pugh B and C individuals. No individuals discontinued treatment because of adverse events. (Published online and not available via PubMed.)

AM RF-EMF in other cancer types

The use of AM RF-EMF via the TheraBionic® device has been proposed in other cancer types, although the device does not have FDA approval outside of use in HCC. Evidence from three individual case reports demonstrated early clinical feasibility and potential antitumor activity of AM RF-EMF. The first case, a 38-year-old with recurrent gliosarcoma/glioblastoma after failure of surgery, radiation, chemotherapy, immunotherapy, and targeted therapy, exhibited both clinical and radiographic improvement within six weeks of initiating daily AM RF-EMF treatment. MRI demonstrated reduced enhancement consistent with treatment response, and the individual self-reported functional gains. No adverse events related to AM RF-EMF were reported; treatment was discontinued after three months due to intracranial bleeding determined to be unrelated to therapy (Jimenez et al., 2025). A second case involved a 47-year-old with multiply recurrent, 1p/19q-codeleted oligodendroglioma following multiple surgeries, chemotherapy regimens, and radiation. Use of glioblastoma-specific frequencies three times daily in combination with ongoing bevacizumab resulted in radiographically stable disease on MRI after two months of treatment. Mild, transient oral discomfort was the only reported side effect. (Jimenez et al., 2025). The third case involved an individual with triple-negative breast cancer and a large calvarial/brain metastatic lesion, daily exposure to breast-cancer–specific modulation frequencies resulted in substantial radiologic regression of the intracranial tumor. MRI demonstrated decreased tumor size, reduced intracranial extension, and resolution of mass effect. The clinical benefit persisted for approximately 11 months, exceeding the typical median survival (< 4 months) for individuals with brain metastases from triple-negative breast cancer. No treatment-related adverse events were reported (Sharma et al., 2019). While these findings are promising, the evidence is limited to individual compassionate-use cases and therefore cannot establish efficacy or generalize to broader populations. Controlled clinical trials are necessary to determine treatment effectiveness, durability of response, optimal treatment parameters, and patient selection criteria.

Professional Societies/Organizations: The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology on Hepatocellular Carcinoma (Version 1.2026 — March 10, 2026) did not address amplitude-modulated radiofrequency electromagnetic fields therapy.

The American Association for the Study of Liver Diseases (AASLD) Practice Guidance on Prevention, Diagnosis, and Treatment of Hepatocellular Carcinoma did not address amplitude-modulated radiofrequency electromagnetic fields therapy (Singal, et al, 2023).

Alternating Electric Field Therapy/Tumor Treating Fields (TTFields)

Electric tumor treatment fields (TTFields) therapy, also known as alternating electric field therapy, has been proposed for the treatment of several types of cancer. The inferred mechanism of action is disruption of the rapid cell division exhibited by cancer cells by alternating electrical currents. The fields alter the tumor cell polarity at an intermediate frequency. Ultimately, this can lead to immunogenic cancer cell death. In some cancer types, this immunogenic cell death may theoretically induce an immune response activating T cells that recognize tumor-specific antigens, leading to increased T-cell infiltration at the tumor site. Healthy cells are not damaged by the

TTFields because they do not display the same division rate and electrical properties of cancer cells (Novocure GmbH, 2026). The alternative to TTFields therapy is standard of care, often including surgery, chemotherapy, or radiation therapy (or a combination thereof). TTFields therapy offers a novel means of additional treatment that can be added to existing therapies.

Several TTFields devices are marketed for the treatment of specific cancers. Each system is a wearable, non-invasive, portable, battery or power-supply operated device designed for continuous use throughout the day or night. Each device is tailored to the application of TTFields for a specific cancer. The systems consist of an electric field generator, portable batteries, and transducer arrays. The arrays are attached to the area of the body to be treated (e.g., scalp, chest, or abdomen) using hydrogel pads. Physicians trained and certified in the use of TTFields import MRI brain data into planning software to plot the most effective configuration of transducer arrays for the individual's tumor location (Chaudry, et al., 2015; Connelly, et al., 2016; Trusheim, et al., 2017). The devices produce alternating electrical fields at low intensity (1-3 V/cm) and intermediate frequency (100-300 kHz). Frequencies per device are tailored to the cell type being treated (Novocure GmbH, 2026). Devices must be worn continuously for a prescribed number of hours per day and compliance with wearing the device is key. Research indicates that greater compliance leads to more optimal results (Ballo, et al., 2023; Toms, et al., 2019).

U.S. Food and Drug Administration (FDA): Electric tumor treatment fields devices currently approved or cleared by the FDA are regulated as Class III medical devices. These devices are typically approved through the pre-market approval (PMA) or humanitarian device exemption (HDE) pathways. TTFields devices are classified under the FDA product codes SDA, SHC, or NZK.

See Appendix for a list of FDA approved/cleared devices.

Literature Review:
TTFields for Glioblastoma

Song et al. (2020) conducted a single arm pilot study to report initial experience evaluating toxicity and tolerability of scalp-sparing radiation with concurrent TTFields. The study included adult individuals (age ≥ 18 years) with a Karnofski Performance Score (KPS) of ≥ 60 with newly diagnosed glioblastoma. All individuals received concurrent scalp-sparing radiation, standard concurrent temozolomide, and TTFields. Maintenance therapy included standard temozolomide and continuation of TTFields. Radiation treatment was delivered through TTFields arrays. The primary outcome was safety and toxicity for concurrent TTFields with chemoradiation. The secondary endpoint was median progression-free survival. The study reported the first ten individuals in the trial at a median follow-up of 7.9 months (2.9 to 17.9 months). All individuals completed concurrent chemoradiation plus TTF without radiation or TTF treatment interruption or discontinuation. Scalp dose constraints were achieved for all individuals, with mean dose having a median value of 7.7 Gy (range 4.9 to 13.2 Gy), D20cc median 22.6 Gy (17.7 to 36.8 Gy), and D30cc median 19.8 Gy (14.8 to 33.4 Gy). Average daily use during concurrent phase had median value of 83.5% and 77% for maintenance. There was no related ≥ Grade 3 toxicity. Skin toxicity (erythema, dermatitis, pruritus) was noted in 80% of individuals and was limited to Grade 1 events which resolved spontaneously or responded to topical medications. Eight individuals (80%) had progression, with median progression-free survival of 6.9 months (range 2.8 to 9.6 months). The authors concluded that concurrent TTFields with scalp-sparing chemoradiation appears to be a safe and feasible treatment option with limited toxicity and that a future randomized prospective trial is warranted to define therapeutic advantages of concurrent TTFields with chemoradiation.

Stupp et al. (2015) reported an interim analysis of a multicenter, open-label, randomized phase 3 trial (designated the EF-14 trial) designed to test the efficacy and safety of TTFields in

combination with temozolomide for treatment of glioblastoma after initial treatment with chemoradiation. The study included 210 individuals randomized to TTFields plus temozolomide and 105 individuals randomized to temozolomide alone and conducted at a median follow-up of 38 months. Results included that median progression-free survival in the intent-to-treat population was 7.1 months (95% CI, 5.9-8.2 months) in the TTFields plus temozolomide group and 4.0 months (95% CI, 3.3-5.2 months) in the temozolomide alone group (hazard ratio [HR], 0.62 [98.7% CI, 0.43-0.89]; P=.001). Median overall survival in the per-protocol population was 20.5 months (95% CI, 16.7-25.0 months) in the TTFields plus temozolomide group (n=196) and 15.6 months (95% CI, 13.3-19.1 months) in the temozolomide alone group (n=84) (HR, 0.64 [99.4% CI, 0.42-0.98]; P=.004). The authors concluded that in this analysis of individuals with glioblastoma who had completed standard chemoradiation therapy, the addition of TTFields to maintenance temozolomide chemotherapy significantly prolonged progression-free and overall survival.

Stupp et al. (2017) reported on the final analysis of the EF-14 trial noted above. This included all 695 patients with median follow-up of 40 months and minimum follow-up of 24 months. Participating individuals were randomized 2:1 to TTFields plus maintenance temozolomide chemotherapy (n = 466) or temozolomide alone (n = 229). 92% of included individuals completed the trial (637 individuals). The primary end point was progression-free survival. The secondary end point was overall survival. Median progression-free survival was 6.7 months in the TTFields-temozolomide group (95% CI, 61-8.1 months) and 4.0 months in the temozolomide-alone group (95% CI, 3.8-4.4 months). Median overall survival was 20.9 months in the TTFields-temozolomide group (95% CI, 19.3-22.7 months) vs 16.0 months (95% CI, 14.0-18.4 months) in the temozolomide-alone group. Systemic adverse event frequency was 48% in the TTFields-temozolomide group and 44% in the temozolomide-alone group. Mild to moderate skin toxicity underneath the transducer arrays occurred in 52% of individuals who received TTFields-temozolomide compared to none in individuals who received temozolomide alone. The authors concluded that the data demonstrated tolerability of the device and survival benefits consistent with prior analyses.

Kim et al. (2020) reported on subgroup of individuals that participated in the above Stupp et al. (2017) trial and included individuals with newly diagnosed glioblastoma at eight sites in Korea (n=39). The primary outcomes assessed were progression-free survival and overall survival specific to this South Korean population. Safety was also assessed. The median progression-free survival in the TTFields plus temozolomide arm was 6.2 months (95% CI 4.2-12.2) versus 4.2 months (95% CI 1.9-11.2) with chemotherapy alone (p = 0.67); slightly better than the reported median progression-free survival in the overall study population. Notable differences from the overall study population included a lower rate of skin irritation (30% in this South Korean population versus 52% in the overall study population) and better overall survival. Median overall survival in this Korean population subset was 27.2 months (95% CI 21-NA) with TTFields-temozolomide; in the overall trial population, reported median overall survival was 20.9 months with TTFields-temozolomide. No TTFields-related serious adverse events were reported. The authors noted that this subgroup analysis was limited by its small sample size. In conclusion, there was no difference in clinical outcomes between this subgroup of South Korean individuals and the overall study population. The safety and efficacy of TTFields in Korean individuals is supported by this data.

Stupp et al. (2012) also conducted an additional trial to evaluate the effectiveness of NovoTTF-100A I recurrent glioblastoma (EF-11 trial). 237 individuals were randomly assigned either TTFields monotherapy (n = 120) or active control chemotherapy (n = 117). Over 80% of the individuals had failed two or more prior lines of chemotherapy and 20% had failed bevacizumab. It is important to note that methyl-guanin-methyl-transferase (MGMT) gene promoter methylation

was not assessed in this trial. 93 individuals from the TTFields treatment group completed four weeks of therapy. One-year survival proportion was 20% in both treatment and control groups, and 2- and 3-year survival were 8% (treatment group) versus 5% and 1% (control group). The response rate was statistically non-significant (14% versus 9.6%, p = 0.19). The hazard ratio for death was 0.86 (95% CI 0.66, 1.12) in favor of the TTFields device, from which the authors determined that TTFields may be at least equivalent to active chemotherapy. Measure of quality-of-life favored treatment with TTFields in areas of cognitive, emotional, and role function. Ultimately, the trial did not reach its primary end-point of improved survival compared to active chemotherapy. The study was limited by the lack of a treatment-free control and heterogeneous study population.

Ballo et al. (2023) performed a systematic review and meta-analysis to evaluate the overall survival benefit in TTFields-treated individuals with newly diagnosed glioblastoma. Included in the systematic review were nine studies (one randomized control trial, two single-cohort studies, and six comparative studies), seven of which compared the TTFields plus chemotherapy to standard of care alone (n = 1430). These seven studies were used for the pooled analysis for overall survival. Data demonstrated an improvement in overall survival of individuals who received TTFields in addition to their chemotherapy. The median survival was 22.6 months (95% CI 17.6–41.2) in those who received TTFields versus 17.4 months in those who did not (95% CI 14.4–21.6). Two-year overall survival rate was 46.8% (95% CI 33.8–64.8) for TTFields groups and 32.3% (95% CI 22.5–46.5) for non-TTFields groups. Four-year overall rate was 22.7% (95% CI 12.5–41.4) in those who received TTFields and 8.0% (95% CI 3.8–16.6) in those who did not. Additionally, the study demonstrated survival benefit was improved with compliant device usage of at least 75%. Heterogeneity amongst included studies was noted to be low, demonstrating a robust pooled effect. Limitations of this systematic review and meta-analysis include the potential for overestimation of treatment effect due to the inclusion of non-randomized, retrospective studies. The authors concluded that the data support the overall survival benefit conferred by the use of TTFields treatment.

Li et al. (2022) published results of a systematic review and meta-analysis to determine the safety and efficacy of TTFields in recurrent glioblastoma. Nine studies (2 randomized controlled trials, 4 prospective studies, and 3 retrospective cohorts) comprising a total of 1,048 individuals with recurrent glioblastoma were included. Among studies contributing to comparative overall survival (OS) analyses, 942 individuals received TTFields and 531 individuals received control therapy. Eligible individuals had pathologically confirmed glioblastoma with radiographically or histologically confirmed recurrence; inclusion criteria required clinical studies reporting OS (Kaplan–Meier curves or hazard ratios), 1-year survival, and/or cutaneous toxicity. Exclusion criteria included non-human studies, case reports, reviews/meta-analyses, non-recurrent gliomas, other malignancies, and studies lacking usable outcome data. The intervention was continuous TTFields therapy, while comparators consisted of physician's choice chemotherapy or usual care. Primary outcomes were overall survival hazard ratio, 1-year overall survival rate, and incidence of treatment-related skin toxicity; follow-up durations varied across included trials but generally extended until death or last available survival assessment. Pooled analysis demonstrated a statistically significant improvement in overall survival with TTFields compared with control (HR 0.75, 95% CI 0.63–0.89; p = 0.001). The pooled 1-year survival proportion among TTFields-treated individuals was 47% (95% CI 0.29–0.67), though with substantial heterogeneity. The pooled incidence of cutaneous toxicity was 48%, consistent with known device-related adverse effects. Limitations include reliance on a small number of randomized trials, inclusion of heterogeneous study designs (with several single-arm and retrospective studies), variability in patient characteristics (e.g., performance status, MGMT methylation, recurrence number), and inconsistent reporting of follow-up duration and subgroup outcomes, which limit precision and

generalizability. Despite these limitations, the authors concluded the meta-analysis demonstrates the efficacy of TTFields in recurrent glioblastoma.

Regev et al. (2021) conducted a systematic review and meta-analysis of TTFields in glioblastoma. The authors included 20 studies, including two unblinded randomized trials (EF-14 and EF-11) alongside multiple single-arm and observational studies, with a total of 1,636 adult individuals (542 newly diagnosed, 1,094 recurrent) evaluated for efficacy. Also included were three conference presentations. All included individuals were adults (≥ 18 years) with GBM. The analysis assessed overall survival (OS), progression-free survival (PFS), survival rates at fixed intervals (6, 12, 24 months, etc.), and safety endpoints. Across all studies, TTFields was administered via a wearable device (Optune) typically alongside standard-of-care therapy (adjuvant temozolomide after surgery/radiotherapy in newly diagnosed GBM, or with salvage treatments in recurrence), and outcomes were compared to those with standard therapy without TTFields. The meta-analysis pooled survival outcomes and found that, in newly diagnosed GBM, combined-modality therapy with TTFields yielded a pooled median OS of about 21.7 months (95% CI 19.6–23.8) and median PFS ~7.2 months, with 1- and 2-year survival rates noticeably improved relative to historical standard care. In recurrent GBM, pooled analysis (driven largely by single-arm data) showed a median OS of ~10.3 months (95% CI 8.3–12.8) and PFS ~5.7 months, outcomes that appear higher than those seen with chemotherapy alone in prior trials (median OS ~6–7 months). TTFields demonstrated a favorable safety profile. Across > 11,000 treated individuals, no systemic toxicities were attributed to the device, and the most common adverse events were localized, device-related skin reactions (primarily mild-to-moderate scalp dermatitis, ~38% of individuals). Key inclusion criteria in these studies ensured individuals had adequate performance status to use the device, and follow-up in the meta-analysis extended to 2–3 years post-treatment for survival endpoints. However, important limitations exist. The evidence base beyond the two included RCTs relies on single-arm, non-comparative studies and post hoc analyses, which carry potential selection bias and heterogeneity in patient populations and adjunct treatments. As a result, the meta-analysis could not perform a traditional comparative efficacy synthesis for recurrent GBM and instead evaluated TTFields outcomes in isolation; thus, the pooled survival estimates (especially in recurrent disease) must be interpreted with caution given differences in study design, patient selection, and the limited number of trials available. Nonetheless, the overall findings provide evidence that adding TTFields to standard therapy significantly prolongs survival in newly diagnosed glioblastoma and may confer a survival benefit in recurrent GBM, with an acceptable safety/tolerability profile.

Taslimi et al. (2021) reported data from a systematic review and network meta-analysis of 15 phase II–III randomized controlled trials (n = 2194 individuals, with ~1383 in experimental arms vs 811 in control arms) in recurrent glioblastoma evaluated multiple treatments, including tumor treating fields (with or without chemotherapy), various anti–vascular endothelial growth factor (VEGF) therapies (e.g., bevacizumab, cediranib), and combination regimens, against standard chemotherapy controls (typically lomustine or physician's choice chemo). Trials were included if they enrolled ≥ 20 individuals per arm with recurrent GBM post standard first-line therapy (maximal resection plus chemoradiation) and were excluded if they mixed non-GBM populations or lacked extractable survival outcomes. Overall bias of the studies included was rated as low. Overall survival (OS) was the primary outcome (with progression-free survival [PFS] being the secondary outcome), measured via hazard ratios (HR); median OS in these studies was generally under one year, reflecting the aggressive course of recurrent disease. There was one study on TTFields that could not be included in the meta-analysis since it did not overlap with other treatment arms. Two studies compared TTFields with or without active second-line chemotherapy against active chemotherapy alone. Within those two studies, there were 120 individuals who received TTFields alone, 144 who received TTFields in addition to active chemotherapy, and 177 who received chemotherapy alone. In these studies, TTFields showed benefit on OS when used

alone (HR = 0.86, 95% CI 0.66–1.2) or with active chemotherapy (HR = 0.695, P = .05). The network meta-analysis found that TTFields combined with an anti-VEGF therapy achieved the highest probability of improved OS compared to standard chemotherapy (e.g., versus lomustine, pooled HR ≈0.51, indicating a statistically significant OS benefit at $p < 0.05$). No single regimen demonstrated a definitive survival advantage across all trials, and the evidence is limited by substantial inter-trial heterogeneity, indirect comparisons, low confidence in effect estimates (rated "low–very low"), and the post hoc nature of the TTFields subgroup analysis. The authors concluded that further high-quality trials are needed to confirm survival benefit.

Magouliotis et al. (2018) conducted a systematic review and meta-analysis of the available literature on individuals with glioblastoma treated with tumor-treating fields (TTFields) plus radio chemotherapy or conventional radio chemotherapy alone, to compare the efficacy and safety of the two methods. Six studies were included in the review with a total number of 1,806 individuals. 1,769 individuals were included in the quantitative analysis. The results noted increased median overall survival (weighted mean difference (WMD) 3.29 [95% confidence interval (CI) 2.37, 4.21] $p < 0.00001$). This improved median overall survival was shown in both newly diagnosed and recurrent glioblastoma. Improved survival in TTFields treatment groups was demonstrated at one year (odds ratio (OR) 1.81 [95% CI 1.41, 2.32]; $p<0.00001$) and two years (OR 2.33 [95% CI 1.73, 3.14]; $p < 0.00001$). Median progression-free survival (WMD 2.35 [95% CI 1.76, 2.93]; $p < 0.00001$) along with progression-free survival at six months (WMD 6.86 [95% CI 5.91, 7.81]; $p<0.00001$) improved for the individuals treated with TTFields. Survival at three years was comparable between the two groups (OR 1.62 [95% CI 0.98, 2.66]; $p = 0.06$). TTFields were associated with fewer adverse events compared to chemotherapy along with similar incidence of skin irritation. Limitations of this study are those of the included studies themselves; only two studies were randomized control trials, with the rest being prospective or retrospective studies. The authors concluded that TTFields are a safe and efficient novel treatment modality.

As shown above, data supports the efficacy of TTFields use in GBM, with evidence being strongest in newly diagnosed disease. Taken as a whole, the literature demonstrates that therapy with TTFields offers a relatively safe option for improving survival in select individuals with glioblastoma.

TTFields for Mesothelioma

Ceresoli et al. (2019) conducted a prospective, single-arm, phase 2 trial (STELLAR study) to test the activity of TTFields delivered to the thorax in combination with systemic chemotherapy for the front-line treatment of individuals with unresectable malignant pleural mesothelioma. The study included 80 treatment-naive individuals with histologically confirmed unresectable malignant pleural mesothelioma, aged at least 18 years, had an Eastern Cooperative Oncology Group performance status of 0-1, and at least one measurable or evaluable lesion according to modified Response Evaluation Criteria in Solid Tumors for mesothelioma. Individuals received continuous TTFields at a frequency of 150 kHz to the thorax and concomitant chemotherapy with intravenous pemetrexed (500 mg/m2 on day 1) plus intravenous platinum (either cisplatin 75 mg/m2 on day 1 or carboplatin area under the curve 5 on day 1) every 21 days for up to six cycles. Individuals not progressing after completion of chemotherapy received TTFields as maintenance treatment until progression, patient or physician decision, or unacceptable toxic effects. The primary endpoint of the trial was overall survival. Secondary endpoints were progression-free survival, objective response, and toxicity. Survival analyses were done in the intention-to-treat population, and safety analyses were done in all individuals who received at least one day of TTFields treatment. Median follow-up was 12.5 months (IQR 7.4-16.6). Median overall survival was 18.2 months (95% CI 12.1-25.8). Median progression-free survival was 7.6 months (95% CI 6.7-7.8). Epithelioid histology showed the most favorable overall survival and progression-free survival. Skin reaction

was the only adverse event associated with TTFields and was reported as grade 1-2 in 53 (66%) individuals, and as grade 3 in four (5%) individuals. No treatment-related deaths were observed. Overall, the results of this study were similar to results reported in other trials of chemotherapy regimens in malignant pleural mesothelioma. The authors emphasized that in STELLAR the results were achieved without an increase in systematic toxicity related to chemotherapy. The trial was limited by the study design (lack of a control), and the lack of independent radiological review. The authors concluded that the trial showed encouraging overall survival results demonstrating that TTFields an active and safe combination for front-line treatment of unresectable malignant pleural mesothelioma. Further investigation with randomized trials is warranted to demonstrate whether TTFields results in better outcomes when compared to chemotherapy.

Kutuk et al. (2022) reported a retrospective, single-center, real-world observational study evaluating TTFields in combination with pemetrexed and platinum-based chemotherapy for unresectable malignant pleural mesothelioma. The study included five adult individuals total, with no control or comparator arm; all individuals received the investigational regimen. Inclusion criteria were histologically confirmed unresectable, locally advanced or metastatic malignant pleural mesothelioma treated under an FDA Humanitarian Device Exemption protocol between 2019–2021, with ECOG performance status 0–1; exclusion criteria were not explicitly predefined but reflected real-world clinical contraindications and prior treatment heterogeneity. The intervention consisted of continuous TTFields therapy applied to the thorax plus standard-dose pemetrexed (500 mg/m²) with carboplatin (AUC 5) or cisplatin every 21 days for up to six cycles, while the effective comparator was historical outcomes with chemotherapy alone rather than an internal control. Outcomes assessed included objective tumor response per modified RECIST for malignant pleural mesothelioma, progression-free survival (PFS), overall survival (OS), device usage, and treatment-related toxicities. Median TTFields usage was 12.5 hours per day (52%) during the first 3 months, decreasing to 8.9 hours per day (37%) thereafter, and no formal statistical comparisons were performed; therefore, no statistically significant differences ($p < 0.05$) in survival or response could be demonstrated. At a median follow-up of 5.4 months (range 1.1–20.9), median OS and PFS were not reached, with reported 6- and 12-month PFS rates of 80% and 53%, respectively, but these outcomes were descriptive and uncontrolled. Device-related toxicity was universal, with 100% of individuals developing grade 1–2 dermatitis, and 40% discontinuing TTFields early. Major limitations include the extremely small sample size, absence of randomization or comparator arm, short and heterogeneous follow-up, lack of predefined statistical hypothesis testing, reliance on descriptive outcomes only, and potential selection and confounding biases due to prior varied therapies.

Randomized trials which compare standard chemotherapy with and without concurrent TTF therapy are needed to demonstrate any potential incremental benefit of this therapy over the current standard of care.

TTFields for Non-Small Cell Lung Cancer (NSCLC)

Leal et al. (2023) published findings from a phase III trial evaluating TTFields plus chemotherapy in metastatic non-small cell lung cancer versus chemotherapy alone. LUNAR was a pivotal open-label phase 3 randomized trial (130 sites, 19 countries) evaluating TTFields added to standard systemic therapy versus standard therapy alone in metastatic NSCLC after progression on platinum-based chemotherapy. A total of 276 individuals were enrolled and randomized 1:1 to TTFields plus standard therapy (n=137) or standard therapy alone (n=139). Standard therapy (pre-selected per investigator) was either an immune checkpoint inhibitor (e.g., nivolumab, pembrolizumab, or atezolizumab) or docetaxel, given according to guidelines, with TTFields applied continuously in the combination arm. Key inclusion criteria were adults ≥ 22 years, ECOG performance status 0–2, any histology, with radiological disease progression on or after ≥ 1

platinum-based regimen. Key exclusions included significant organ dysfunction (e.g., severe hematologic, hepatic, renal, or cardiac impairment), recent cerebrovascular accident (within 6 months), or another active malignancy within 3 years. Median follow-up was approximately 10 months in both arms. The primary endpoint was overall survival (OS). OS was prolonged in the TTFields arm. Median OS was 13.2 months (95% CI 10.3–15.5) versus 9.9 months (8.1-11.5) with standard therapy alone (hazard ratio 0.74, p=0.035). In the immunotherapy subgroup, TTFields plus immune checkpoint inhibitor yielded median overall survival of 18.5 vs 10.8 months with immunotherapy alone (HR 0.63, p=0.030), whereas in the docetaxel subgroup OS was 11.1 vs 8.7 months for TTFields plus docetaxel versus docetaxel alone (HR 0.81, p=0.28, not significant). Secondary endpoints such as progression-free survival (median ~4.8 vs 4.1 months in TTFields vs control; HR 0.85, p=0.23) and objective response rate (20.4% vs 17.3%; p=0.50) did not show a significant difference between arms. Safety profiles were similar aside from expected mild-to-moderate skin irritation with TTFields, and TTFields did not exacerbate systemic therapy toxicities. Limitations of the trial included the open-label nature (no sham device) potentially introducing bias in subjective endpoints. The study was stopped early at 276 individuals (vs ~534 planned) based on interim analysis for ethical considerations, which reduced sample size and limits statistical power for subgroup analyses. Additionally, only a few individuals with brain metastases were included (due to initial exclusion and later amendment for inclusion), which may limit generalizability to that subgroup.

LUNAR is the first and currently only randomized controlled trial of TTFields in NSCLC, representing initial evidence base in this setting. While it provides evidence of an overall survival benefit with TTFields in refractory NSCLC, more research is needed for confirmation before broad adoption.

TTFields for NSCLC Brain Metastases

Mehta et al. (2026) conducted a pivotal, phase III trial (METIS) to evaluate the safety, efficacy, and neurocognitive and quality of life outcomes of TTFields in individuals with brain metastases from advanced NSCLC. 298 adults with 1–10 newly diagnosed, unresectable NSCLC brain metastases (each ≤ 3 cm; cumulative volume ≤ 15 cm^3) and no EGFR/ALK/ROS1/BRAF mutations were randomized 1:1 to stereotactic radiosurgery (SRS) followed by TTFields versus stereotactic radiosurgery (SRS) alone. After a median ~9-month follow-up, TTFields significantly prolonged time to intracranial progression (TTIP; HR 0.72, p = 0.044), with a 12-month intracranial progression rate of ~47% vs 59% favoring TTFields. However, TTFields conferred no significant improvement in overall survival (median ~11.3 vs 10.6 months, p = 0.763) or neurocognitive outcomes (p = 0.0607). In a post hoc subgroup of individuals on immune checkpoint inhibitors (n = 118), TTFields plus SRS showed more pronounced effects (e.g., distant intracranial progression was significantly delayed [HR 0.41, p = 0.0087; TTIP HR ~0.63, borderline significance]). Limitations included the trial's open-label design without a sham device, broad inclusion criteria, and control-arm crossover (17 individuals received TTFields after progression). The authors speculated that the findings may indicate that TTFields could reduce the need for whole-brain radiation therapy or salvage SRS.

Further studies of TTFields in brain metastases are needed to determine whether overall survival outcomes can be improved with this therapy and to better define the specific patient population that could benefit.

TTFields for Liver Cancer

HEPANOVA was a prospective, single arm, historical control study conducted at six sites across six European countries. It was conducted to investigate the efficacy and safety of TTFields (150 kHz)

therapy concomitant with sorafenib in individuals with advanced HCC. The primary endpoint was the overall response rate (ORR) compared with historical controls. ORR was defined as the percentage of individuals who experienced a complete or partial response (RECIST version 1.0 for HCC). Inclusion criteria included but was not limited to: Adults (≥ 18 years of age) with HCC diagnosed by biopsy or by typical imaging criteria (CT/MRI) and alfa fetoprotein, BCLC stage 0–C, a CTP score of 5–8 points (corresponding to grade A-B8), an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2 and life expectancy of ≥ 12 weeks were eligible for enrollment. Exclusion criteria included but was not limited to: if they were candidates for surgical resection or local treatment (e.g., TACE, SIRT, radio-frequency thermal ablation, microwave ablation or surgery) or had concurrent or prior malignancy requiring anti-tumor treatment.
27 individuals with HCC were enrolled and received TTFields (150 kHz) therapy (ITT population). One patient in the ITT population did not receive concomitant sorafenib treatment. Six individuals (22%; all with a CTP score of 7–8 [i.e., class B]) died before the first follow-up scan at 12 weeks; therefore, imaging data were only available for the response analysis for 21 individuals.
Of the 27 individuals included in the intent-to-treat population, 11 (41%) individuals received ≥ 12 weeks of treatment with TTFields; five individuals received ≥ six months of treatment with TTFields. Results demonstrated that TTFields (150 kHz) concomitant with sorafenib resulted in numerical (but not statistically significant) improvement in outcomes in individuals with advanced HCC as compared to historical controls and without an increase in systemic toxicity. The ORR (primary endpoint) was numerically higher by approximately twofold but was not significantly different for TTFields concomitant with sorafenib vs. historical control for sorafenib monotherapy: 9.5% vs. 4.5%, respectively; all responses were partial. Adverse Events (AE): In total, 26 individuals (96%) experienced ≥1 AE; the most frequent AEs were diarrhea (n = 15, 56%), asthenia (n = 11, 41%), decreased appetite (n = 8, 30%) and ascites (n = 6, 22%). There were nine individuals (33%) who reported ≥1 mild–moderate (grade 1–2) AEs, and the most frequently reported AEs were diarrhea (48%) and asthenia (33%). In addition, 16 individuals (59%) had severe (grade 3–4) AEs. The authors noted, "given the potential for added benefit with TTFields in this high-risk patient population with unmet needs, the concurrent use of TTFields with current SOC treatment warrants further investigation in a larger, randomized, phase III clinical study" (Gkika, et al., 2022).

Large, high-quality, randomized trials are needed to demonstrate any potential incremental benefit of this therapy over the current standard of care.

TTFields for Pancreatic Cancer

Babiker et al. (2025) published results from a randomized, open label, phase III trial (PANOVA-3) evaluating the use of TTFields in locally advanced pancreatic adenocarcinoma. Eligible for inclusion were adults age 18 years and older with unresectable, locally advanced, biopsy-confirmed, and previously untreated pancreatic adenocarcinoma who had a life expectancy ≥ 3 months and Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-2. The primary objective of the study was to determine whether first-line TTFields in combination with gemcitabine/nab-paclitaxel improves overall survival. Secondary objectives of the study included progression-free survival, local progression-free survival, and pain-free survival. A total of 571 individuals were enrolled and assigned to TTFields with chemotherapy (n=285) or chemotherapy alone (n=286). Follow-up visits occurred every 4 weeks. Data demonstrated that overall survival was statistically improved in the TTFields treatment group with a median overall survival of 16.2 months (95% CI, 15.0 to 18.0) versus 14.2 months in the chemotherapy alone group (95% CI, 12.8 to 15.4). Overall response rate was not significantly improved in the TTFields group (36.1% [95% CI, 30.0 to 42.4] versus 30.0% [95% CI, 24.3 to 36.2]). Pain-free survival was extended in the TTFields treatment group compared to chemotherapy alone (median, 15.2 months [95% CI, 10.3 to 22.8] versus 9.1 months [95% CI, 7.4 to 12.7]). Distant progression-free survival was improved with

TTFields (median, 13.9 months [95% CI, 12.2 to 16.8] versus 11.5 months [95% CI, 10.4 to 12.9]). The primary adverse events related to TTFields included skin irritation. There were no fatal adverse events related to TTFields. (Babiker et al., 2025)

Outside of the PANOVA-3 trial, there is a paucity of high-quality, in vivo studies on the use of TTFields in pancreatic cancer. Additional studies are needed to confirm the benefit of TTFields for pancreatic cancer.

Professional Societies/Organizations: American Society of Clinical Oncology (ASCO): The American Society of Clinical Oncology (ASCO) guideline on Therapy for Diffuse Astrocytic and Oligodendroglial Tumors in Adults made a conditional recommendation for the use of TTFields therapy with adjuvant temozolomide in individuals with newly diagnosed supratentorial glioblastoma. This recommendation was given an evidence quality rating of moderate. The recommendation cited findings from the EF-14 trial, noting that the trial provides evidence for the use of TTFields but limitations of the trial, concerns of overestimation of effect, and lack of other trials led to only a weak recommendation in favor of TTFields. (Mohile, et al., 2021)

The American Society of Clinical Oncology (ASCO) Living Guideline on Therapy for Stage IV Non-Small Cell Lung Cancer Without Driver Alterations, 2026.3.0, addressed the emerging use of TTFields therapy in NSCLC. The guidelines cited the promising findings of the phase III LUNAR trial but stated "given this study was conducted in the setting of an evolving treatment landscape the role for tumor treating field in the modern treatment paradigm is unknown". (Reuss, et al., 2026)

The American Society of Clinical Oncology (ASCO) guideline on Treatment of Pleural Mesothelioma also addressed the use of TTFields therapy. The guideline stated there was insufficient evidence to make a recommendation on the addition of TTFields to pemetrexed plus platinum-based chemotherapy, citing the findings of the STELLAR study. This recommendation was given an evidence quality rating of very low, and strength of recommendation was not applicable. (Kindler, et al., 2025)

American Society for Radiation Oncology (ASTRO): The American Society for Radiation Oncology (ASTRO) clinical practice guideline for Radiation Therapy for WHO Grade 4 Adult-Type Diffuse Glioma included a recommendation for the use of TTFields. The guideline noted the findings of the EF-14 trial and gave a conditional recommendation for the use of TTFields for individuals with supratentorial WHO grade 4 diffuse glioma. The guideline stated "the recommendation according to ASTRO's Guideline methodology is conditional with a moderate quality of evidence because there is presently 1 well-conducted RCT and currently variable consensus with adoption in national practices, reflecting that while most informed clinicians would choose alternating electric field therapy, a substantial minority may not" (Yeboa, et al., 2025).

National Comprehensive Cancer Network (NCCN): The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology on Central Nervous System Cancers (Version 3.2025 – December 5, 2025) included the use of alternating electric field therapy in the preferred adjuvant treatment regimen for individuals diagnosed with supratentorial glioblastoma and a good Karnofsky Performance Score (≥ 60). This recommendation was classified as category 1 (based upon high-level evidence [≥ 1 randomized phase 3 trials or high-quality, robust meta-analyses] and uniform consensus [≥ 85% support of the panel] that the intervention is appropriate). The panel noted that support for this therapy was based on the results of the EF-14 clinical trial. The Guidelines also included the use of alternating electric field therapy as a consideration for the treatment of recurrent or progressive supratentorial glioblastoma. This recommendation was classified as category 2B (based upon lower-level evidence with ≥ 50% support of the panel but < 85% support of the panel that the intervention is appropriate). The panel noted they were divided

on this recommendation as the results of the EF-11 clinical trial did not clearly demonstrate efficacy.

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology on Pancreatic Adenocarcinoma (Version 2.2026 – April 22, 2026) did not include the use of alternating electric field therapy in their treatment algorithm.

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology on Non-Small Cell Lung Cancer (Version 5.2026 – March 13, 2026) did not include the use of alternating electric field therapy in their treatment algorithm.

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology on Mesothelioma: Pleural (Version 2.2026 – October 3, 2025) did not include the use of alternating electric field therapy in their treatment algorithm.

Health Equity Considerations

Health equity is the highest level of health for all people; health inequity is the avoidable difference in health status or distribution of health resources due to the social conditions in which people are born, grow, live, work, and age.

Social determinants of health are the conditions in the environment that affect a wide range of health, functioning, and quality of life outcomes and risks. Examples include safe housing, transportation, and neighborhoods; racism, discrimination and violence; education, job opportunities and income; access to nutritious foods and physical activity opportunities; access to clean air and water; and language and literacy skills.

Appendix

FDA Approved/Cleared Devices

Amplitude-Modulated Radiofrequency Electromagnetic Fields

Device or Product	Identifier	Manufacturer
TheraBionic P1	H220001	TheraBionic, Inc.

Tumor Treating Fields

Each Novocure Optune device listed below has been FDA approved for the treatment of specific cancer types.

- Optune Gio® was FDA approved via the pre-market approval pathway for adults age 22 years of age or older for the treatment of newly diagnosed, supratentorial glioblastoma following maximal debulking surgery, and completion of radiation therapy together with concomitant standard of care chemotherapy. It is also approved for adults age 22 years of age or older for the treatment of recurrent supratentorial GBM, to be used as monotherapy and as an alternative to standard medical therapy after surgical and radiation options have been exhausted.
- Optune Lua® was FDA approved via the humanitarian device exemption pathway for treatment of adult patients with unresectable, locally advanced or metastatic, malignant pleural mesothelioma (MPM) to be used concurrently with pemetrexed and platinum-based chemotherapy. It is also approved for adult patients with metastatic NSCLC who have

progressed on or after a platinum-based regimen, to be used concurrently with PD-1/PD-L1 inhibitors or docetaxel.
- Optune Pax® was FDA approved via the pre-market approval pathway for the treatment of adult patients with locally advanced pancreatic cancer, concomitant with gemcitabine and nab-paclitaxel.

Device or Product	Identifier	Manufacturer
Novo-TTF-100A System/Optune Gio®	P100034	Novocure, GmbH
Optune Lua®	P230042	Novocure, GmbH
Optune Pax®	P250034	Novocure, GmbH

Note: Coverage decisions are not based solely on FDA approval. Device or product names are provided for example purposes only. Their inclusion does not indicate endorsement or preference for any specific brand or model. This list is not intended to reflect all available products or technologies.

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Revision Details

Type of Revision	Summary of Changes	Date
Focused Review	• Title change. • Added policy statement for tumor treating fields.	9/15/2026
Annual Review	• No clinical policy statement changes.	4/15/2026

Effective 9/15/2026

Type of Revision	Summary of Changes	Date
Initial Review	• New policy statement added	7/15/2025