

# Electric Tumor Treatment Field Therapy

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[Instructions for Use](#)

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Related Policy
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## Coverage Rationale

The following is proven and medically necessary for treating newly diagnosed histologically confirmed **Supratentorial glioblastoma (GBM)**:

- The use of U.S. Food and Drug Administration (FDA) approved devices to generate electric tumor treatment fields (TTF) when used according to FDA labeled indications, contraindications, warnings, and precautions and when all of the following criteria are met:
  - Debulking surgery has been completed; and
  - Treatment with radiation therapy has been completed; and
  - Individual is receiving Temozolomide (TMZ) as the only cancer drug; and
  - Individual has a Karnofsky Performance Status (KPS) score of  $\geq 60$  or Eastern Cooperative Oncology Group (ECOG) Performance Status  $\leq 2$ ; and
  - Individual has been counselled that the electric TTF device must be worn at least 18 hours daily

When all of the above criteria are met for newly diagnosed GBM (ndGBM), an initial 3 months of electric TTF therapy will be approved.

The following is proven and medically necessary for treating radiologically confirmed recurrence of GBM (rGBM) in the **Supratentorial region of the brain**:

- The use of FDA approved devices to generate electric TTF after initial chemotherapy when used according to FDA labeled indications, contraindications, warnings, and precautions and when all of the following criteria are met:
  - The device is used as the only treatment; and
  - Individual has a KPS score of  $\geq 60$  or ECOG Performance Status  $\leq 2$ ; and
  - Individual has been counselled that the electric TTF device must be worn at least 18 hours daily

When all of the above criteria are met for rGBM, an initial 3 months of electric TTF therapy will be approved.

**Subsequent approval(s) for continuation beyond the initial 3 months of electric TTF for treatment of histologically confirmed Supratentorial GBM is based on:**

- Magnetic resonance imaging (MRI) scan has been performed  $\leq 2$  months prior to request and documents no evidence of disease progression; and
- Individual with ndGBM continues to receive TMZ as the only cancer drug or the device is used as the only treatment for an individual with rGBM; and
- KPS score of  $\geq 60$  or ECOG Performance Status  $\leq 2$ ; and
- Documentation that the individual has been using the electric TTF device at least 18 hours daily

Due to insufficient evidence of efficacy, the use of devices to generate electric TTF is unproven, and not medically necessary when the criteria above are not met and for all other indications including but not limited to the following:

- Treatment of tumors other than GBM
- Use of electric TTF therapy with concurrent medical therapy [e.g., bevacizumab (BEV) or chemotherapy] for treatment of rGBM

Computer software used for therapeutic radiology clinical treatment planning in conjunction with electric TTF therapy is unproven and not medically necessary due to insufficient evidence of efficacy.

## Medical Records Documentation Used for Reviews

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. Medical records documentation may be required to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the service requested; refer to the protocol titled [Medical Records Documentation Used for Reviews](#).

## Definitions

**Eastern Cooperative Oncology Group (ECOG) Scale of Performance Status:** A standard criteria for measuring how the disease impacts a person's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability (e.g., walking, working, etc.). (ECOG-ACRIN Cancer Research Group)

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

**Karnofsky Performance Status (KPS):** A standard way of measuring the ability of cancer patients to perform ordinary tasks. KPS scores range from 0 to 100; a higher score means a person is better able to carry out daily activities. For example, a KPS of 60 means a person requires occasional assistance but is able to care for most of their personal needs. KPS may be used to determine a patient's prognosis, to measure changes in a patient's ability to function, or to decide if a patient could be included in a clinical trial. [National Cancer Institute (NCI), 2019, West & Jin, 2015]

Grade	Karnofsky Performance Status (KPS)
100	Normal, no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort, some signs, or symptoms of disease
70	Cares for self but unable to carry on normal activity or to do active work
60	Requires occasional assistance but is able to care for most of personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated although death not imminent
20	Very ill; hospitalization and active supportive care necessary
10	Moribund
0	Dead

(Table: ECOG-ACRIN Cancer Research Group)

**Supratentorial:** A term used to describe the upper portion of the brain comprised of the cerebrum, ventricles, choroid plexus, hypothalamus, pineal gland, pituitary gland, and optic nerve. (NCI, 2019)

**Temozolomide (TMZ):** An oral alkylating chemotherapy drug used in the treatment of some brain cancers. It is a first-line treatment for glioblastoma. (NCI, 2019)

## Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
77299	Unlisted procedure, therapeutic radiology clinical treatment planning

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HCPCS Code	Description
A4555	Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only
E0766	Electrical stimulation device used for cancer treatment, includes all accessories, any type
E0767	Intrabuccal, systemic delivery of amplitude-modulated, radiofrequency electromagnetic field device, for cancer treatment, includes all accessories

## Description of Services

Electric tumor treatment field (TTF) therapy (also known as tumor-treating fields, TTFs, and ETTFs) is based on the principle that low intensity, intermediate frequency electric fields (100 to 300 kHz) disrupt cell division and may destroy proliferating cells in brain tumors. (Rulseh et al, 2012)

Glioblastoma multiforme (GBM) is the most prevalent and primary malignant brain tumor in adults; for those with newly diagnosed glioblastoma (ndGBM), the initial standard treatment consists of debulking surgery (when feasible), followed by radiation and chemotherapy. (NCCN, 2023)

Refer to the [U.S. Food and Drug Administration \(FDA\)](#) section for additional information.

The Optune kit contains the portable electric field generator (Optune device), insulated electrode (INE), transducer arrays, power supply, and additional supplies. Prior to treatment, transducer arrays are placed on the individual's scalp according to the tumor's location, which is then covered by a lightweight white cap that resembles a bandage. The individual receives the noninvasive TTF treatment for at least 18 continuous hours per day for a minimum of 4 weeks. As the Optune device is portable, individuals can carry out every-day activities. Treatment parameters are preset by the manufacturer so that no electrical output adjustments are available to the individual being treated. The individual being treated, or caregiver, must learn to change and recharge depleted device batteries and to connect to an external power supply overnight. In addition, the transducer arrays need to be replaced once to twice a week, and the scalp needs to be re-shaved to maintain optimal contact.

The NovoTAL™ (transducer array layout) system is an optional simulation software for use in clinical treatment planning with Optune therapy that may be leased from the manufacturer. Its purpose is to determine the optimal location of the transducer arrays based on the individual's most recent magnetic resonance imaging (MRI) scan, head size, and tumor location.

TTF technology is also being studied through ongoing clinical trials as a treatment for other solid tumors such as non-small cell lung cancer, brain metastasis, pancreatic cancer, ovarian cancer, and mesothelioma.

### Glioblastoma

In 2023, Ballo et al. performed a systematic review and meta-analysis on the association of Tumor Treating Fields (TTFields) therapy with survival in newly diagnosed glioblastoma (ndGBM). The authors concluded the literature review to identify clinical studies evaluating overall survival (OS) for individuals treated with TTFields. A total of 1430 individuals were included in the studies that compared the addition of TTFields therapy to standard of care (SOC) chemoradiotherapy versus SOC alone. The meta-analysis included comparative studies that show a significant improvement in OS for those receiving TTFields and SOC versus SOC alone. This systematic review and meta-analysis showed a median OS of 22.6 months for those who received TTFields and 17.4 months for those who did not receive TTFields. For those reporting data on device usage (n = 1015), an average usage rate of  $\geq 75\%$  was consistently associated with prolonged survival. The limitations of the study included the risk of bias and overestimations of treatment effects. The authors concluded that adding TTFields to standard chemoradiotherapy significantly prolongs OS for those newly diagnosed with Glioblastoma multiforme (GBM) treated in the real world. Future studies are essential in investigating the role of TTFields treatment duration for individual outcomes and assessing the clinical benefits for high-unmet need populations.

In 2022, Li and associates explored studies to evaluate the efficacy and safety of TTFields for treating recurrent glioblastoma (rGBM) through a systematic review and meta-analysis. The outcomes measured were OS, hazard ratio (HR), 1-year survival rate, and cutaneous toxicity. The results of the exploration included a total of 1048 individuals who had rGBM and received TTField treatment. The participants were divided into two groups: the TTField group and the control group. The OS time between the TTField and control groups was HR 0.75, with a pooled 1-year OS rate and incidence of cutaneous toxicity of 0.47 and 0.48, respectively. The authors concluded that TTField therapy is effective for rGBM. However, the most relevant trials should assess individuals with rGBM's baseline characteristics such as age, Karnofsky Performance Status (KPS), methylguanine-DNA methyltransferase (MGMT) methylation status, and the number of recurrent tumors. The risk of rashes caused by long-term wearing of devices should be considered.

Li and colleagues conducted a systematic review and meta-analysis in 2022 to review the literature about the influencing factors on the efficacy of TTFields with two experimentally supported factors: the dose of dexamethasone and compliance of TTFields to perform a meta-analysis. The results of the exploration revealed that the median OS is conspicuously longer in the TTFields group when the dexamethasone is  $\leq 4.1$  mg, and those whose compliance with TTFields treatment  $\geq 75\%$  have a significantly lower OS risk than those compliant with TTFields treatment  $< 75\%$ . The limitations of this exploration included significant heterogeneity in the analysis of the dose of dexamethasone, the restricted English articles, and a small number of included articles. The authors concluded that TTFields are a safe and efficient treatment modality. The dose of dexamethasone  $\leq 4.1$ mg of TTFields treatment and the compliance of TTFields treatment  $\geq 75\%$ ,  $\geq h$  per day is beneficial to the prognosis of those with glioblastoma. (Included in the 2019 ECRI clinical evidence assessment.)

Dongpo et al., 2022 guided a network Meta-analysis on the efficacy and safety of Bevacizumab (BEV) combined with other therapeutic regimens for treating rGBM and to further explore the differences in the effectiveness of each treatment in randomized controlled trials (RCTs) and nonrandomized-controlled-trials (non-RCTs). The results of this exploration showed that in six months, the OS of those receiving BEV combination therapy was ranked from high to low as follows: Bev + rindopepimut, Bev + lomustine (CCNU), CCNU, TTFields + Bev, Bev, Bev + irinotecan (Iri), Bev + temozolomide (TMZ), Bev + vorinostat, Bev + onartuzumab, Bev + dasatinib, Bev + carboplatin, Bev + trebananib, Bev + VB-111, TMZ, PCV, VB-111, and carboplatin. Ranked from high to low, the progression-free survival (PFS) was ranked as follows: Bev + CCNU, Bev + rindopepimut, Bev + dasatinib, Bev + vorinostat, Bev, Bev + Iri, Bev + TMZ, CCNU, Bev + carboplatin, TMZ, Bev + VB-111, PCV, Bev + trebananib, carboplatin, and VB-111. The authors compared the total incidence of serious adverse events (AEs) ( $\geq 3$ ) and discovered that the Bev + vorinostat and Bev + trebananib were safer than Bev, while other regimens were not as safe. A descriptive analysis showed that Bev + rindopepimut also appeared safer than Bev. In subgroup analysis, Bev + CCNU therapy had the highest 6-month OS and 6-month progression-free survival (6-month PFS) among RCTs. Among non-RCTs, Bev + Iri therapy showed the highest 6-month OS and good 6-m PFS. The limitations of the study included the small number of noncontributing trials, small sample sizes, and the paucity of relevant, high-quality, large-sample, original studies, reducing the strength of the evidence. According to the network meta-analysis results, the authors concluded that both Bev + CCNU and Bev + rindopepimut could be considered effective therapies for treating rGBM. Among them, Bev + rindopepimut therapy seems safer and more effective. Moreover, the authors found that Bev + Iri was an effective therapy in a retrospective study. An analysis of the evidence is necessary with a larger number of relevant, high-quality, large sample RCTs and non-RCTs.

Regev et al. (2021) conducted a systematic review and meta-analysis of evaluating TTFields mechanism of action, safety, and efficacy, for both ndGBM and rGBM. Twenty studies met the pre-defined inclusion criteria, including 1636 participants (542 ndGBM and 1094 rGBM), and 11 558 individuals (6403 ndGBM and 5155 rGBM) analyzed for the clinical outcomes and safety endpoints, separately. This study demonstrated improved clinical efficacy and a good safety profile of TTFields. For ndGBM, pooled median OS and PFS were 21.7 [95% confidence interval (CI) = 19.6-23.8] and 7.2 (95%CI

= 6.1-8.2) months, respectively. For rGBM, pooled median OS and PFS were 10.3 (95%CI = 8.3-12.8) and 5.7 (95%CI = 2.8-10) months, respectively. Compliance of  $\geq 75\%$  was associated with an improved OS and the predominant AEs were dermatologic, with a pooled prevalence of 38.4% (95%CI = 32.3-44.9). Preclinical studies demonstrated TTFields' diverse molecular mechanism of action, potential synergistic efficacy and suggested possible benefits for certain populations. The findings showed that TTFields had significantly better emotional function and reported significantly lower incidence of side effects. Also, TTFields users had better emotional, physical, and cognitive functions than social and role functioning. The study showed that TTFields frequently affected multiple aspects of the individuals' daily lives; however, 70% would recommend TTFields to others, and 67% would reuse the device. This study supports the clinical benefit, safety, and potential therapeutic synergism of TTFields for treating GBM, alongside the standard-of-care treatment protocol. (Included in the 2019 ECRI clinical evidence assessment). (Mrugala et al., 2014, Stupp et al., 2017, Wong et al., 2015 are included in this review.)

A systematic review and a Bayesian network meta-analysis were performed by Chen et al. (2021) to compare and rank active therapies in rGBM. The authors obtained a treatment hierarchy using the surface under the cumulative ranking curve and mean ranks. A cluster analysis was conducted to aggregate the separated results of three outcomes. A total of 1,667 citations were identified, and 15 eligible articles with 17 treatments remained in the final network meta-analysis. Pairwise comparison showed no difference in the 6-m PFS rate, objective response rate (ORR), and OS. Among the reports, CCNU corresponded to the highest grade 3-4 AE rates. Ranking and cluster analysis indicated that BEV plus CCNU and regorafenib had a higher efficacy on the ORR, 6-m PFS rate and OS, and that BEV monotherapy or BEV combined with active drug therapies was advantageous for the ORR and 6-m PFS rate. Additionally, TTFields plus BEV showed a higher SUCRA value in OS. The authors concluded that according to ranking and cluster analysis, BEV plus CCNU and regorafenib are the primary recommendations for treatment. BEV monotherapy alone or combined with active drug therapies recommended in those with severe neurological symptoms. Limitations included inconsistency among researchers, which may have biased the statistical results. In addition, the published results lag behind current therapy options. New therapies, including neoadjuvant checkpoint inhibitors and laser interstitial thermotherapy, have not been included. The findings of this study need to be validated by well-designed studies. Further investigation is needed before the clinical usefulness of this procedure is proven.

Dono et al. (2021) performed a retrospective review of an institutional database with 530 individuals with infiltrating gliomas to evaluate the survival effects of TTFields in a cohort of those with isocitrate dehydrogenase wild-type (IDH-WT) rGBM, and to investigate the possible clinical characteristics or genomic alterations that may predict responsiveness to TTFields. People with IDH-WT rGBM receiving TTFields at first recurrence were included. Tumors were evaluated by next-generation sequencing for mutations in 205 cancer-related genes. The log-rank and multivariate Cox regression analysis examined post-progression survival (PPS). A total of 149 individuals with rGBM were identified of which 29 (19%) were treated with TTFields. No difference in median PPS was seen between those with rGBM who received versus those who did not receive TTFields (13.9 versus 10.9 months,  $p = 0.068$ ). However, within the TTFields-treated group ( $n = 29$ ), PPS was improved in PTEN-mutant ( $n = 14$ ) versus PTEN-WT ( $n = 15$ ) rGBM, (22.2 versus 11.6 months,  $p = 0.017$ ). Within the PTEN-mutant group ( $n = 70$ , 47%), those treated with TTFields ( $n = 14$ ) had longer median PPS (22.2 versus 9.3 months,  $p = 0.005$ ). No PPS benefit was observed in PTEN-WT patients receiving TTFields ( $n = 79$ , 53%). TTFields therapy conferred a PPS benefit in PTEN-mutant rGBM. The authors concluded that understanding the molecular mechanisms underpinning the differences in response to TTFields therapy could help elucidate the mechanism of action of TTFields and identify the individuals with rGBM most likely to benefit from this therapeutic option. This study is limited by its retrospective observations. In addition, a small sample size makes it difficult to decide whether these conclusions can be generalized to a larger population. Further research with RCTs is needed to confirm these findings.

Ram et al. (2021) performed a subgroup analysis of the multicenter, phase III, EF-14 randomized clinical trial subgroup analysis of individuals with ndGBM to evaluate the safety and efficacy of TTFields in elderly people. All 134 participants who are  $\geq 65$  years of age were included (TTFields/TMZ combination,  $n = 89$ ; TMZ monotherapy,  $n = 45$ ; 2:1 ratio of randomization). PFS and OS were analyzed using Kaplan-Meier methodology ( $\alpha = 0.05$ ). Health-related quality-of-life (HRQoL) was assessed using the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire QLQ-C30 supplemented with the brain tumor module (QLQ-BN20). AEs were evaluated using Common Terminology Criteria for AEs (CTCAE) v4.0. The PFS was 6.5 months in those randomized to the treatment group with TTFields/TMZ combination versus 3.9 months in those treated with TMZ monotherapy (HR, 0.47; 95% CI, 0.30-0.74;  $p = 0.0236$ ). The OS was 17.4 months in those treated with TTFields/TMZ combination versus 13.7 months in people treated with TMZ monotherapy (HR, 0.51; 95% CI, 0.33-0.77;  $p = 0.0204$ ). Annual survival rates with TTFields/TMZ versus TMZ monotherapy were 39% (95% CI, 29-50%) versus 27% (95% CI, 15-41%;  $p = 0.072$ ) at two years, 19% (95% CI, 11-29%) versus 11% (95% CI, 4-23%;  $p = 0.135$ ) at three years, and 15% (95% CI, 7-25%) versus 0% at five years, respectively. There were no differences between groups in the pre-selected items of HRQoL assessment. Grade  $\geq 3$  systemic AEs were 46% in the TTFields/TMZ group versus 40% in the TMZ monotherapy group, without statistically significant difference between the two groups. The only TTFields-related AEs were reversible scalp skin reactions, with grades 1-2



and grade 3 skin reactions reported by 51% and 2% of participants, respectively. The authors concluded that combining TTFIELDS with maintenance TMZ improved PFS and OS in older adults with ndGBM in the phase III EF-14 clinical trial, without increases in systemic toxicity or negatively affecting patient HRQoL. TTFIELDS-related skin AEs were low-grade and manageable. Limitations of this analysis include the small sample sizes of both treatment groups due to the limited number of people enrolled in the EF 14 trial who were 65 years of age or older. There is also a lack of available molecular data in ~20% of people; 4% of TTFIELDS plus TMZ-treated patients had an IDH mutation compared with 0% of the TMZ-treated people; and only one had a 1p19q codeletion (TTFIELDS plus TMZ group). Long-term evaluations of the results and prospective randomized studies are still needed. (Clinical Trial Identifier: NCT00916409)

Jin et al. (2020) conducted a systematic review and meta-analysis to compare the efficacy and safety of treatments based on the Stupp protocol for older adults with ndGBM and to determine the optimal treatment option for those with different O-6-MGMT promoter methylation statuses. The authors estimated HRs for OS and odds ratios (ORs) for AEs of grade 3 or higher (AEs  $\geq$  3). Twenty-one RCTs including 6478 people treated with 21 different treatment strategies, were included. Results of the pooled HRs indicated that TTFIELDS combined with the Stupp protocol resulted in the most favorable OS for those with and without MGMT promoter methylation. Subgroup analyses by the two MGMT promoter statuses indicated that lomustine-TMZ plus radiotherapy or TTFIELD combination therapy was associated with the best OS for those with methylated MGMT promoter [HR, 1.03; 95% credible interval (CI), 0.54-1.97], and standard cilengitide combination therapy or TTFIELD combination treatment was linked with the best OS for those with unmethylated MGMT promoter (HR, 1.05; 95% CI, 0.67-1.64). Regarding AEs  $\geq$  3, there were no significant differences in pooled ORs. However, Bayesian ranking profiles that verified intensive cilengitide combination therapy and TTFIELD combination therapy have a similar possibility of causing the least toxicity. Results showed that TTFIELD combination therapy was associated with increased survival, regardless of the MGMT promoter methylation status, and a relatively tolerated safety profile compared with other combination treatments. The best treatment options for those with glioblastoma with different MGMT promoter methylation statuses were different. These findings help establish a SOC and plan for adults with ndGBM. [Stupp et al., (2017) and Stupp et al., (2015) are included in this review]

Marenco-Hillebrand et al. (2020) conducted a systematic review to describe the current status and advances in the survival of those with glioblastoma by analyzing median OS through time and between treatment modalities. Full-text glioblastoma papers with human subjects  $\geq$  18 years old and  $n \geq$  25 were included for evaluation. The central tendency of median overall survival (MOS) was 13.5 months (2.3-29.6) and cumulative 5-year survival was 5.8% (0.01%-29.1%), with a significant difference in survival between studies that predate versus postdate the implementation of TMZ and radiation [12.5 (2.3-28) vs 15.6 (3.8-29.6) months,  $p < 0.001$ ]. Within clinical trials, the highest MOS involved TTFIELDS with 20.7 (range 20.5–20.9) months. According to the authors, therapies such as TTFIELD provide a means of prolonging the survival of those with glioblastoma.

Kim et al. (2020) reported on Koreans newly diagnosed with GBM who participated in the EF-14 trial. Thirty-nine participants of the EF-14 trial were enrolled at eight sites in South Korea. Participants (24 TTFIELDS/TMZ; 14 TMZ alone) received: TTFIELDS (200 kHz) for  $> 18$  h/day; TMZ at 120-150 mg for five days per a 28-day cycle. Safety and efficacy were assessed. Baseline characteristics were balanced in the two arms, and the mean age was 52.1 years; 66.7% were male with a mean KPS of 90. Safety incidence was comparable between the two arms. In the TTFIELDS/TMZ arm, 30% suffered from skin irritation versus 52% in the entire study population. No TTFIELDS-related serious AEs were reported. The median PFS in the TTFIELDS/TMZ arm was 6.2 months (95% CI 4.2-12.2) versus 4.2 (95% CI 1.9-11.2) with TMZ alone ( $p = 0.67$ ). Median OS was 27.2 months (95% CI 21-NA) with TTFIELDS/TMZ versus 15.2 months (95% CI 7.5-24.1; HR 0.27,  $p = 0.01$ ) with TMZ alone. The authors concluded that MOS and 1- and 2-year survival rates were higher with TTFIELDS/TMZ and similar to the entire EF-14 population. According to the authors, these results demonstrate the efficacy and safety of TTFIELDS in this population of Individuals with ndGBM.

A retrospective analysis was performed by Shi et al. (2020) with unsolicited, post-marketing surveillance data from TTFIELDS treated individuals with high-grade glioma (October 2011-February 2019) using Medical Dictionary for Regulatory Activities (MedDRA) v21.1 preferred terms, stratified by region [US, EMEA (Europe, Middle East, Africa), Japan], diagnosis (ndGBM, rGBM, anaplastic astrocytoma/oligodendroglioma, other brain tumors), and age [ $< 18$  (pediatric), 18-64 (adults),  $\geq 65$  (older adult); years of age]. This analysis aimed to assess the safety of TTFIELDS in real-world, clinical practice settings, using global post-marketing surveillance data from a large cohort. Of 11,029 individuals, 53% were diagnosed with ndGBM and 39% were diagnosed with rGBM at any line of disease recurrence. Most were adults (73%), 26% were older adults, and the male-to-female ratio was  $\sim 2:1$  (close to published ratios of typical GBM populations). The most commonly reported TTFIELDS-related AE was array-associated skin reaction, occurring in those with ndGBM (38%), rGBM (29%), anaplastic astrocytoma/oligodendroglioma (38%), and other brain tumors (31%); as well as 37% of pediatric, 34% of adult, and 36% of older adults. Most skin AEs were mild/moderate and manageable. Other TTFIELDS-related AEs in those with ndGBM/rGBM included under-array heat sensation (warmth; 11%, 10%, respectively) and electric sensation (tingling; 11%, 9%, respectively), and headache (7%, 6%, respectively). The authors concluded that his TTFIELDS safety surveillance analysis in  $> 11,000$  people revealed no new safety concerns, with a favorable safety

profile comparable with published TTFields/GBM trials. The safety profile remained consistent among subgroups, suggesting feasibility in multiple populations, including older adults. Limitations included the retrospective and observational design. Safety data were collated only from those who were TTFields-treated and reported AEs; therefore, the incidence of the overall cohort and sub-groups is likely overestimated. In addition, no efficacy, survival, or standardized QoL assessment data were included. This analysis did not translate research data into guidelines to improve patient care, and there is no evidence that this analysis will affect patient management. (Included in the systematic review and meta-analysis by Regev et al., 2021.)

A Hayes Health Technology Assessment report published in 2019 on TTFields (Optune) for treating glioblastoma provides a Hayes rating of C for using TTFields as monotherapy in adults (22 years of age and older) with rGBM following surgery and radiotherapy. A Hayes rating of C is also provided for TTField treatment with concomitant TMZ in adults (22 years of age and older) with ndGBM following surgery and radiation therapy with concomitant chemotherapy. A small, low-quality body of evidence suggests that TTField therapy results in OS and PFS at least equivalent to chemotherapy in patients with GBM. A small, low-quality body of evidence suggests that TTField plus TMZ increases OS and PFS in those with ndGBM compared with TMZ alone. The health technology annual review performed in 2021 reveals no changes in current ratings of C. In 2023, 13 newly published studies may meet the inclusion criteria set out in the 2019 report. The newly published literature indicates that no new applications of the technology have been identified since the publication of the 2019 health technology assessment and did not impact the current ratings of C.

ECRI conducted a clinical evidence assessment in 2019, updated in 2024, on the Optune Gio (Novocure, Ltd.) for treating rGBM. Evidence from three systematic reviews shows that Optune Gio and best standard care (BSC) chemotherapy results are similar in OS in those with rGBM. However, TTField enables individuals to avoid chemotherapy-associated AEs (i.e., serious hematologic AEs, diarrhea, nausea, infection, anorexia, muscle weakness) but does result in more skin site reactions and falls than BSC. Whether TTFields has clinical value for those with rGBM may depend on which outcomes are most important to the individuals and clinician. TTField plus BEV may increase OS in some people more than BSC alone, but additional studies are needed to ensure firm conclusions.

Toms et al. (2019) analyzed the compliance data from participants who received TTFields/TMZ in a subgroup analysis of the phase III EF-14 trial (Stupp et al., 2017) to correlate TTFields compliance with PFS and OS and identify potential lower boundary for compliance with improved clinical outcomes. Compliance was assessed by usage data from the NovoTTF-100A device and calculated as monthly percentage of TTFields delivery. Those treated with TTFields/TMZ were segregated into subgroups by percent monthly compliance. A Cox proportional hazard model controlled for sex, extent of resection, MGMT methylation status, age, region, and performance status was used to investigate the effect of compliance on PFS and OS. A threshold value of 50% compliance with TTFields/TMZ improved PFS and OS versus TMZ alone, with improved outcomes as compliance increased. At compliance > 90%, median survival was 24.9 months (28.7 months from diagnosis) and the 5-year survival rate was 29.3%. The authors concluded that a compliance threshold of 50% with TTFields/TMZ correlated with significantly improved OS and PFS versus TMZ alone. People with compliance > 90% showed extended median and 5-year survival rates.

Magouliotis et al. (2018) systematically reviewed the literature for individuals with glioblastoma treated with TTFields plus radio chemotherapy or conventional radio chemotherapy alone to compare the efficacy and safety of the two methods. Six studies met the inclusion criteria, incorporating 1806 participants for the qualitative analysis and 1769 for the quantitative analysis. This study reveals increased median OS at one year and two years and median PFS along with PFS at six months for those treated with TTFields. Survival at three years was comparable between the two groups. TTFields were associated with fewer AEs compared to chemotherapy, along with a similar incidence of skin irritation. The authors indicated that this review suggests that TTFields are a safe and efficient novel treatment modality.

Stupp et al. (2017) reported final outcomes from the randomized, open-label trial of 695 individuals with glioblastoma whose tumor was resected or biopsied and had completed concomitant radiochemotherapy (median time from diagnosis to randomization, 3.8 months) and Optune therapy. Of the 695 randomized participants [median age, 56 years; IQR, 48-63; 473 men (68%)], 637 (92%) completed the trial. Median PFS from randomization was 6.7 months in the TTFields-TMZ group and 4.0 months in the TMZ-alone group (HR, 0.63; 95% CI, 0.52-0.76;  $p < .001$ ). MOS was 20.9 months in the TTFields--TMZ group vs 16.0 months in the TMZ-alone group (HR, 0.63; 95% CI, 0.53-0.76;  $p < .001$ ). Systemic AE frequency was 48% in the TTFields--TMZ group and 44% in the TMZ-alone group. Mild to moderate skin toxicity underneath the transducer arrays occurred in 52% of those who received TTFields--TMZ vs no patients who received TMZ alone. In the final analysis of this randomized clinical trial of those with glioblastoma who had received standard radiochemotherapy, the addition of TTFields to maintenance TMZ chemotherapy vs maintenance TMZ alone, resulted in statistically significant improvement in PFS and OS. These results are consistent with the previous interim analysis. (Included in the 2023 systematic review and meta-analysis by Ballo et al., 2023 and the systematic review and meta-analysis by Regev et al., 2021.)

In a secondary analysis of the Stupp et al. (2017) trial, Taphoorn et al. (2018) examined the association of TTFields therapy with PFS and HRQoL among individuals with glioblastoma. Of the 695 participants in the study, 639 (91.9%) completed the baseline HRQoL questionnaire. Of these individuals, 437 (68.4%) were men; the mean (SD) age was 54.8 (11.5) years. Health-related quality of life did not differ significantly between treatment arms except for itchy skin. Deterioration-free survival was significantly longer with TTFields for global health (4.8 vs 3.3 months;  $p < .01$ ); physical (5.1 vs 3.7 months;  $p < .01$ ) and emotional functioning (5.3 vs 3.9 months;  $p < .01$ ); pain (5.6 vs 3.6 months;  $p < .01$ ); and leg weakness (5.6 vs 3.9 months;  $p < .01$ ), likely related to improved PFS. Time to deterioration, reflecting the influence of treatment, did not differ significantly except for itchy skin (TTFields worse; 8.2 vs 14.4 months;  $p < .001$ ) and pain (TTFields improved; 13.4 vs 12.1 months;  $p < .01$ ). Role, social, and physical functioning were not affected by TTFields. The addition of TTFields to standard treatment with TMZ for those with glioblastoma results in improved survival without a negative influence on HRQoL except for more itchy skin, an expected consequence from the transducer arrays.

In a multinational, open-label, randomized phase III trial (EF-14 trial), Stupp et al. (2015) compared Optune in combination with TMZ to TMZ alone in 700 individuals aged 18 and over with ndGBM. The interim report revealed that in the intent-to-treat population, those treated with TTFields plus TMZ showed a statistically significant increase in PFS the primary endpoint, compared to TMZ alone (median PFS 7.1 months versus 4.0 months, HR = 0.62,  $p = 0.0013$ ). In the per-protocol population, those treated with TTFields plus TMZ demonstrated a statistically significant increase in OS, a powered secondary endpoint, compared to TMZ alone (median OS 20.5 months versus 15.6 months, HR = 0.64,  $p = 0.0042$ ). In the intent-to-treat population, the median OS was 19.6 months versus 16.6 months, respectively, HR = 0.74 ( $p = 0.0329$ ). The two-year survival rate was 50 percent greater with TTFields plus TMZ versus TMZ alone: 43 percent versus 29 percent. The trial's independent data monitoring committee concluded that the study met its endpoints at its pre-specified interim analysis of the first 315 participants with 18 months or more of follow-up. The committee recommended that the trial be terminated early for success and that all control participants be offered TTFields therapy even prior to progression. In addition, the authors reported that the trial showed Optune could be safely combined with TMZ. There was no significant increase in systemic toxicities from Optune reported in combination with TMZ versus TMZ alone. The most common adverse reaction from Optune treatment was mild to moderate skin irritation, which according to the authors was easily managed, reversible and did not result in treatment discontinuation. This clinical trial has some important limitations. Patient enrollment occurred only after the end of radiochemotherapy, leading to some variation in the delivery of standard treatment of TMZ and radiotherapy. Participants who had progressed early during radiochemotherapy were not eligible for randomization, thus excluding those with very poor prognoses. There is likely reporting bias for second-line therapies after tumor progression because, in the TTFields plus TMZ group, TTFields were to be continued, and thus, more detailed treatment information has been tracked for this group.

## Tumors Other Than Glioblastoma

There is a lack of published evidence from RCTs examining the long-term safety and effectiveness of TTField as a treatment for tumors other than GBM, including non-small cell lung brain metastasis, pancreatic cancer, ovarian cancer and mesothelioma.

Leal and associates (2023) conducted a randomized, open-label, pivotal phase III (LUNAR) study of TTField therapy in metastatic non-small-cell lung cancer. A total of 276 participants from 130 sites in 19 countries who had metastatic non-small cell lung cancer progressing on or after platinum-based therapy, with squamous or non-squamous histology and ECOG performance status of 2 or less, were included. The participants of the study were randomly assigned (1:1) to TTFields therapy and standard systemic therapy ( $n = 137$ ) or standard therapy alone ( $n = 139$ ). The primary outcome measured was OS in the intention-to-treat population and the safety of those who received any study therapy according to the treatment received. The study's results demonstrated that OS was significantly longer with TTFields therapy and standard therapy than with standard therapy alone. In the safety population ( $n = 267$ ), serious AEs of any cause were reported in 70 (53%) of 133 participants receiving TTFields therapy plus standard therapy and 51 (38%) of 134 receiving standard therapy alone. The most frequent grade 3-4 AEs were leukopenia [37 (14%) of 267], pneumonia [28 (10%)], and anemia [21 (8%)]. TTFields therapy-related AEs were reported in 95 (71%) of 133 participants; these were mostly [81 (85%)] grade 1-2 skin and subcutaneous tissue disorders. There were three deaths related to standard therapy (two due to infections and one due to pulmonary hemorrhage) and no deaths associated with TTFields therapy. Study limitations include the open-label design, the study enrolled a small number of individuals with brain metastases, potentially affecting the generalizability of these findings to that population, and participants accrual proceeded more slowly than planned in the original study design. LUNAR was started before the advent of standard genetic profiling by next-generation sequencing in non-small cell lung cancer, and thus little information about the relationship between TTFields therapy efficacy and tumor genetic subtype is available. The authors concluded that TTFields therapy added to standard therapy significantly improved OS compared with standard therapy alone in metastatic non-small-cell lung cancer after progression on platinum-based therapy without exacerbating systemic toxicities. This data suggests that TTFields therapy is efficacious in metastatic non-small-cell lung cancer and should be considered as a treatment option to manage the disease in this setting. The study is registered with ClinicalTrials.gov, [NCT02973789](https://clinicaltrials.gov/ct2/show/study/NCT02973789).



Ceresoli et al. (2019) conducted a prospective, single-arm, phase II trial (STELLAR) 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. Participants were at least 18 years old, had an Eastern Cooperative Oncology Group performance status of 0-1, and had at least one measurable or evaluable lesion according to modified Response Evaluation Criteria in Solid Tumors for mesothelioma. Participants received continuous TTFields at a frequency of 150 kHz to the thorax and concomitant chemotherapy with intravenous pemetrexed (500 mg/m<sup>2</sup> on day 1) plus intravenous platinum (either cisplatin 75 mg/m<sup>2</sup> on day one or carboplatin area under the curve five on day 1) every 21 days for up to six cycles. Those 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 OS. Survival analyses were done in the intention-to-treat population, and safety analyses were done in all participants who received at least one day of TTFields treatment. A total of 80 participants were enrolled in the study. Median follow-up was 12.5 months. MOS was 18.2 months (95% CI 12.1-25.8). The most common grade 3 or worse AEs were anemia [nine (11%) participants], neutropenia [seven (9%)], and thrombocytopenia [four (5%)]. Skin reaction was the only AE associated with TTFields and was reported as grade 1-2 in 53 (66%) participants, and as grade 3 in four (5%) people. No treatment-related deaths were observed. According to the authors, the trial showed encouraging OS results, with no increase in systemic toxicity. TTFields (150 kHz) delivered to the thorax concomitant with pemetrexed and platinum was an active and safe combination for front-line treatment of unresectable malignant pleural mesothelioma. The lack of a comparison group limits the conclusions that can be drawn from the study. The authors indicated that further investigation in a randomized trial is warranted.

## **NovoTAL™ Simulation System**

The NovoTAL™ software utilizes magnetic resonance imaging (MRI) measurements for head size and tumor location obtained from axial and coronal T1 postcontrast sequences to determine the optimal paired transducer array configuration that will deliver the maximal field intensity at the tumor site. There is limited published clinical evidence related to the NovoTAL™ simulation system, and insufficient data to support improved long-term health outcomes with its use. This includes a small case series (Connelly et al., 2016), a human head model (Wenger et al., 2016), and a user group survey (Chaudhry et al., 2015). A framework for the use of NovoTAL in treatment planning has been proposed by Trusheim et al. (2017)

## **Clinical Practice Guidelines**

### ***American Society of Clinical Oncology (ASCO) and Society for NeuroOncology (SNO)***

In 2022, Mohile et al. published the ASCO and SNO clinical guidelines for diffuse astrocytic and oligodendroglial tumors in adults. This guideline recommends Alternating electric field therapy may be added to adjuvant TMZ in people with newly diagnosed supratentorial glioblastoma, IDH-wildtype, CNS WHO grade 4 who have completed chemoradiation therapy (Type: evidence-based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: weak).

### ***European Association of Neuro-Oncology (EANO)***

In 2021, Weller et al. published updated recommendations from the EANO due to the revision of the WHO Classification of Tumors of the Central Nervous System. The revisions have led to major changes in how the ESMO routinely diagnoses and treats those with gliomas.

Recommendations:

- The SOC for individuals with IDH-wild-type glioblastoma aged < 70 years and with a KPS ≥ 70 includes resection as feasible, or biopsy followed by involved-field radiotherapy and concomitant radiotherapy and six cycles of maintenance TMZ chemotherapy (EORTC 26981-NCIC CE.3). C: I; L: A.
- TMZ might only be active in patients with *MGMT* promoter-methylated tumors, while its activity in those with *MGMT* promoter-unmethylated tumors is probably marginal. C: II; L: B.
- Older adults not considered candidates for TMZ chemoradiotherapy should be treated based on *MGMT* promoter methylation status (NOA-08, Nordic Trial) with radiotherapy (such as 15 × 2.66 Gy) or TMZ (5 out of 28 days) alone. C: II; L: B.
- At recurrence, standards of care are less well defined. Surgery and radiotherapy might be considered. Nitrosourea regimens, TMZ rechallenge, and, considering the country-specific label, bevacizumab (BEV) are options for pharmacotherapy, but their impact on OS remains unproven. When available, recruitment into appropriate clinical trials should be considered. C: II; L: B.

Furthermore, the ESMO advocates against using any treatment beyond confirmed progression on that same treatment, including BEV and tumor-treating fields, because the clinical benefit of this practice has not been established. Several chemotherapy regimens commonly used to treat other tumor types, including irinotecan and platinum compounds, are known not to be active against gliomas and should, therefore, not be used in this setting.

## **National Comprehensive Cancer Network (NCCN)**

The NCCN Clinical Practice Guideline for Central Nervous System Cancers, anaplastic gliomas/glioblastoma includes standard brain radiation therapy (RT) + concurrent temozolomide and adjuvant temozolomide + alternating electric field therapy for individuals with good performance status [(KPS)  $\geq$  60] and either methylated or unmethylated/indeterminate MGMT promoter status, in whom maximal, safe resection was not feasible with the following footnote: "Alternating electric field therapy is only an option for those with supratentorial disease" (category 1). For recurrence of GBM (GLIO-5), the guideline considers alternating electric treatment fields for glioblastoma after surgery, radiation, and chemotherapy (category 2B). The guideline recommends that follow-up MRI of the brain be done 2 to 8 weeks after RT, then every 2–4 months for three years, then every 3–6 months indefinitely. (NCCN, 2023)

NCCN clinical practice guidelines for Central Nervous System Cancers (2022) state that based on results of the open-label phase III EF-14 clinical trial, concurrent treatment with adjuvant TMZ and alternating electric fields is FDA approved and recommended for individuals with ndGBM 70 years of age or younger who have good PS. It should also be considered a reasonable treatment option for patients older than 70 years of age with good PS and ndGBM who are treated with standard focal brain radiation and concurrent daily TMZ (p. MS-16). Alternating electric field therapy is also FDA-approved for treating rGBM based on the safety results of this medical device from the EF-11 clinical trial. Due to a lack of clear efficacy data, the NCCN panel is divided about recommending it (p. MS-17). However, managing recurrent tumors depends on the extent of the disease and the person's condition. A panel discussion update was in progress at the time of the publication. (June 2022)

Currently, NCCN Category 1 recommendations for patients aged 70 years and younger with a good PS, regardless of the tumor's MGMT methylation status, include standard brain RT plus concurrent and adjuvant TMZ with or without alternating electric field therapy (p. MS-18). Category 1 treatment recommendations for patients older than 70 years of age with ndGBM, a good PS, and MGMT promoter methylated tumors include hypo-fractionated brain RT plus concurrent and adjuvant TMZ or standard brain RT plus concurrent and adjuvant TMZ and alternating electric field therapy. For those patients older than 70 years with ndGBM, a good PS, and with MGMT unmethylated or indeterminate tumors, hypo-fractionated brain radiation with concurrent and adjuvant TMZ is preferred, but standard brain RT plus concurrent and adjuvant TMZ and alternating electric field therapy is also a reasonable option for those elderly patients who want to be treated as aggressively as possible. (p. MS-19)

## **National Institute for Health and Care Excellence (NICE)**

According to the 2018 NICE guidelines titled 'Brain tumors (primary) and brain metastases in over 16s' for the Management of newly diagnosed grade IV glioma (glioblastoma) following surgery or if surgery is not possible (or has been declined), the guidelines state:

- Do not offer TTFeld as part of managing a newly diagnosed grade IV glioma (glioblastoma).

For the Management of recurrent high-grade glioma (recurrent grade III and grade IV glioma):  
When deciding on treatment options for people with recurrent high-grade glioma, take into account:

- Karnofsky performance status
- The person's preferences
- Time from last treatment
- Tumor molecular markers
- What their last treatment was

Additional recommendations include:

- Do not offer TTFeld as part of managing recurrent high-grade glioma (updated 2021)

## **U.S. Food and Drug Administration (FDA)**

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

The Optune Treatment Kit, formerly the NovoTTF-100A System (Novocure) was approved by the FDA in April 2011, as a novel device to treat adults aged 22 years or older with glioblastoma (GBM) that recurs or progresses after receiving chemotherapy and radiation therapy. The FDA categorizes the Optune as a stimulator, low electric field, tumor treatment; refer to the following website for the initial Premarket Approval information:

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P100034>. (Accessed May 14, 2024)

A supplemental FDA premarket approval was received in October 2015 for Optune with Temozolomide in adults with newly diagnosed, Supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy

together with concomitant standard of care chemotherapy. Refer to the following website for more information: <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P100034S013>. (Accessed May 14, 2024)

The FDA has approved a humanitarian device exemption (HDE) application for the NovoTTF™-100L System for mesothelioma. Refer to the following website for more information: [https://www.accessdata.fda.gov/cdrh\\_docs/pdf18/H180002B.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf18/H180002B.pdf). (Accessed May 14, 2024)

Refer to the following website for additional information on supplemental FDA approvals for the Optune using product code NZK: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm>. (Accessed May 14, 2024)

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The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by UnitedHealthcare Medical Technology Assessment Committee. [2024T0582M]

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## Policy History/Revision Information

Date	Summary of Changes
11/01/2024	<p><b>Coverage Rationale</b></p> <ul style="list-style-type: none"><li>Revised coverage criteria for:<ul style="list-style-type: none"><li>Use of U.S. Food and Drug Administration (FDA) approved devices to generate electric tumor treatment fields (TTF) for treating: <b><i>Newly Diagnosed Histologically Confirmed Supratentorial Glioblastoma (GBM)</i></b><ul style="list-style-type: none"><li>Added criterion requiring “debulking surgery has been completed”</li><li>Replaced criterion requiring “the individual has been counselled that the device must be worn at least 18 hours daily” with “the individual has been counselled that the <i>electric TTF</i> device must be worn at least 18 hours daily”</li></ul></li><li><b><i>Radiologically Confirmed Recurrence of GBM (rGBM) in the Supratentorial Region of the Brain</i></b></li></ul></li></ul>



Date	Summary of Changes
	<ul style="list-style-type: none"> <li>▪ Replaced criterion requiring “the individual has been counselled that the device must be worn at least 18 hours daily” with “the individual has been counselled that the <i>electric TTF</i> device must be worn at least 18 hours daily”</li> <li>○ Subsequent approval(s) for continuation of electric TTF beyond the initial 3 months for treatment of histologically confirmed Supratentorial GBM; replaced criterion requiring “documentation that the individual has been using the device at least 18 hours daily” with “documentation that the individual has been using the <i>electric TTF</i> device at least 18 hours daily”</li> </ul> <p><b>Definitions</b></p> <ul style="list-style-type: none"> <li>● Updated definition of: <ul style="list-style-type: none"> <li>○ Eastern Cooperative Oncology Group (ECOG) Scale of Performance Status</li> <li>○ Karnofsky Performance Status (KPS)</li> </ul> </li> </ul> <p><b>Supporting Information</b></p> <ul style="list-style-type: none"> <li>● Updated <i>Description of Services, Clinical Evidence, FDA, and References</i> sections to reflect the most current information</li> <li>● Archived previous policy version CANCER 039.13</li> </ul>

## Instructions for Use

This Clinical Policy provides assistance in interpreting UnitedHealthcare Oxford standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare Oxford reserves the right to modify its Policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice.

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