Molina Clinical Policy
Electric Tumor Treatment Fields for Glioblastoma: Policy No. 353
Last Approval: 12/11/2024
Next Review Due By: December 2025

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

Glioblastomas (glioblastoma multiforme, astrocytoma, or GBM) are rare, aggressive, complex, and treatment-resistant cancers, accounting for 50.1% of all primary malignant brain tumors (National Brain Tumor Society 2024). In 2023, an estimated 14,490 people in the United States were expected to be diagnosed with glioblastoma, with a median diagnosis age of 65 (National Brain Tumor Society, 2024). Although the risk of glioblastoma increases with age, incidence rates among older adults have remained steady over the past two decades. DynaMed (2024) reports, “The age-adjusted annual incidence is about 3 per 100,000 persons, with higher rates in persons ≥ 55 years old.” Approximately 10,000 people in the United States die annually due to glioblastomas (National Brain Tumor Society 2024). The 5-year survival rate for glioblastoma is approximately 6.9%, with an average survival time of only 8 months, which has remained stable for decades (National Brain Tumor Society 2024).

Glioblastomas are classified on a scale from I to IV based on their growth rate, with grade I representing slow growth and grade IV indicating aggressive, rapid growth. Glioblastomas commonly emerge directly as grade IV tumors rather than progressing through earlier stages (NORD 2023). Symptoms include headaches, seizures, confusion, memory loss, muscle weakness, visual changes, language deficits, and cognitive changes. Treatment options include a combination of surgery, chemotherapy, radiation therapy, and alternating electric field therapy (NORD 2023). The standard of care for newly diagnosed patients with glioblastoma is debulking surgery followed by combination chemotherapy using temozolomide and radiation therapy. Essentially all newly diagnosed patients relapse despite the best available treatment (median time to recurrence of approximately 7 months). At the time of recurrence, treatment options for patients are limited with chemotherapy being indicated for the majority of patients and approximately 20% of patients may undergo repeat surgery ([1-3]Batchelor 2024).

Electric tumor treatment fields, also known as alternating electric field therapy and tumor treatment field therapy (TTFT), are a non-invasive cancer treatment that is delivers low-intensity (1–3 V/cm) and intermediate-frequency (100–300 kHz) alternating electric fields through cutaneous transducer arrays that are configured to provide optimal tumor-site coverage (Rominiyi et al. 2021). This therapy is administered using Novocure (Optune™ or NovoTFF-100A System), which emits alternating electric fields to disrupt the rapid cell division characteristic of cancer cells. Novocure has been approved for use in patients with recurrent glioblastoma or as a concomitant treatment with temozolomide in patients with newly diagnosed glioblastoma. The Optune™ system is intended to treat patients with glioblastoma by using transducer arrays placed on the patient’s scalp according to the tumor’s location. Patients use the device on an outpatient basis, wearing it for at least 18 hours per day over periods ranging from 4 weeks to several months. Intended benefits include stabilizing the disease, having fewer treatment-related adverse events, and improving quality of life (Optune 2023, 2019).

Regulatory Status
The NovoTTF-100A device received premarket approval from the Food and Drug Administration (FDA) on April 8, 2011, as a Class 3 device under Product Code NZK for the treatment of patients with recurrent glioblastoma multiforme (FDA 2011). Approval was extended to patients with newly diagnosed glioblastoma in combination with emozolomide in 2015 (FDA 2015). The NovoTTF-100A device received an FDA-approved name change to the Optune on September 28, 2014 (FDA 2014). A subsequent FDA-approved name change to the Optune Gio was approved on August 14, 2023 (FDA 2023).

COVERAGE POLICY

Electric Tumor Treatment Field (ETTF) Therapy when used according to FDA labeled indications, contraindications, warnings, and precautions, may be **considered medically necessary** for an initial 90-day therapy when **ALL** the following criteria are met:

1. Member is age 22 years or older
2. Member has histologically confirmed supratentorial glioblastoma (World Health Organization grade IV astrocytoma)
3. Member has completed all applicable treatments such as debulking surgery, standard chemotherapy, and/or radiation therapy
4. Member meets ONE of the following indications:
   a. For newly diagnosed glioblastoma: Temozolomide is the only cancer drug being received concurrently with ETTF therapy
   b. For recurrent glioblastoma: ETTF therapy is the only therapy being administered
5. Karnofsky Performance Score of ≥ 60 or Eastern Cooperative Oncology Group Performance Status ≤ 2
6. Member can adhere to therapy that includes treatment to be provided by a trained individual or caregiver that can apply the device daily and Member is willing to wear the device at least 18 hours per day
7. Member is free from **ALL** the following contraindications:
   a. Cardiac pacemaker or implantable defibrillator
   b. Deep brain, spinal cord, or vagus nerve stimulator
   c. Major skull defect (e.g., missing section of calvarium)
   d. Metal within brain (e.g., aneurysm clip, bullet fragment)
   e. Programmable ventriculoperitoneal shunt
   f. Pregnancy
   g. Known sensitivity to conductive hydrogels (e.g., gels used on electrocardiogram stickers or transcutaneous electrical nerve stimulation electrodes)

Electric Tumor Treatment Field (ETTF) Therapy when used according to FDA labeled indications, contraindications, warnings, and precautions, may be **considered medically necessary** beyond the initial 90-day approval when **ALL** the following criteria are met:

1. Member continues to meet ALL the above criteria
2. Documentation of a completed clinical re-evaluation affirming continued therapy will be beneficial
3. Magnetic resonance imaging scan performed two (2) to four (4) months prior to request confirming no evidence of disease progression
4. Documentation indicating that the Member has been using the device ≥ 18 hours a day

Limitations and Exclusions

Electric tumor treatment field therapy is considered **experimental, investigational, and unproven** due to a lack of evidence for any indication not listed above. *This policy only applies to the use of tumor treatment field therapy for glioblastoma. For other indications, please refer to the utilization management review hierarchy.*

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is

not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

The body of evidence is sufficient to determine that electric tumor treatment field therapy (ETTF) in patients with newly diagnosed glioblastoma demonstrates a health benefit. Clinical trials have shown that ETTF with temozolomide have a median overall survival that is longer than temozolomide alone. Medical literature for ETTF is insufficient to determine net health benefits in recurrent glioblastoma. Evidence is limited to small and individual studies with serious limitations, including lack of a control or comparator group, high loss to follow-up, and lack of statistical comparisons. Randomized controlled trials and cohort studies of sufficient size and design are needed to further investigate the safety and efficacy of ETTF in patients with recurrent glioblastoma.

Systematic Reviews and Meta-Analyses

Ballo et al. (2023) completed a meta-analysis and systematic review to determine "whether a constant survival benefit has been observed in the real-world setting, and whether device usage has played a role." Researchers included studies that evaluated overall survival in patients with newly diagnosed glioblastoma treated with ETTF. A total of seven studies comparing ETTF in addition to chemoradiotherapy (standard of care) to chemoradiotherapy alone were included in the pooled analysis. The seven studies included a total of 1430 patients with 748 treated with ETTF and chemoradiotherapy and 682 treated with chemoradiotherapy alone. The median age of those treated with ETTF and chemoradiotherapy ranged from 48-61 years compared to 48-65 years for those treated with chemoradiotherapy alone. Maximum age ranges were 63-81 for those treated with ETTF and chemoradiotherapy compared to 75-83 years for those treated with chemoradiotherapy alone. Pooled results for overall survival were reported as percentages at two-years and four-years. In addition, the median overall survival was reported in number of months. The overall survival rates for those treated with ETTF and chemoradiotherapy were 46.8% at 2-years and 22.7% at 4-years compared to 32.3% at 2-years and 8.0% at 4-years for those treated with chemoradiotherapy alone. Median overall survival was 22.6 months for ETTF combined with chemoradiotherapy and 17.4 months for chemoradiotherapy alone. Researchers noted that improved survival rates were noted in the ETTF with chemoradiotherapy group when the average device usage was ≥ 75% ($p < 0.001$).

Shah et al. (2020) conducted a systematic review that evaluated prior studies on the efficacy of ETTF in patients with high-grade gliomas. A total of 852 studies conducted through February 2019 were initially reviewed for inclusion however, nine were included in the final review (two pilot clinical trials, two randomized clinical trials, and five retrospective studies). There were 1191 patients identified who received ETTF. Increased survival was noted among newly diagnosed glioblastoma patients however, this increase was not noted for recurrent glioblastoma patients.

Non-Randomized Studies, Retrospective Reviews, and Other Evidence

Rominiyi et al. (2021) reviewed the mechanisms by which ETTF mediates anticancer effects. There is minimal research on the pediatric population with respect to the use of chemotherapy and radiotherapy. Research shows that ETTF shows a broad mechanism of action by interrupting a multitude of biological processes (DNA repair, cell permeability and immunological responses, to elicit therapeutic effects). Efficacy was also found in pediatric patients diagnosed with glioblastoma. One study demonstrated that ETTF were tolerable in five pediatric patients with high-grade glioma between the ages 10-20. Three studies demonstrated partial responses when ETTF was paired with chemotherapy and/or radiation. For adults with newly diagnosed glioblastoma, improvements lead to an expected survival of under two years.

Ghiaseddin et al. (2020) reported on the efficacy and tolerance of ETTF in patients with glioblastoma that were studied in two large phase 3 trials. Adherence was reported 75% of the time despite the need for patients to regularly shave their head. Increased survival corresponded with level of usage.

Toms et al. (2019) analyzed compliance data from ETTF and temozolomide patients in a subgroup analysis of the phase 3 EF-14 trial by Stupp et al. (2017). The aim was to correlate ETTF compliance with progression free survival, overall survival, and to identify potential lower boundary for compliance with improved clinical outcomes. Compliance was assessed by usage data from the NovoTTF-100A device and calculated as percentage per month of ETTF delivery. ETTF/temozolomide patients 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 progression free survival and overall survival. A threshold value of 50% compliance with ETTF/temozolomide improved progression free survival and overall survival versus temozolomide alone with improved outcome as compliance increased. With a compliance of >90%, median survival was 24.9 months (28.7 months from diagnosis); the five-year survival rate was 29.3%. In conclusion, a compliance threshold of 50% with ETTF/temozolomide correlated with significantly improved outcome survival and progression free survival versus temozolomide alone. Hence, the evidence supports that the use of ETTF in recurrent GBM is associated with improved overall survival when used consistently with a trend towards higher levels of survival associated with increasing compliance.

Tophoorn et al. (2018) completed a secondary analysis of the Stupp et al. (2017) trial with the goal of examining the association of ETTF with progression-free survival and health-related quality of life among patients with glioblastoma. Of the 695 patients in the study, 639 (92%) completed the baseline health-related quality of life questionnaire. Of these, 437 (68%) were men; mean age was 54.8 (11.5) years. The health-related quality of life did not differ significantly between treatment arms except for itchy skin. Deterioration-free survival was significantly longer with ETTF for global health (4.8 vs 3.3 months); physical (5.1 vs 3.7 months) and emotional functioning (5.3 vs 3.9 months); pain (5.6 vs 3.6 months); and leg weakness (5.6 vs 3.9 months). These are related to improved progression-free survival. Time to deterioration (reflecting the influence of treatment) did not differ significantly except for itchy skin (ETTF worse; 8.2 vs 14.4 months) and pain (ETTF improved; 13.4 vs 12.1 months). Role, social, and physical functioning were not affected by ETTF. The addition of ETTF to standard treatment with temozolomide for patients with glioblastoma resulted in improved survival without a negative influence on health-related quality of life except for increased itchy skin, an expected consequence from the transducer arrays.

National and Specialty Organizations

The **National Comprehensive Cancer Network (NCCN)** (2024) has published a clinical practice guideline related to cancers of the central nervous system. Each treatment pathway is based on the World Health Organization (WHO) grading system for each type of central nervous system tumor, the calculated Karnofsky Performance Score, and patient age (for select cancers). The NCCN recommends enrolling eligible patients into clinical trials as the first step for most treatment pathways. Treatment recommendations for brain tumors include surgical resection (if feasible), radiation therapy, and/or chemotherapy as treatment options. In addition, the NCCN makes the following recommendations regarding the use of ETTF:

- The NCCN denotes ETTF "is only an option for patients with supratentorial disease" for all treatment options that include ETTF.
- **WHO grade 4s IDH-mutant astrocytoma**: ETTF with temozolomide can be considered as a concurrent or adjuvant therapy to standard radiotherapy for patients with a good performance score (Karnofsky Performance Score ≥ 60) (category 2A recommendation).
- **Methylated, indeterminate, or unmethylated glioblastoma and age ≤ 70 years**: Standard radiotherapy with concurrent temozolomide and adjuvant temozolomide with ETTF can be considered as a treatment option for patients with a good performance score (Karnofsky Performance Score ≥ 60) (category 1 recommendation). The NCCN denotes that the "combination of modalities may lead to increased toxicity or radiographic changes." The NCCN also notes this is the preferred treatment pathway for this patient population.
- **Methylated, indeterminate, or unmethylated glioblastoma and age > 70 years**: Standard radiotherapy with concurrent temozolomide and adjuvant temozolomide with ETTF can be considered as a treatment option for patients with a good performance score (Karnofsky Performance Score ≥ 60) who wish to be treated as aggressively as possible (category 1 recommendation). The NCCN denotes that the "combination of modalities may lead to increased toxicity or radiographic changes." The NCCN places preference on enrollment in clinical trials for eligible patients in this patient population.
- **Recurrent or progressive glioblastoma**: ETTF may be considered for glioblastoma (diffuse/multiple or local) (category 2B recommendation). Preference is given to participation in a clinical trial or resection prior to ETTF if a local recurrence is resectable.

The **American Society of Clinical Oncology (ASCO)** and the **Society for Neuro-Oncology (SNO)** published guidelines for therapies for diffuse astrocytic and oligodendroglial tumors in adults (Mohile et al. 2022). The guidelines recommend that ETTF "may be added to adjuvant [temozolomide] in people with newly diagnosed supratentorial glioblastoma, IDH-wildtype, [central nervous system] WHO grade 4 who have completed chemoradiation therapy." The recommendation is based on a "moderate" quality of evidence with a "weak" strength of recommendation.

The **Congress of Neurological Surgeons (CNS)** published guidelines for the role of cytotoxic chemotherapy and other therapies in the management of *progressive* glioblastoma in adults (Germano et al. 2022). The guidelines state that ETTF may be considered when used in conjunction with chemotherapy. However, "there is insufficient evidence to recommend [ETTF] to increase overall survival in adult patients with [progressive glioblastoma]." The recommendation is graded as level III.

The **Congress of Neurological Surgeons (CNS)** also published guidelines for the role of "emerging developments" in the management of *newly diagnosed* glioblastoma (Farrell et al. 2020). The guidelines state "the use of [ETTF] is recommended for patients with newly diagnosed glioblastoma who have undergone debulking and completed concurrent chemoradiation without progression of disease at the time of [ETTF] initiation." The recommendation is graded as level II.

SUPPLEMENTAL INFORMATION

Definitions (NCI date unknown):

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.

Response Assessment in Neuro-Oncology (RANO): Progression criteria is defined as ≥ 25% increase in enhancing disease or worsening neurologic status in the setting of stable or increasing steroid use.

Supratentorial: The upper portion of the brain comprised of the cerebrum, ventricles, choroid plexus, hypothalamus, pineal gland, pituitary gland, and optic nerve. Examples of tumors that form in the supratentorium are glioblastomas, pineal region tumors, and ependymomas.

Temozolomide: Also called Temodar. An oral alkylating chemotherapy drug used in the treatment of some brain cancers and is considered a first-line treatment for glioblastoma.

CODING & BILLING INFORMATION

NOTE: CMS does not have a National Coverage Determination (NCD) for electric tumor treatment field therapy however, there is a Local Coverage Determination (LCD) (L34823) for Tumor Treatment Field Therapy (TTFT). Effective 10/1/2015; revision effective date 1/1/2020.

CPT (Current Procedural Terminology)

Code	Description
77299	Unlisted procedure, therapeutic radiology clinical treatment planning [when specified as plan for Electric Tumor Treatment Field Therapy for Glioblastoma]

HCPCS (Healthcare Common Procedure Coding System)

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

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

12/11/2024	Policy reviewed. Coverage criteria updated to clarify temozolomide treatment criteria, continuation criteria updated and revised. IRO peer reviewed on December 5, 2024, by a practicing physician board certified in Internal Medicine, Medical Oncology.
02/14/2024	Policy reviewed, no changes to criteria. Updated Overview, Summary of Medical Evidence, and References. IRO Peer Review on January 31, 2024, by a practicing, board-certified physician with a specialty in Medical Oncology.
02/08/2023	Policy reviewed, no changes to criteria, updated references.
02/09/2022	Policy reviewed; TTF now covered for recurrent glioblastoma; updated Summary of Medical Evidence and Reference sections.
02/08/2021	Policy reviewed, no changes to criteria.
04/23/2020	New policy. IRO Peer Review in January 2020 by a practicing, board-certified neurologist.

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