Tumor Treatment Field Therapy for Glioblastoma

MEDICAL POLICY NUMBER: 173

Effective Date: 8/1/2022
Last Review Date: 7/2022
Next Annual Review: 7/2023

INSTRUCTIONS FOR USE: Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Company reserves the right to determine the application of medical policies and make revisions to medical policies at any time. The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement. Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

SCOPE: Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

PLAN PRODUCT AND BENEFIT APPLICATION

☒ **Commercial** ☒ **Medicaid/OHP*** ☐ **Medicare****

*Medicaid/OHP Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

**Medicare Members

This *Company* policy may be applied to Medicare Plan members only when directed by a separate *Medicare* policy. Note that investigational services are considered **"not medically necessary"** for Medicare members.

COVERAGE CRITERIA

Newly Diagnosed Glioblastoma

Initial 3-month TTF Trial

I. An initial 3-month trial of tumor treatment field (TTF) therapy may be considered **medically necessary** as a treatment of newly diagnosed glioblastoma multiforme when **all** of the following criteria are met (A.-E.):

   A. Glioblastoma is located in the supratentorial region; **and**
   B. Karnofsky performance scale (KPS) of 60% or greater **or** the Eastern Cooperative Oncology Group (ECOG) performance scale of 2 or lower; **and**
   C. TTF therapy is administered after chemotherapy and radiation therapy; **and**
   D. TTF therapy is administered concurrently with temozolomide (TMZ); **and**
   E. None of the following contraindications are present (1.-6.):
      1. Active implanted medical device; **or**
      2. Bullet fragments; **or**
      3. Pregnancy; **or**
      4. Shunts; **or**
      5. Skull defects; **or**
      6. Treatment of other tumors

II. An initial 3-month trial of tumor treatment field therapy is considered **not medically necessary and not covered** when criterion I. is not met.

Continuation of TTF

III. Subsequent use (> 3-months) of tumor treatment field (TTF) therapy may be considered **medically necessary** as a treatment of newly diagnosed glioblastoma multiforme when **all** of the following criteria are met (A.-E.):

A. Initial TTF trial criteria I.A-E above have been met; **and**
B. Current Karnofsky performance scale (KPS) of 60% or greater **or** the Eastern Cooperative Oncology Group (ECOG) performance scale of 2 or lower; **and**
C. Magnetic resonance imaging (MRI) is performed every 2-4 months and demonstrates no disease progression; **and**
D. Clinical documentation indicates the TTF device has been applied daily; **and**
E. Clinical documentation indicates the TTF device has been worn a minimum of 18 hours daily.

IV. Subsequent use of (> 3-months) of tumor treatment field therapy is **considered not medically necessary and not covered** when criterion III. is not met.

Recurrent Glioblastoma

V. Tumor treatment field (TTF) therapy is considered **investigational and not covered** when the above criteria are not met, including, but not limited to TTF therapy as a treatment of recurrent glioblastoma multiforme.

Link to Evidence Summary

POLICY CROSS REFERENCES

None

- Policy Title with hyperlink, MPXXX
- Policy Title with hyperlink, MPXXX
- Policy Title with hyperlink, MPXXX

The full Company portfolio of current Medical Policies is available online and can be accessed here.

POLICY GUIDELINES

BACKGROUND

Glioblastoma

According to Hayes, "Glioblastoma (GBM) is a fast-growing glioma that develops from glial cells in the brain. GBM is the most prevalent and malignant intracranial tumor, representing as m!uch as 30% of

primary brain tumors."[1] The annual incidence of glioblastoma is approximately 2 to 3 new cases per 100,000 people. Although glioblastomas occur in individuals in every age group, they are more prevalent in people between 45 and 70 years of age and the overall prognosis is poor, even with the best standard of care. Hayes reports that with, "optimal treatment, the median survival time is approximately 10 to 14 months. Only a third of patients survive for 1 year following diagnosis of GBM, and < 5% live beyond 5 years. Patients with recurrent GBM have a median survival time of just 5 to 7 months.[1,2]

Treatment

According to Hayes, "The current standard of care for newly diagnosed GBM patients is debulking surgery, followed by combination chemotherapy using temozolomide (TMZ) and radiation therapy. Virtually all patients with newly diagnosed GBM relapse despite best available treatment, with a median time to recurrence of approximately 7 months. At the time of disease recurrence, treatment options for GBM patients are limited. Approximately 20% of patients may undergo repeat surgery. Carmustine polymer wafers may be placed intraoperatively in the surgical cavity during repeat surgery. Rarely, patients may undergo reirradiation. For the majority of recurrent GBM patients, chemotherapy is indicated. In the United States, combination treatment with chemotherapy and the angiogenesis inhibitor bevacizumab has been approved for recurrent GBM and certain other cancers. However, approximately 40% to 60% of recurrent GBM patients are either unresponsive to bevacizumab or experience serious adverse events following treatment."[1]

Tumor Treatment Fields Therapy

Tumor treatment fields (TTF) therapy (also referred to as Optune, Novocure, or NovoTFF-100A System) has been proposed as a stand-alone treatment of recurrent glioblastoma and as a concomitant treatment with temozolomide (TMZ) therapy in patients with newly diagnosed glioblastoma. TTF therapy is a non-invasive portable device which delivers low-intensity alternating electrical fields to the brain via electrodes applied to the scalp. Cancer cells are exposed to the electrical fields at intermediate frequency which is purported to inhibit cancer cell division and cancer progression. Patients are to use the device on an outpatient basis by placing transducers on a shaved scalp for a minimum of 18 hours a day for 4 weeks to several months.[2]

PERFORMANCE SCALES

Table 1: Karnofsky Performance Scale (KPS)

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS	RATING (%)	CRITERIA[3]
Able to carry on normal activity and to work; no special care needed.	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.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
	40	Disabled; requires special care and assistance.

Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Table 1: Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	ECOG PERFORMANCE STATUS[4]
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 house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

REGULATORY STATUS

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Approval or clearance by the Food and Drug Administration (FDA) does not in itself establish medical necessity or serve as a basis for coverage. Therefore, this section is provided for informational purposes only.

In 2011, the Optune System (previously known as the NovoTTF-100A System) by Novocure was granted FDA approved through premarket approval (PMA). The Optune System was indicated as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune is approved for the treatment of recurrent glioblastoma multiforme (GBM) following histologically-or radiologically-confirmed recurrence in the supra-tentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.[5]

In 2015, Optune with temozolomide was approved as indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.[5]

CLINICAL EVIDENCE AND LITERATURE REVIEW

EVIDENCE REVIEW

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of TTF therapy for patients with new and recurrent glioblastoma. Below is a summary of the available evidence identified through June 2022:

Systematic Reviews

- In 2021 Regev and colleagues completed a systematic review and meta-analysis on Tumor-Treating Fields for the treatment of glioblastoma.[6] Twenty studies, incorporating 2 randomized control trial, 5 prospective single-arm clinical trials, 1 prospective observational study, 2 registry-based studies, 3 retrospective studies, 1 case series, and 3 post hoc analyses. Additionally, three conference presentations that have not yet been published in peer-reviewed journals were included due to the importance of their findings. This included a total of 1,636 patients analyzed for clinical outcomes and 11,558 patients analyzed for safety endpoints. Patients had an improved overall survival with the addition of tumor treatment fields therapy when compared to control group at 20.9 vs 16.0 months respectively. Efficacy of clinical significance was harder to distinguish with recurrent glioblastoma patients, hindered also by earlier stage of disease follow-up between different studies influencing overall survival. However, a consistent prolonged median overall survival of up to 2 months was noted when compared to control groups. A review of safety analysis yielded no known systemic toxicity noted. The main adverse event was mild to moderate dermatitis, which occurred in 38.4% of patients. No unexpected safety issues on concomitant use of ventricular shunts or implanted cardiac devices were shown, although the authors recommend that this trend be cautiously considered under further validation is performed.

- In 2020, Shah and colleagues published a systematic review of tumor treating fields for high-grade gliomas.[7] The review included 9 studies, totalling 1191 patients who received TTF. Two studies were pilot clinical trials, 2 were randomized clinical trials, and 5 were retrospective studies. Only randomized data were analyzed, and the authors found that TTF improved survival for newly diagnosed glioblastoma patients but not for recurrent glioblastoma patients. Both randomized trials are detailed below. This systematic review has a number of limitations, the greatest limitation being that only 2 studies were analyzed and each looked at a different patient group. Therefore, this publication acts as a literature review, and cannot be used to draw any conclusions about efficacy of TTF across trials. The authors concluded that further investigation is needed on TTF as a treatment for glioblastoma.

- In 2018, the Washington State Health Care Authority conducted a systematic review evaluating the safety, efficacy and cost of tumor treating fields (TTFs) for the treatment of glioblastomas (GBM).[8] Independent investigators systematically searched the literature through May 2018, identified eligible studies, assessed study quality and extracted data. Outcomes of interest included overall survival (OS), progression-free survival (PFS), quality of life (QOL), functional status and safety outcomes. In total, 15 articles published on the basis of 11 primary research studies were included for review. Six studies (2 RCTs and 4 observational studies) provided evidence on efficacy, whereas an additional 10 provided evidence on safety. One cost-efficacy study was also included. Same sizes ranged from 42 to 1,446. Overall quality of evidence ranged from “very low” to “low.” Despite positive results across outcomes over a median follow-up of 40 months, validity was limited by the small quantity low quality of studies (e.g. small sample sizes, lack of blinding, selection bias, attrition, poor treatment adherence, heterogeneous

results). Investigators concluded with "very low to low certainty" that the addition of TTF to usual care with TMZ increases OS and PFS among patients with newly-diagnosed glioblastoma.

- In 2016 (updated 2020), Hayes conducted a systematic review of evidence regarding the use of the tumor treating fields (TTF) (Optune) system for patients with recurrent glioblastoma and as a concomitant treatment with temozolomide (TMZ) therapy in patients with newly diagnosed glioblastoma.[1] Searching the literature through November 2019, a total of 7 studies were identified and included for review (2 studies for newly diagnosed glioblastoma and 5 with recurrent glioblastoma). Sample sizes ranged from 10 to 695 patients, and follow-up periods varied from 2.5-4 months. Outcomes of interest included overall survival, progression-free survival, tumor response to treatment, quality of life and safety. The Hayes assessment found that a small and low quality body of evidence suggested that in patients with recurrent and newly diagnosed glioblastoma, TTF was comparable with chemotherapy in increases in overall survival (OS) and progression free survival (PFS). Hayes assigned a "C" rating (potential but unproven benefit) for TTF monotherapy in adult patients (22 years of age and older) with recurrent glioblastoma (GBM) following surgery and radiotherapy; and a "C" rating for TTF treatment with concomitant temozolomide in adult patients (22 years of age and older) with newly diagnosed GBM following surgery and radiation therapy with concomitant chemotherapy. These ratings reflect positive but low-quality evidence from 2 randomized controlled trials and 1 very-poor-quality cohort study suggesting that TTF is more effective than chemotherapy in his patient population. The Rating also reflects the very small quantity of data available for this indication." The low rating assigned for newly diagnosed GBM (D2), was primarily based on an overall lack of studies (2 studies considered) available compared to recurrent GBM (5 studies considered). Evidence was judged insufficient to establish patient selection criteria.

<u>Randomized Controlled Trials</u>

Newly Diagnosed GBM

- In 2018, Taphoorn and colleagues conducted a secondary analysis of EF-14 (Stupp et al. 2017)[9], measuring health-related quality of life outcomes for patients with newly diagnosed glioblastoma.[10] Researchers found statistically longer deterioration-free survival for TTF/TMZ patients compared to the TMZ group for global health status, physical and emotional functioning, pain and leg weakness. Excluding progressive disease as an event, TTF/TMZ group outcomes were only statistically improved for pain, and significantly worsened for itchy skin.[10]

- In 2017, Stupp et al., published final findings from the above trials.[9] Reported outcomes were progression-free survival and overall survival. The TTF/TMZ group showed statistically significant improvements compared to the TMZ only treatment group in both median progression-free survival (6.7 months vs.4.0 months; HR, 0.63; 95% CI, 0.52-0.76; P < .001) and median overall survival (20.9 months vs. 16.0 months; HR, 0.63 95% CI, 0.53-0.76; P<.001).

- In 2015, Stupp et al., published interim findings from their randomized controlled trial (RCT) comparing TTF (Optune, Novocure Ltd.) therapy used in combination with temozolomide (TMZ) versus TMZ alone as maintenance therapy in patients with newly diagnosed GBM after chemoradiation therapy.[11] Patients were randomized to TTF/TMZ (n=466) or TMZ only (n=229) and were required to be 18 years or older, with confirmed supratentorial GBM, Karnofsky

Performance Status (KPS) score of ≥ 70%, and be progression-free after de-bulking surgery or biopsy and chemoradiation with concurrent TMZ. Patients receiving TTF had 4 transducer arrays placed on a shaved scalp which connected to a portable device set to 200-kHz. Transducer layout was determined using proprietary mapping software system for TTF to optimize intensity of treatment (NovoTAL, Novocure Ltd). Patients were not blinded due to ethical concerns. Magnetic resonance imaging (MRI) was performed every other month after initial baseline MRI to monitor for disease progression. The study enrolled a total of 695 patients across 83 centers; however, the study was terminated early due to results of an interim analysis which demonstrated the TTF/TMZ group experienced a 3 month improvement in PFS and 5 month improvement in OS compared to the TMZ only group. A total of 315 subjects (n = 210 TTF/TMZ vs. 105 TMZ only) were enrolled at the interim analysis. At 2-year follow-up, 43% of TTF/TMZ group were alive compared to 29% in the TMZ only group (p = .006).

Recurrent GBM

- In 2017, Kesari et al. published a *post-hoc* analysis of the Stupp et al. RCT, examining TFF when added to second-line treatment after first disease recurrence among patients.[12] One hundred thirty-one patients with recurrence from both the original TTF/TMZ and TMZ-only groups received TTF plus chemotherapy (Bevacizumab alone or with cytotoxic chemotherapy) versus chemotherapy alone. Median overall survival was significantly longer in TTF/chemotherapy versus chemotherapy alone (11.8 months vs.9.2 months; HR 0.70; 95%CI, 0.48-1; P=0.049). Limitations include the *post-hoc* nature of the analysis and some cross-over from patients who did not receive TTF as initial therapy (13 out of 131).

- In 2012, Stupp and colleagues published an RCT which compared TTF therapy to the best standard of care chemotherapy in 237 patients with recurrent GBM. [13] Patients were randomized in a 1:1 fashion with 120 patients randomized to the TTF group and 117 patients randomized to the active control group. A variety of failed therapies were employed in the active control group, including bevacizumab and 80% of subjects in this group had previously failed 2 or more regimens. The primary end-point was OS and secondary end-points included PFS at 6 months and total time to progression (TTP), 1 year survival rate, quality of life (QOL), and radiological response. Limitations of this study include a loss of participants in the TTF group (n=27, 22%) due to noncompliance or device usability issues. No significant differences were observed in the established primary end point of OS. At a median follow-up of 39 months 220 (93%) of the participants had died with a 0.6 month difference in median survival between groups (6.6 months in the TTF group vs. 6.0 months in the active control group; p=0.27). In addition, no significant differences were observed in PFS (at 6 month follow-up: 21.4% in the TTF group vs. 15.1% in the active control group; p=0.13) or in 2- or 3- year survival rates (8% and 4% in the TTF group vs. 5% and 1% in the active control group).

<u>Nonrandomized Trials</u>

Non-randomized registry and retrospective studies have been published which suggest TTF may improve OS rates in patients with recurrent GBM; however, these studies are limited by a lack of randomization and comparison to standard treatments.[14-19]

CLINICAL PRACTICE GUIDELINES

National Comprehensive Cancer Network (NCCN)

The NCCN (1.2022) clinical practice guidelines addressing Central Nervous System Cancers state that alternating electric field therapy may be considered in the following circumstances:[20]

Primary GBM
(category 1 recommendation)

- Good performance status (KPS ≥ 60); and
- MGMT promotor status
  - In patients ≤ 70 years with methylated MGMT promotor status; or
  - In patients > 70 years with methylated, unmethylated, or indeterminate MGMT promotor status; and
    - In conjunction with standard radiation therapy and concurrent and adjuvant temozolomide (TMZ)

Recurrent GBM
(2B recommendation: based on non-uniform panel consensus)

- Diffuse or multiple recurrence; or
- Local, resectable or unresectable (or resection not recommended/elected) recurrence

The guideline stated that the panel was divided about recommending alternating electric field therapy for the treatment of recurrent glioblastoma due to the lack of clear efficacy data.

National Institute for Health and Care Excellence (NICE)

In July 2018 (updated January 2021), NICE published guidelines regarding brain tumors (primary) and brain metastases in adults. Having reviewed the evidence for both primary and recurrent GBM treatment, the panel concluded that TTF improvements in OS and PFS were not sufficient to justify the therapy's additional cost.[21]

The NICE guidelines state:

"Do not offer tumour-treating fields (TTF) as part of management of a newly diagnosed grade IV glioma (glioblastoma)."
"Do not offer tumour treating fields (TTF) as part of management of recurrent high-grade glioma."[21]

EVIDENCE SUMMARY

Low-quality but consistent evidence indicates that tumor treating fields are a safe and effective therapy for the treatment of patients with newly diagnosed and glioblastoma. Rates of overall survival, progression-free survival and quality of life are at least comparable to chemotherapy at median follow-up of 40 months. Additional RCTs with larger sample sizes and longer follow-up are necessary to isolate the effect of TTF therapy in patients with recurrent GBM and to definitively establish patient selection criteria. The NCCN supports the use of TTF for the treatment of newly-diagnosed glioblastoma when

used in conjunction with standard radiation therapy and adjuvant temozolomide, but remains divided in its recommendation of TTF for the treatment of recurrent glioblastoma.

There is insufficient evidence to support the use of TTF for recurrent glioblastoma multiforme. Further studies of good methodological quality are required to establish safety and efficacy of TTF over standard treatment in this population. Clinical guidelines either do not recommend TTF for recurrent glioblastoma, or, in the case of NCCN, remain divided in recommending the treatment. Therefore, TTF for recurrent glioblastoma multiforme is considered investigational.

BILLING GUIDELINES AND CODING

Prior-Authorization is required for initial TTF therapy and then every 3-months after initial therapy.

CODES*		
HCPCS	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 Notes:**

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

REFERENCES

1. Hayes Inc. Tumor Treating Fields (Optune) for Treatment of Glioblastoma. https://evidence.hayesinc.com/report/dir.novocure3306#home. Published 2019. Accessed 6/20/2022.
2. ECRI Institute. Tumor Treating Fields Therapy (Optune) for Recurrent Glioblastoma. https://www.ecri.org/components/ProductBriefs/Pages/26741.aspx?tab=1. Published 2019. Accessed 6/20/2022.
3. National Palliative Care Research Center. Karnofsky Performance Scale Index. http://www.npcrc.org/files/news/karnofsky_performance_scale.pdf. Accessed 6/20/2022.
4. ECOG-ACRIN Cancer Research Group. ECOG Performance Status. https://ecog-acrin.org/resources/ecog-performance-status. Published 2020. Accessed 6/20/2022.

5. Food and Drug Administration. Premarket Approval (PMA). Optune System. Updated 3/9/2021. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P100034S013. Accessed 6/20/2022.
6. Regev O, Merkin V, Blumenthal DT, Melamed I, Kaisman-Elbaz T. Tumor-Treating Fields for the treatment of glioblastoma: a systematic review and meta-analysis. *Neuro-Oncology Practice.* 2021;8(4):426-440.
7. Shah PP, White T, Khalafallah AM, Romo CG, Price C, Mukherjee D. A systematic review of tumor treating fields therapy for high-grade gliomas. *Journal of Neuro-Oncology.* 2020;148(3):433-443.
8. Washington State Health Care Authority. Tumor treating fields, (Optune) - re-review: Final evidence report. https://www.hca.wa.gov/assets/program/tumor-treating-fields-final-report-20181016.pdf. Published 2018. Accessed 6/20/2022.
9. Stupp R, Taillibert S, Kanner A, et al. Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma: A Randomized Clinical Trial. *JAMA.* 2017;318(23):2306-2316.
10. Taphoorn MJB, Dirven L, Kanner AA, et al. Influence of Treatment With Tumor-Treating Fields on Health-Related Quality of Life of Patients With Newly Diagnosed Glioblastoma: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Oncology.* 2018;4(4):495-504.
11. Stupp R, Taillibert S, Kanner AA, et al. Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma: A Randomized Clinical Trial. *JAMA.* 2015;314(23):2535-2543.
12. Kesari S, Ram Z, Investigators E-T. Tumor-treating fields plus chemotherapy versus chemotherapy alone for glioblastoma at first recurrence: a post hoc analysis of the EF-14 trial. *CNS oncology.* 2017;6(3):185-193.
13. Stupp R, Wong ET, Kanner AA, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. *European journal of cancer.* 2012;48(14):2192-2202.
14. Mrugala MM, Engelhard HH, Tran DD, et al. Clinical practice experience with NovoTTF-100A™ system for glioblastoma: the Patient Registry Dataset (PRiDe). Paper presented at: Seminars in oncology2014.
15. Rulseh AM, Keller J, Klener J, et al. Long-term survival of patients suffering from glioblastoma multiforme treated with tumor-treating fields. *World journal of surgical oncology.* 2012;10(1):220.
16. Villano JL, Williams LE, Watson KS, et al. Delayed response and survival from NovoTTF-100A in recurrent GBM. *Medical Oncology.* 2013;30(1):338.
17. Wong ET, Lok E, Swanson KD, et al. Response assessment of NovoTTF-100A versus best physician's choice chemotherapy in recurrent glioblastoma. *Cancer medicine.* 2014;3(3):592-602.
18. LIU Y, STRAWDERMAN MS, WARREN KT, et al. Clinical Efficacy of Tumor Treating Fields for Newly Diagnosed Glioblastoma. *Anticancer Research.* 2020;40(10):5801-5806.
19. Bokstein F, Blumenthal D, Limon D, Harosh CB, Ram Z, Grossman R. Concurrent Tumor Treating Fields (TTFields) and Radiation Therapy for Newly Diagnosed Glioblastoma: A Prospective Safety and Feasibility Study. *Frontiers in Oncology.* 2020;10.
20. National Comprehensive Cancer Network. Central Nervous System Cancers - Version 1.2022. Published 6/2/2022. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed 6/17/2022.
21. National Institute for Health and Care Excellence. Brain tumours (primary) and brain metastases in adults. https://www.nice.org.uk/guidance/ng99. Published 2021. Accessed 6/16/2022.

POLICY REVISION HISTORY

DATE	REVISION SUMMARY
2/2023	Converted to new policy template.