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”).

APPLIES TO:

All lines of business except Medicare

BENEFIT APPLICATION

Medicaid 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.

POLICY CRITERIA

Newly Diagnosed Glioblastoma

Initial 3-month TTF Trial

I. For commercial members, an initial 3-month trial of tumor treatment field (TTF) therapy may be considered **medically necessary and covered** as a treatment of newly diagnosed glioblastoma multiforme when all of the following criteria are met:

   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 contraindicates are present:
   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

**Continuation of TTF**

II. For commercial members, subsequent use (> 3-months) of tumor treatment field (TTF) therapy may be considered medically necessary and covered as a treatment of newly diagnosed glioblastoma multiforme when all of the following criteria are met:

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.

**Recurrent Glioblastoma**

III. For commercial members, 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.
### KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

<table>
<thead>
<tr>
<th>Rating (%)</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Normal no complaints; no evidence of disease.</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease.</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort; some signs or symptoms of disease.</td>
</tr>
<tr>
<td>70</td>
<td>Cares for self; unable to carry on normal activity or to do active work.</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance, but is able to care for most of his personal needs.</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent medical care.</td>
</tr>
<tr>
<td>40</td>
<td>Disabled; requires special care and assistance.</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled; hospital admission is indicated although death not imminent.</td>
</tr>
<tr>
<td>20</td>
<td>Very sick; hospital admission necessary; active supportive treatment necessary.</td>
</tr>
<tr>
<td>10</td>
<td>Moribund; fatal processes progressing rapidly.</td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
</tr>
</tbody>
</table>

### Eastern Cooperative Oncology Group (ECOG) Performance Status

<table>
<thead>
<tr>
<th>Grade</th>
<th>ECOG Performance Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>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</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care; confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled; cannot carry on any self-care; totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>
**HCPCS CODES**

**All Lines of Business Except Medicare**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A4555</td>
<td>Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only</td>
</tr>
<tr>
<td>E0766</td>
<td>Electrical stimulation device used for cancer treatment, includes all accessories, any type</td>
</tr>
</tbody>
</table>

**DESCRIPTION**

**Glioblastoma**

According to Hayes and the ECRI Institute, “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 much as 30% of primary brain tumors.” 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.”¹²

**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

REVIEW OF EVIDENCE

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 October 2018:

Systematic Reviews

- In March of 2016, Hayes conducted a systematic review of evidence regarding the use of the Novocure system for patients with recurrent glioblastoma and as a concomitant treatment with temozolomide (TMZ) therapy in patients with newly diagnosed glioblastoma.¹ A total of 8 studies were identified and included in the review (2 studies for newly diagnosed glioblastoma and 4 with recurrent glioblastoma). The Hayes assessment found that a small and low quality body of evidence suggested that in patients with recurrent and newly diagnosed glioblastoma, Novocure was comparable with chemotherapy in increases in overall survival (OS) and progression free survival (PFS). Hayes issued the following ratings:
  
  o “C – For Novocure monotherapy in adult patients (22 years of age and older) with recurrent glioblastoma (GBM) following surgery and radiotherapy. This Rating reflects some positive but low-quality evidence suggesting that Novocure is as effective as chemotherapy in this patient population. The Rating also reflects the small body of evidence available, small sample sizes, and lack of concurrent control or comparator groups in most studies.

  o D2 – For Novocure 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. This Rating reflects positive but very-low-quality evidence from 1 randomized controlled trial and 1 very-poor-quality cohort study suggesting that Novocure is more effective than chemotherapy in this patient population. The Rating also reflects the very small quantity of data available for this indication.”¹
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). However, the only well-designed RCT which demonstrated superiority of TTF therapy compared to standard chemotherapy evaluated patients with newly diagnosed GBM. No RCT was identified which demonstrated superiority of TTF over standard of care treatments in patients with recurrent GBM.

In February 2018, Hayes conducted an annual review of the evidence and found one newly published study on TTF. Reviewing this study’s abstract alone, Hayes concluded that the, “results of this study will not change the conclusions and/or ratings in the existing Hayes report.”

- In 2016, the ECRI Institute updated their review of TTF therapy (Optune) for recurrent GBM. Three studies were included in the review (1 randomized controlled trial, 1 single-arm pilot trial and 1 patient registry retrospective review) to address 4 key questions:

  o **Key Question 1**
    How does the effectiveness of TTF therapy compare with that of other treatment options for patients with recurrent GBM?

    **Finding:**
    - At 24-month follow-up, overall survival of patients treated with TTF therapy and patients treated with [best standard chemotherapy] BSC was not different. Strength of evidence: Moderate.
    - The evidence does not permit us to determine how [quality of life] QOL compares between patients who received TTF therapy and patients who received BSC because study authors reported insufficient information to draw a conclusion. Strength of evidence: Very low.

  o **Key Question 2**
    How does the effectiveness of TTF therapy compare with that of palliative therapy alone for treating recurrent GBM?

    **Finding:**
    - Our searches did not identify any studies that provided data to address this question.

  o **Key Question 3**
    How do AEs reported for TTF therapy compare with AEs reported for other treatments for recurrent GBM?
Finding:

- TTF causes a lower rate of treatment-emergent serious hematologic AEs than BSC. Strength of evidence: Moderate.
- Treatment-emergent serious metabolism and nutrition disorders or vascular disorders of patients treated with TTF therapy and those treated with BSC are not different. Strength of evidence: Low.
- The evidence does not permit us to determine how treatment-emergent serious gastrointestinal AEs or nervous system disorders of patients treated with TTF therapy and patients treated with BSC compare because study authors reported too few events on which to base a conclusion. Strength of evidence: Very low.
- TTF causes a lower rate of thrombocytopenia, leukopenia, diarrhea, and infections than BSC. Strength of evidence: Moderate.
- TTF causes a lower rate of nausea, anorexia, muscle weakness, and alopecia than BSC. Strength of evidence: Low.
- TTF causes a higher rate of skin site reactions, falls, and rashes than BSC. Strength of evidence: Low. (No skin site reaction AEs were severe or life threatening.)

Key Question 4:
What [adverse events] AEs are reported in studies of TTF therapy?

Finding:

- The most common reported AE for TTF therapy is skin reaction at the site where the electrodes contact the scalp. This AE was easily treated with antibiotics, corticosteroids, or electrode relocation. Other common AEs reported...include neurologic disorders, seizures, headaches, pain and discomfort, and falls.”

Randomized Controlled Trials

Newly Diagnosed GBM

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. 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).³

In 2017, Stupp et al., published final findings from the above trials. 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).⁴

Taphoorn et al. (2018) conducted a secondary analysis of EF-14 (Stupp et al. 2017)⁴, measuring health-related quality of life outcomes for patients with newly diagnosed glioblastoma. 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.⁶

In 2017, an expert roundtable (sponsored by Novocure, Inc.) convened at the American Society of Clinical Oncology published recommendations from their 2015 meeting. The panel recommended TTF plus TMZ for patients diagnosed with newly diagnosed glioblastoma without contraindications.⁵

**Recurrent GBM**

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. 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).⁷

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. 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). Evidence regarding the use of TTF therapy to improve PFS and OS in patients with recurrent glioblastoma remains limited to a single RCT which demonstrated no difference in OS or PFS compared to chemotherapy and one *post-hoc* analysis with cross-group contamination. 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. Additional, well-designed RCTs are needed to isolate the effect of TTF therapy in patients with recurrent GBM.

**CLINICAL PRACTICE GUIDELINES**

**National Comprehensive Cancer Network (NCCN)**

The NCCN (1.2018) clinical practice guidelines regarding Central Nervous System Cancers indicate alternating electric field therapy be considered in the following circumstances:

**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)

In its 2018 update, the NCCN upgraded adjuvant alternating electric field therapy — when used as an initial therapy along with temozolomide — from a category 2A to a category 1 recommendation.

**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

For recurrent glioblastoma, the NCCN guidelines states that, “due to the lack of efficacy, not all panelists recommend the treatment”.13
National Institute for Health and Care Excellence (NICE)

In July 2018, 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.14

**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 Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days’ notice of policy changes that are restrictive in nature.

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.

**REGULATORY STATUS**

Mental Health Parity Statement

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.

**REFERENCES**

2. ECRI Institute, Tumor Treating Fields Therapy (Optune) for Recurrent Glioblastoma; Published 7/2/2012; Updated: 7/20/2016; Accessed 11/02/2018


15. Centers for Medicare & Medicaid Services Local Coverage Determination (LCD): Tumor Treatment Field Therapy (TTFT) (L34823); Effective: 10/01/2015; Last updated: 01/01/2017; Accessed: 11/02/2018.

16. Centers for Medicare & Medicaid Services Local Coverage Article (LCA): Tumor Treatment Field Therapy (TTFT) (A52711); Effective: 10/01/2015; Last updated: 01/01/2017; Accessed: 11/02/2018.
