Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: Keystone First Community HealthChoices	**Submission Date**: June 29, 2021
Policy Number: CCP.1164	**Effective Date:** 7/2015 **Revision Date:** June 1, 2021
Policy Name: Tumor treatment fields for glioblastoma	

Type of Submission – Check all that apply:

- ☐ **New Policy**
- ☑ **Revised Policy***
- ☐ **Annual Review – No Revisions**
- ☐ **Statewide PDL**

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any clarifying information for the policy below:

Please see revisions below using tracked changes.

Name of Authorized Individual (Please type or print): Akintayo, Akinlawon, MD	**Signature of Authorized Individual:**

Keystone First
Community HealthChoices

Tumor treatment fields for glioblastoma

Clinical Policy ID: CCP.1164

Recent review date: 6/2021

Next review date: 10/2022

Policy contains: Alternating electric fields; tumor treatment fields; electric tumor treatment fields; Optune; glioblastoma multiforme; Temozolomide.

Keystone First Community HealthChoices has developed clinical policies to assist with making coverage determinations. Keystone First Community HealthChoices' clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Keystone First Community HealthChoices when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Keystone First Community HealthChoices' clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Keystone First Community HealthChoices' clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First Community HealthChoices will update its clinical policies as necessary. Keystone First Community HealthChoices' clinical policies are not guarantees of payment.

Coverage policy

The use of tumor treatment fields for glioblastoma multiforme delivered through the Optune® (Novocure, Portsmouth, New Hampshire) device is clinically proven and, therefore, medically necessary when all of the following conditions are met):

For newly-diagnosed glioblastoma multiforme:

- Diagnosis is histologically confirmed.
- Member is 22 years of age or older.
- Karnofsky Performance Score (good performance status) is at least 60.
- Maximal debulking surgery has been performed.
- Radiation therapy with concomitant standard of care chemotherapy has been performed.
- The treatment is administered with temozolomide.

For recurrent glioblastoma multiforme:

- Diagnosis is histologically or radiologically confirmed in the supra-tentorial region of the brain.
- Member is 22 years of age or older.
- Device is used as monotherapy.
- Surgical, radiation, and chemotherapy options have been exhausted (Food and Drug Administration, 2015; National Comprehensive Cancer Network, 2020).

]For any determinations of medical necessity for medications, refer to the applicable state approved pharmacy policy.

Limitations

Initial approval is for a period of three months.

Contraindications include:

- Member has an active implanted medical device (e.g., deep brain stimulator, spinal cord stimulator, vagus nerve stimulator, pacemaker, defibrillator, or programmable shunt).
- Member has a skull defect (i.e., missing bone with no replacement) or bullet fragment(s).
- Member is sensitive to conductive hydrogels like the gel used on electrocardiogram stickers or transcutaneous electrical nerve stimulation electrodes (Food and Drug Administration, 2015).

All other uses of tumor treatment fields for glioblastoma are not clinically proven/investigational, and therefore, not medically necessary.

Alternative covered services

- Radiation therapy.
- Temozolomide chemotherapy.
- GLIADEL® Wafer in combination with surgical resection.
- Stereotactic radiosurgery.
- Re-operation for additional tumor resection.

Background

Glioblastoma multiforme is the most frequently occurring primary brain tumor in the United States, affecting some 17,000 patients each year (Thakkar, 2014). The median survival rate for glioblastoma multiforme is 14 to 15 months. A few patients may survive five years, representing less than 3 percent of all glioblastoma multiforme patients. Because of the discouraging prognosis for those suffering from glioblastoma multiforme when treated with traditional therapies, there has been a search for alternative treatment modalities that can provide localized treatment without adversely impacting normal brain tissue.

Tumor treatment fields are low-intensity (1 – 3 volts/CM), intermediate frequency (100 – 300 KHz) alternating electrical fields established through insulated electrodes on the skin around the region of a malignant tumor. Tumor cells undergoing mitosis may be destroyed, leaving non-dividing cells unaffected. The electrodes are enclosed in insulated ceramic discs contained in disposable transducer arrays placed within an adhesive bandage, and attached to the shaved scalp (Rominiyi, 2021).

On September 24, 2014, the U.S. Food and Drug Administration cleared Optune® (Novocure, Portsmouth, New Hampshire) as a class III device, a category of intervention generally reserved for the highest-risk devices and therefore subject to the highest level of regulatory control. Optune was approved for patients 22 years of age and older, with a new diagnosis of supratentorial, histologically confirmed glioblastoma multiforme, to be used following maximal debulking surgery and completion of radiotherapy, concurrently with standard of care chemotherapy. The treatment is also approved as monotherapy for recurrent cases of glioblastoma multiforme (Food and Drug Administration, 2015).

The components of the system consist of four transducer arrays embedded in adhesive patches, each of which contains nine insulated ceramic discs, a cable, a portable electric field generator, four rechargeable batteries

(one of which is used at a time and lasts four to six hours), and a backpack. Optune is currently the sole device approved for delivering alternating electric fields for the treatment of glioblastoma. Optune was previously known as the NovoTTF-100A System, which was approved by the Food and Drug Administration in 2011 for use in recurrent glioblastoma (Fabian, 2019).

Findings

The 2020 National Comprehensive Cancer Network guideline on central nervous system cancers recommends alternating electric field therapy as one option for adjuvant treatment of new cases of glioblastoma, in combination with temozolomide and standard radiation therapy, for patients age 70 or over with a Karnofsky Performance Score of at least 60. It also recommends alternating electric field therapy for recurrent cases (all ages), as monotherapy (National Comprehensive Cancer Network, 2020).

The National Institute for Health and Care Excellence recommends not offering tumor treating fields to patients with either new or recurring grade IV glioblastoma (National Institute for Health and Care Excellence, 2021).

A review by Portuguese experts declares tumor treatment fields to be the first major advance in glioblastoma therapy in over a decade, and endorses it as an option for newly-diagnosed patients with no contraindications (Fernandes, 2017).

The American Academy of Neurological Sciences issued a systematic review and guideline on glioblastoma multiforme treatment. The guideline made no mention of tumor treatment fields, but did make a broad recommendation that patients refractory to treatment enroll in clinical trials (Olson, 2014).

A systematic review of nine trials (two randomized, two pilot clinical, and five retrospective, n = 1,191) showed tumor treating fields for glioblastoma to improve survival for newly-diagnosed patients but not for patients with recurrence. The primary adverse reaction to the treatment was skin reactions (Shah, 2020).

A systematic review/meta-analysis of 21 trials and 21 treatment strategies for glioblastoma (n = 6,478) documented that tumor treating fields plus the Stupp protocol achieved the most favorable overall survival. Authors observed intensive cilengitide combination therapy and tumor treating field combination therapy have cause the least toxicity (Jin, 2020).

A review of eight clinical trials, six of which were ongoing at publication, found tumor treating fields for newly diagnosed and recurrent glioblastoma to be efficacious, with minimal toxicity. Authors encourage more studies to further optimize patient selection, determine cost-effectiveness, and assess impact on quality (Mittal, 2018).

A review of two randomized trials compared treatment fields plus temozolomide to the drug alone. The first (n = 237) showed the combination had a lower rate of severe adverse events (16% versus 6%) but a higher rate of mild/moderate events (14% versus 2%), with similar overall and progression-free survival. The second (n = 695) showed the combination had higher average survival, progression-free (6.7 months versus 4.0 months) and overall (20.7 versus 16.0), both $P < .001$. Adverse effect rates were similar (48% versus 44%) (Zhu, 2017).

A systematic evidence-based analysis studies from 1978-2018 of adult glioblastoma patients found median overall survival was 13.5 months. However, the highest average survival (20.7 months) was found in clinical trials of tumor treating fields, eclipsing bevacizumab (18.2) and vaccines (19.2) (Marenco-Hillembrand, 2020).

A literature review explored the promise offered by tumor treatment fields, as a new and different approach to glioblastoma. It cited results from the literature, but added that long-term results are needed to make clinicians more comfortable with the device. It also states that clinical trials of tumor treatment fields in treating diseases other than glioblastoma may make the device more acceptable and familiar (Fabian, 2019).

References

On March 1, 2021, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “glioblastoma,” “tumor treatment fields,” and “alternating electric fields.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

Amagouliotis DE, Asprondini EK, Svokos KA, Tasiopoulou VS, Svokos AA, Toms SA. Tumor-treating fields as a fourth treating modality for glioblastoma: A meta-analysis. *Acta Neurochir (Wien)*. 2018;160(6):1167-1174. Doi: 10.1007/s00701-018-3536-6.

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Rominiyi O, Vanderlinden A, Clenton SJ, *et al.* Tumour treating fields therapy for glioblastoma: current advances and future directions. *Br J Cancer.* 2021;124:697-709. Doi: 10.1038/s41416-020-01136-5.

Shah PP, White T, Skalafallah AM, Romo CG, Price C, Mukherjee D. A systematic review of tumor treating fields therapy for high-grade gliomas. *J Neurooncol*. 2020;148(3):433-443. Doi: 10.1007/s11060-020-03563-z.

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Policy updates

3/2015: initial review date and clinical policy effective date: 7/2015

2016: Policy references updated.

3/2017: Policy references updated.

4/2018: Policy references updated.

5/2019: Policy references updated.

3/2020: Policy references updated.

6/2021: Policy references updated.