Tumor treating fields, (Optune®) – re-review

Clinical Expert

Jason K. Rockhill, MD, PhD
Co-Director of the Gamma Knife Center at Harborview Medical Center
Clinical Co-Director of Alvord Brain Tumor Center, University of Washington
Associate Professor, Department of Radiation Oncology, University of Washington
Associate Professor, Department of Neurological Surgery, University of Washington
Applicant Name | Jason K. Rockhill, MD, PhD
---|---
Address | Department of Radiation Oncology, UW School of Medicine
| 1959 NE Pacific St., Room NN136
| Seattle, WA 98195

1. **Business Activities**

(a) If you or a member of your household was *an officer or director of a business* during the immediately preceding calendar year and the current year to date, provide the following:

<table>
<thead>
<tr>
<th>Title</th>
<th>Business Name &amp; Address</th>
<th>Business Type</th>
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</table>

(b) If you or a member of your household *did business under an assumed business name* during the immediately preceding calendar year or the current year to date, provide the following information:

<table>
<thead>
<tr>
<th>Business Name</th>
<th>Business Address</th>
<th>Business Type</th>
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<tbody>
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</table>

2. **Honorarium**

If you *received an honorarium of more than $100* during the immediately preceding calendar year and the current year to date, list all such honoraria:

<table>
<thead>
<tr>
<th>Received From</th>
<th>Organization Address</th>
<th>Service Performed</th>
</tr>
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<tbody>
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</tbody>
</table>

3. **Sources of Income**

(a) Identify *income source(s) that contributed 10% or more of the combined total gross household income* received by you or a member of your household during the immediately preceding calendar year and the current year to date.

<table>
<thead>
<tr>
<th>Source Name &amp; Address</th>
<th>Received By</th>
<th>Source Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Washington</td>
<td>Jason Rockhill</td>
<td>salary</td>
</tr>
<tr>
<td>UWP</td>
<td>Jason Rockhill</td>
<td>salary</td>
</tr>
<tr>
<td>University of Washington</td>
<td>wife</td>
<td>salary</td>
</tr>
<tr>
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</tbody>
</table>
(b) Does any income source listed above relate to, or could it reasonably be expected to relate to, business that has, or may, come before the Committee?

☒ Yes ☐ No

The University of Washington Medical Center provides care for patients shoes coverage can be determined by the HTCC
If “yes”, describe: Click here to enter text.
Click here to enter text.

(c) Does an income source listed above have a legislative or administrative interest in the business of the Committee?

☐ Yes ☒ No
If “yes”, describe: Click here to enter text.
Click here to enter text.
Click here to enter text.

4. Business Shared With a Lobbyist
If you or a member of your household shared a partnership, joint venture, or similar substantial economic relationship with a paid lobbyist, were employed by, or employed, a paid lobbyist during please list the following:
(Owning stock in a publicly traded company in which the lobbyist also owns stock is not a relationship which requires disclosure.)

<table>
<thead>
<tr>
<th>Lobbyist Name</th>
<th>Business Name</th>
<th>Type Business Shared</th>
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<tbody>
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Provide the information requested in items 5, 6, and 7 below only if:
(a) Your response involves an individual or business if you or a member of your household did business with, or reasonably could be expected to relate to business that has or may come before the Health Technology Clinical Committee.
(b) The information requested involves an individual or business with a legislative or administrative interest in the Committee.

5. Income of More Than $1,000
List each source (not amounts) of income over $1,000, other than a source listed under question 3 above, which you or a member of your household received during the immediately preceding calendar year and the current year to date:

<table>
<thead>
<tr>
<th>Income Source</th>
<th>Address</th>
<th>Description of Income Source</th>
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</thead>
<tbody>
<tr>
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</tbody>
</table>
**6. Business Investments of More Than $1,000**

(Do not list the amount of the investment or include individual items held in a mutual fund or blind trust, a time or demand deposit in a financial institution, shares in a credit union, or the cash surrender value of life insurance.)

If you or a member of your household had a personal, beneficial interest or investment in a business during the immediate preceding calendar year of more than $1,000, list the following:

<table>
<thead>
<tr>
<th>Business Name</th>
<th>Business Address</th>
<th>Description of Business</th>
</tr>
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</tbody>
</table>

**7. Service Fee of More Than $1,000**

(Do not list fees if you are prohibited from doing so by law or professional ethics.)

List **each person for whom you performed a service for a fee of more than $1,000** in the immediate preceding calendar year or the current year to date.

<table>
<thead>
<tr>
<th>Name</th>
<th>Description of Service</th>
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</table>

I certify that I have read and understand this Conflict of Interest Form and the information I have provided is true and correct as of this date.

Print Name  
Jason K. Rockhill, MD, PhD

Check One:  
☐ Committee Member  
☐ Subgroup Member  
☒ Contractor

Signature  
Date 10-11-18
Curriculum Vitae
Sept 20, 2018

Personal Data:

Jason K. Rockhill, M.D., Ph.D.
1959 NE Pacific Street, Box 356043
University of Washington
Seattle, WA 98195

jkrock@uw.edu (professional)

Birthplace: Seattle, WA

Education:

Medical - Medical Degree (MD), 1998. University of Illinois College of Medicine - Urbana/Champaign. Completed as part of the Medical Scholars Program (M.D./Ph.D. Program).


Undergraduate - Bachelor of Science, - double degree in Biology-Chemistry and Physics with Departmental Honors, 1989. Claremont McKenna College, Claremont, CA. Dr. Robert Pinnell and Dr. David Sadava, Research Advisors. Research interest in solid-phase silylating reagents.

Postgraduate Training:

Residency - University of Washington Cancer Center, Department of Radiation Oncology, July 2000 - June 2004.

Internship - University of Illinois College of Medicine – Urbana/Champaign General Internal Medicine, May 1999 – May 2000.


Faculty Positions Held:

Associate Professor, Department of Radiation Oncology, University of Washington, Seattle, WA. July 2010 – current.

Associate Professor, Department of Neurological Surgery, University of Washington, Seattle, WA. July 2010 – current.

Assistant Professor, Department of Radiation Oncology, University of Washington, Seattle, WA. July 2004 – June 2010.

Assistant Professor, Department of Neurological Surgery, University of Washington, Seattle, WA. July 2004 – June 2010.
Hospital Positions Held:

Clinical Co-Director of Alvord Brain Tumor Center, UW Medicine. Responsible along with the Co-Director from the Department of Neurology for the development and implementation of clinical care protocols, and strategic planning for brain tumor patients. Jan 2016 – current.

Clinical Director of Alvord Brain Tumor Center, UW Medicine. Responsible for the development and implementation of clinical care protocols for brain tumor patients. Jan 2015 – December 2015.

Co-Director of the Gamma Knife Center at Harborview Medical Center. Responsible along with Co-Director from the Department of Neurosurgery for strategic planning, development of protocols and procedures, and supervision of treatment team. Jul 2007 – current.

Associate Residency Training Director for Radiation Oncology, University of Washington School of Medicine. Responsible for assisting in curriculum development for resident education and development of resident research. Role in maintaining ACGME compliance in resident training. Jan 2011 – December 2015.


Member of Community Internship Program, Harborview Medical Center. June 2009 – December 2014.


Member of University of Washington Faculty Senate. Sept 2006 – Sept 2008.

Fred Hutchinson/University of Washington Cancer Consortium - Program in Neuro-Oncology Jun 2004 – current.

Honors:

Seattle Metropolitan Magazine “Top Doc”. August 2015.
Contributions to the University of Illinois at Urbana/Champaign College of Medicine Award. Co-Recipient with Dr. Carol Rockhill, Oct 2006.
Harold M. and Ann Flood-Swartz Award for Best Student Presentation at the Spring Medical Scholars Program Research Symposium. Feb 1997.
University of Illinois, Department of Biochemistry, Travel Award. 1996.
University of Illinois College of Medicine Summer Research Award. 1993.
Graduated with Departmental Honors from the Joint Science Department, Claremont McKenna College. May 1989.
Board Certification:

Diplomate of the American Board of Radiology in Radiation Oncology - Jan 2018 – participating in MOC.
Board Certified in Radiation Oncology - June 2007.

Current Licenses:


Professional Organizations:

NCCN Guideline Panel Member CNS – December 2016 – current.
American Society for Therapeutic Radiology and Oncology 2004 - current
American Society of Clinical Oncology 2004 - current
Society for Neuro-Oncology 2004 - current
Radiology Society of North America 2004 - current

Teaching Responsibilities:

Undergraduate:

Graduate Medical Education:
Attending in Radiation Oncology, directly supervising residents in patient care and providing direct teaching in lecture / discussion format, University of Washington Medical School, Seattle, WA July 2004 – current.
Didactics in Radiology to the Neuro-Radiology Fellows yearly about Neuro-Radiation Oncology, University of Washington Medical School July 2004 – current.
Didactics to Neurological Surgery Residents on Radiation Therapy, University of Washington School of Medicine. July 2004 – Current.
Didactics in Otolaryngology on Radiation Therapy, University of Washington School of Medicine. May 2015 - current.
Didactics and Direct Supervision in Palliative Care to Palliative Care Fellows about Palliative Radiation Oncology, University of Washington Medical School. July 2009 – June 2014.
Didactics in Nuclear Medicine to Nuclear Medicine Fellows on Radiation and Brain Tumor Imaging, University of Washington School of Medicine. July 2009 – June 2012.


Doctoral Education:

Consultant:
Multi-Session Stereotactic Radiotherapy with the Leksell Gamma Knife Perfexion, Clinica Shaio, Bogota, Columbia. March 2012.
Multi-Session Stereotactic Radiotherapy with the Leksell Gamma Knife Perfexion for physicians from M.D. Anderson, UCSF, and South Sound Gamma Knife Center.

Invited Talks:
Rockhill JK. “Challenges in Radiation Therapy.” Invited talk for Workshop 4: Cancer Development, Angiogenesis, Progression, and Invasion for the Mathematical Biosciences Institute at Ohio State University, Columbus Ohio, January 26-30, 2009.

Continuing Medical Education:


Rockhill, JK. “Historical Perspective and Advances in Radiation Treatment to the Spine.” Oral presentation for the Spine Review Course, UW Medicine, Seattle WA, Jun 5, 2011


Grand Rounds:

Rockhill JK. “We Personalize Shaping the Target – Can we Personalize the Dose?” University of Washington Department of Radiation Oncology Grand Rounds, April 24, 2013.

Rockhill JK. “Glioblastoma Multiforme - Where are we from a Radiation Oncology Perspective?” University of Washington Department of Radiation Oncology Grand Rounds, Sept 10, 2009.


Editorial Responsibilities:
Reviewer for International Journal of Radiation Oncology● Biology ● Physics
Reviewer for Journal of Neuro Oncology.
Reviewer for Journal of the NCCN

Special Local Responsibilities:
Member of Community Internship Program Harborview Medical Center. Jun 2009 – Jun 2011.
Research Funding:

1R01 CA 16437 (K. Swanson) 02/01/12-7/31/2016
NIH/NCI
(UVIC) Patient-specific Predictive Modeling that Integrates Advanced Cancer Imaging.
Role: Co – Investigator (6.08% salary support)

1R01 NS 060752 (K. Swanson) 12/01/10-07/31/14
NIH
Novel Tools for Evaluation and Prediction of Radiotherapy Response in Individual Glioma Patients
Role: Co – Investigator (2% salary support).

5 R01 CA112505-02 (M. Phillips) 04/10/06-02/28/10
NCI
Multiattribute decision theory for IMRT plan selection
Role: Collaborator (no support)

5 P30 CA015704-33 01/01/06-12/31/06
NCI/Fred Hutchinson Cancer Research Center
The Mechanisms of Cell Death for Malignant Gliomas
The goal of this pilot project was to determine how malignant brain tumor cells express toxicity after radiation exposure.
Role: Pilot Project - Sub-investigator on NCI grant.

Bibliography:

Peer Reviewed:


6. Abecassis IJ, Nerva JD, Barber J, Rockhill JK, Ellenbogen RG, Kim LJ, Sekhar LN. Toward a comprehensive assessment of functional outcomes in pediatric patients with


Book Chapters:

Audio Presentations:

Non-Peer Reviewed:

Other Presentations:


Rockhill JK. “Update on Brain Metastases.” Oral presentation to the University of Washington Medical Oncology/Hematology Fellows, Aug 22, 2009.


Rockhill JK. “Pituitary Tumors.” Oral presentation to the University of Washington Radiation Oncology Residents, April 1, 2005.


Notable Meeting Participation:

Tumor Treating Fields – Re-review

Shana Johnson, MD
Clinical Quality Care Transformation
Health Care Authority
November 16, 2018

Health Technology Clinical Committee

Determination: Tumor Treating Fields

Topic: Novocure (Tumor Treating Fields)
Meeting Date: January 15, 2016
Final Adoption: March 18, 2016

Meeting materials and transcript are available on the HTA website:
www.hta.wa.gov/hta/meetingmaterials/Forms/ExMeetingMaterials.aspx

Number and Coverage Topic:
20160115A – Novocure (Tumor Treating Fields)

HTCC Coverage Determination:
Novocure (Tumor Treating Fields) is not a covered benefit.

HTCC Reimbursement Determination:
Limitations of Coverage: N/A
Non-Covered Indicators: N/A
Factors Prompting TTF Re-review

1. New evidence (Stupp 2017, Taphoorn 2018)
2. Updated society guidelines
3. Stakeholder input

Tumor Treating Fields (TTF)
Medical Director Concerns

<p>| | |</p>
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<tbody>
<tr>
<td>Safety</td>
<td>Low</td>
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<tr>
<td>Efficacy</td>
<td>High</td>
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<tr>
<td>Cost</td>
<td>High</td>
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</tbody>
</table>
State Agency Coverage Policy

**PEBB/ UMP**  Implemented per HTCC
**Medicaid MCO**  Implemented per HTCC
**Medicaid FFS**  Implemented per HTCC

Other Insurers’ Coverage Policies

<table>
<thead>
<tr>
<th>Tumor Treating Field Coverage</th>
<th>New Diagnosis</th>
<th>Recurrent</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Coverage Determination</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Local Coverage Determination</td>
<td>None</td>
<td>None</td>
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<tr>
<td>Regence</td>
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<td>No</td>
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<tr>
<td>Aetna</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Kaiser</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Guideline recommendations

• **National Comprehensive Care Network (NCCN) 2018**
  – New GBM: recommends TTF as an adjunctive treatment for patients with KPS >60 (Category 1)
  – Recurrent GBM: recommends as an adjunct (Category 2B)

• **UK National Institute for Health Care and Excellence (NICE) 2018**
  – Does not recommend
  – Not an efficient use of resources

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**Stupp 2017, JAMA, TTF in glioblastoma**

Figure 2. Kaplan-Meier Survival Curves for Patients Included in the Final Analysis in the Intent-to-Treat Population

![Graphs showing survival analysis](image)

A, Median progression-free survival from randomization for the tumor-treating fields (TTF) plus temozolomide group was 6.7 months and was 4.0 months for the temozolomide-alone group (hazard ratio [HR], 0.63; 95% CI, 0.52-0.76; P < .005). B, Median survival from randomization was 20.9 for the TTF plus temozolomide group vs 16.0 months for the temozolomide-alone group (HR, 0.63; 95% CI, 0.53-0.76; P < .005). Median follow-up was 44 months (range, 25-91 months) in both groups.


- Newly diagnosed GBM (Quality over all evidence low)
  - Increase progression free survival (primary outcome) and overall survival (secondary outcome); small magnitude of effect (Stupp 2017)
  - Quality of life with treatment—data insufficient to assess
  - Minimal harm
  - Not cost-effective (Bernard-Arnoux 2016)
Stupp 2012, TTF in recurrent glioblastoma

- Recurrent GBM (Quality of evidence—very low)
  - No significant survival benefit between groups
  - Designed and statistical analysis for superiority not non-inferiority
  - Based on median OS and use of various chemo agents, unclear if lack of difference between groups may reflect that both treatment groups were ineffective
  - QOL data—open label, high drop-out QOL questionnaire completion; data insufficient to assess

Agency Recommendations

**Tumor Treating Fields: Covered with conditions**

- New diagnosis glioblastoma multiforme
- Histologically confirmed
- Adjunct to surgery (when feasible), radiotherapy, chemotherapy
- Supratentorial
- KPS score > 60
- Shared decision making between provider and patient

**Recurrent GBM, other malignancies: Not covered**
Questions?

For more information:
**Order of scheduled presentations:**

Tumor treating fields, (Optune®)

<table>
<thead>
<tr>
<th>Name</th>
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<tbody>
<tr>
<td>1 Justin Kelly, RN, BSN, Novocure</td>
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</tbody>
</table>
Overview of Presentation

- Background
- Methods
  - Risk of bias assessment
  - Strength of evidence grading
- Results
  - Primary research synthesis
  - Clinical practice guideline synthesis
- Discussion
  - Summary of evidence
  - Limitations
  - Payor coverage policies
Background

Glioblastoma Multiforme (GBM)

• High-grade (i.e., grade IV) gliomas
  • Astrocytic in origin
  • Most commonly present in the supratentorial region (i.e., frontal, temporal parietal, and occipital lobes)

• From 2006 to 2010, the age-adjusted incidence rate of GBM in the U.S. was 3.19 per 100,000 persons
  • Median age at diagnosis: 64 years
  • Rates higher among males than females

• Highly aggressive disease with a very poor prognosis
  • <5% of all patients survive 5 years after diagnosis
  • Median survival is 14-15 months; only 3 months in untreated patients

Images obtained from: https://www.mayfieldclinic.com/PE-Glioma.htm

GBM = glioblastoma.
Treatment of GBM

- **Newly Diagnosed GBM**
  - Surgical resection
  - 6 weeks of radiotherapy with concomitant chemotherapy (TMZ)
  - Minimum of 6 months maintenance chemotherapy (TMZ)

- **Recurrent GBM**
  - No standard of care; treatment options are limited
  - Majority of patients undergo chemotherapy
    - Usually in combination with bevacizumab, an angiogenesis inhibitor

GBM = glioblastoma; TMZ = temozolomide.

Technology Description

Alternating electric fields enter the cancer cell and disrupt mitotic spindle microtubule assembly resulting in dielectrophoretic dislocation of proteins such as tubulin and septin. Ultimately, this interferes with cell division and results in cancer cell death.

Tumor Treating Fields (TTF) externally deliver alternating electric fields that are of very-low intensity and intermediate frequency (i.e., 100 to 300 kilohertz [kHz]) to an area of proliferating cancer cells during the late metaphase and anaphase of mitosis.

Specific frequency used is inversely related to the size of the cancer cells:
- 200 kHz is used for treatment of GBM
- Normal cells, which are affected at -50 kHz, remain unaffected

GBM = glioblastoma.

The Optune® System

- Optune®, previously referred to as the NovoTTF-100A System or Novocure (Novocure Inc.; Haifa, Israel), delivers TTF
- Optune® is portable and operated by the patient
- TTF are delivered through transducer arrays positioned based on the tumor location
  - NovoTAL™ software uses most recent MRI to determine optimal placement
- Requires continuous application (at least 18 hours per day for a minimal duration of 4 weeks, recommended by Novocure) due to no half-life


TTF = tumor treating fields; MRI = magnetic resonance imaging.

Regulatory Status

<table>
<thead>
<tr>
<th>Recurrent GBM</th>
<th>Newly Diagnosed GBM</th>
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<tbody>
<tr>
<td><strong>FDA Approval</strong></td>
<td><strong>October 2015</strong></td>
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<tr>
<td><strong>Indications</strong></td>
<td><strong>Contraindications</strong></td>
</tr>
<tr>
<td>• Age 22 years or older</td>
<td>• Active implanted medical device present (brain, spinal cord, or vagus nerve stimulators, pacemaking, defibrillators, programmable shunts)</td>
</tr>
<tr>
<td>• GBM in supratentorial location</td>
<td>• Skull defect present</td>
</tr>
<tr>
<td>• Confirmed recurrent GBM after chemotherapy</td>
<td>• Known sensitivity to conductive hydrogels</td>
</tr>
<tr>
<td>• <strong>To be used as monotherapy</strong></td>
<td></td>
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<tr>
<td>• As alternative to standard medical therapy after surgical and radiation options exhausted</td>
<td></td>
</tr>
<tr>
<td>• GBM in supratentorial location</td>
<td></td>
</tr>
<tr>
<td>• Confirmed newly diagnosed GBM following maximal debulking surgery and completion of radiation therapy with concomitant standard-of-care chemotherapy</td>
<td></td>
</tr>
<tr>
<td>• <strong>To be used with TMZ</strong></td>
<td></td>
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</tbody>
</table>

GBM = glioblastoma; TMZ = temozolomide.
Policy Context for Washington

- Based on the prior 2015 report, the State of Washington’s Health Technology Clinical Committee voted in January 2016 to not cover Optune®
- This topic was selected for re-review based on newly available published evidence and rated:
  - Low concerns for safety
  - High concerns for efficacy
  - High concerns for cost

Methods
**Analytic Framework**

- Adults and children with GBM or other cancers
- TTFs
- EQ: Overall survival, Progression-free survival, Tumor response and progression, Health-related quality of life, Functional status, Cost, Cost-effectiveness
- CQ: Serious adverse events, Adverse events
- SQ: Serious adverse events, Adverse events (e.g., dermatitis, insomnia, headaches)

CQ = cost question; EQ = efficacy question; GBM = glioblastoma; SQ = safety question; TTF = tumor treating fields.

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**Study Selection for Primary Research Review**

<table>
<thead>
<tr>
<th>Population</th>
<th>Adults or children with a confirmed diagnosis of incident or recurrent GBM or other cancer</th>
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</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>TTFs, with or without concomitant therapy</td>
</tr>
<tr>
<td>Comparator</td>
<td>Chemotherapy; TTF plus chemotherapy or other adjunctive treatments; placebo; no comparator</td>
</tr>
<tr>
<td>Outcomes</td>
<td>EQ: Overall survival; progression-free survival; tumor response and progression; health-related quality of life; functional status</td>
</tr>
<tr>
<td></td>
<td>SQ: Serious adverse events; adverse events (e.g., dermatitis, insomnia, headaches)</td>
</tr>
<tr>
<td></td>
<td>CQ: Cost; cost-effectiveness</td>
</tr>
<tr>
<td>Study Design</td>
<td>EQ: Randomized controlled trials, controlled clinical trials, cohort studies with concurrent or historical comparator group, case-control studies</td>
</tr>
<tr>
<td></td>
<td>SQ: All of the designs listed for EQ plus studies without a comparator (e.g., case series)</td>
</tr>
<tr>
<td></td>
<td>CQ: Cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis</td>
</tr>
<tr>
<td>Setting</td>
<td>Countries categorized as “very high” on United Nations Human Development Index</td>
</tr>
</tbody>
</table>

CQ = cost question; EQ = efficacy question; GBM = glioblastoma; SQ = safety question; TTF = tumor treating fields.
Risk of Bias / Study Quality

Assessed at the individual study level for studies with comparator group(s)

- Cochrane Risk of Bias version 2.0 instrument (RCTs)
  - High risk of bias
  - Some concerns for bias
  - Low risk of bias
- ROBINS-I tool (translated for consistency) (Observational Studies)
  - High risk of bias
  - Some concerns for bias
  - Low risk of bias
- Quality of Health Economic Studies (QHES) instrument (CEA)
  - Good
  - Fair
  - Poor

Strength of the Evidence (SOE) – Modified GRADE approach

- **Strength of evidence ratings**
  - ★★★★★ VERY LOW
  - ★★★★★ LOW
  - ★★★★★★ MODERATE
  - ★★★★★★★ HIGH

- **Domains assessed**
  - Risk of bias
  - Consistency\(^1\)
  - Directness
  - Precision
  - Publication bias

- Bodies of RCT evidence start at **HIGH** SOE
- Observational studies start at **LOW** SOE
- May be downgraded based on domain assessment:
  - No concerns
  - Serious concerns (↓ one level)
  - Very serious concerns (↓ two levels)
- Observational evidence may be upgraded based on:
  - Large effect (↑ one level)
  - Dose response (↑ one level)
  - All confounding & bias accounted for (↑ one level)

\(^1\) We modified the conventional GRADE by downgrading the consistency domain when there was only a single-study body of evidence to evaluate.
Results

Search Results

- Primary Research Synthesis (databases’ inception to 6/16/2018)
  - Titles/Abstracts screened: 423
  - Full text articles screened: 77
  - Full text studies included: 11 studies (15 articles)

New GBM
- EQ1: 2 (3)
- SQ1: 2 (2)
- CQ1: 1 (1)

Recurrent GBM
- EQ1: 4 (7)
- SQ1: 5 (5)
- CQ1: 0 (0)

Other Cancer
- EQ1: 0 (0)
- SQ1: 3 (3)
- CQ1: 0 (0)

- Clinical Practice Guidelines: 6

CQ = cost question; EQ = efficacy question; GBM = glioblastoma; SQ = safety question.
Differences from 2015 Report

- **Newly Diagnosed GBM**
  - EF-14 trial interim results superseded by final results
  - New: Cost-effectiveness analysis

- **Recurrent GBM**
  - New: Observational cohort study
  - 2 articles included in 2015 report are now excluded
    - Subgroup analysis of EF-11 trial data with no eligible data (n=130)
    - Chart review of combination therapy with or without TTF (n=37)

- **Other Cancer**
  - New: Case series

---

Strength of Evidence Comparisons

**Newly diagnosed GBM**
- TTF + TMZ vs. TMZ alone

**Recurrent GBM**
- TTF vs. second-line therapy
- TTF + second-line therapy vs. second-line therapy alone

**Other cancers**
- No comparisons

GBM = glioblastoma; TMZ = temozolomide; TTF = tumor treating fields.
## Results

### New GBM: TTF+TMZ vs. TMZ alone

1 trial, 1 observational study, 1 cost-effectiveness analysis

---

### Newly Diagnosed GBM – Included Studies

<table>
<thead>
<tr>
<th>Study Characteristics</th>
<th>Participant Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EF-14 Trial</strong></td>
<td>• Median age = 56 to 57 years old</td>
</tr>
<tr>
<td><strong>Funding:</strong> Novocure Ltd.</td>
<td>• Median KPS score = 90 (range 60 to 100)</td>
</tr>
<tr>
<td><strong>Countries:</strong> 83 centers in Austria, Canada, Czech Republic, France, Germany, Israel, Italy, South Korea, Sweden, Switzerland, United States</td>
<td>• Mean time between diagnosis and randomization = 3.7 to 3.8 months</td>
</tr>
<tr>
<td><strong>Risk of Bias:</strong> Some concerns (OS, PFS, Safety) to high (QOL) risk of bias</td>
<td></td>
</tr>
<tr>
<td><strong>Intervention:</strong> TTF + TMZ (n=466)</td>
<td></td>
</tr>
<tr>
<td><strong>Comparator:</strong> TMZ (n=229)</td>
<td></td>
</tr>
</tbody>
</table>

| **Observational Pilot Study:** Cohort study with historical and concurrent comparator groups | |
| **Funding:** Novocure Ltd. | |
| **Country:** Czech Republic | |
| **Risk of Bias:** High risk of bias (OS, PFS) | |
| **Intervention:** TTF + TMZ (n=10) | |
| **Comparator:** TMZ (historical control) (n=NR) | |
| **Comparator:** TMZ (concurrent control) (n=32) | • Median age of historical control group = 54 years |
| | • KPS score ≥70 in the intervention group and >60 in the historical control group |
| | • Patients in the intervention group were at least 4 weeks post-radiation therapy when assigned to receive TTF with maintenance TMZ therapy |
| | • No other details provided |

---

GBM = glioblastoma; KPS = Karnofsky Performance Status; NR = not reported; OS = overall survival; PFS = progression-free survival; QOL = quality of life; TMZ = temozolomide; TTF = tumor treating fields.
Newly Diagnosed GBM – Included Studies (cont’d)  

**Study Characteristics** | **Analysis Details**
--- | ---
Cost-effectiveness analysis (Markov model) | • Hypothetical cohort of 1,000 people  
Funding: None declared | • French health care payor perspective  
Country: France | • Lifetime horizon, discounted at 4%, costs in 2014 Euros  
Quality: Good | • Direct health care costs excluding cost of surgery and concomitant radiotherapy and TMZ  
Intervention: TTF + TMZ | • Effectiveness data from interim analysis of EF-14 trial data  
Comparator: TMZ | • QALYs not used because of lack of published data on health-state utilities associated with GBM

GBM = glioblastoma; QALY = quality adjusted-life-years; TMZ = temozolomide; TTF = tumor treating fields.

Newly Diagnosed GBM – EQ1  

**Overall Survival (OS)**

1 RCT  
★★★★ LOW  
For benefit with TTF  

RCT: Median OS was 20.9 months with TTF+TMZ and 16.0 months with TMZ alone; HR 0.63 (95% CI, 0.53 to 0.76) over median 40 months of follow up.

Observational: Consistent with RCT in direction of effect (but not magnitude); median OS was >39 months with TTF+TMZ and 14.7 months with TMZ alone.

**Progression-free Survival (PFS)**

1 RCT  
★★★★ LOW  
For benefit with TTF  

RCT: Median PFS was 6.7 months with TTF+TMZ and 4.0 months with TMZ alone; HR 0.63 (95% CI, 0.52 to 0.76) over median 40 months of follow up. At 6 months, 56% of TTF+TMZ group and 37% of TMZ alone group were progression-free.

Observational: Consistent with RCT in direction of effect (but not magnitude); median PFS was 38.8 months with TTF+TMZ and 7.8 months with TMZ alone.

CI = confidence interval; EQ = efficacy question; GBM = glioblastoma; HR = hazard ratio;  
RCT = randomized controlled trial; TMZ = temozolomide; TTF = tumor treating fields.
Newly Diagnosed GBM – EQ1

Quality of Life (QOL) and Functional Status

<table>
<thead>
<tr>
<th>1 RCT</th>
<th>10000 VERY LOW</th>
</tr>
</thead>
<tbody>
<tr>
<td>For benefit with TTF</td>
<td></td>
</tr>
</tbody>
</table>

Time to sustained decline in functional status scores was significantly longer with TTF+TMZ than TMZ alone:
- Karnofsky Performance Status: HR 0.79 (95% CI, 0.66 to 0.95)
- Mini Mental State Examination: HR 0.80 (95% CI, 0.67 to 0.95)

Significantly more patients in TTF+TMZ than TMZ alone group experienced stable or improved global health status, pain, weakness of legs, and physical/cognitive/emotional functioning on the EORTC-QLQ.

CI = confidence interval; EORTC-QLQ = European Organization for Research and Treatment Quality of Life Questionnaire; EQ = efficacy question; GBM = glioblastoma; HR = hazard ratio; QOL = quality of life; RCT = randomized controlled trial; TMZ = temozolomide; TTF = tumor treating fields.

Newly Diagnosed GBM – SQ1

Adverse events (AEs)

<table>
<thead>
<tr>
<th>1 RCT</th>
<th>10000 LOW</th>
</tr>
</thead>
<tbody>
<tr>
<td>For minimal harm with TTF</td>
<td></td>
</tr>
</tbody>
</table>

Mild to moderate dermatologic AEs were reported by half of patients receiving TTF; the addition of TTF to TMZ treatment did not significantly increase the rates of systemic AEs (P=0.58).

In the pilot study, adverse events were only reported for the intervention group (n=10)
- No serious AEs
- All patients reported grade 1 or 2 (i.e., mild to moderate) dermatitis and none reported grade 3 or 4 (i.e., severe or disabling) dermatitis.
- All of the mild to moderate AEs were attributed to underlying disease (headache, seizures), TMZ treatment (anemia, thrombocytopenia, leucopenia), or other treatments (elevated liver function, hyperglycemia); no severe or disabling AEs were reported.

GBM = glioblastoma; RCT = randomized controlled trial; SQ = safety question; TMZ = temozolomide; TTF = tumor treating fields.
Newly Diagnosed GBM – CQ1

Cost-effectiveness

1 Cost-effectiveness analysis

The discounted payor perspective ICER, in 2014 USD, was $817,001 (95% CI, $612,352 to $1,021,651) per life year gained.

If the monthly costs for the Optune® system and support were reduced to $2,740 per month from $27,398 per month (price discounted by approximately 90%), the discounted ICER would be $97,562.

Results

Recurrent GBM: TTF vs. Second-line Therapy

1 trial, 2 observational studies, 1 case series

CQ = cost question; GBM = glioblastoma; ICER = incremental cost-effectiveness ratio; USD = U.S. dollars.

GBM = glioblastoma; TTF = tumor treating fields.
### Recurrent GBM – Included Studies

<table>
<thead>
<tr>
<th>Study Characteristics</th>
<th>Participant Characteristics</th>
</tr>
</thead>
</table>
| **EF-11 Trial** | • Median age = 54 years  
| Funding: Novocure Ltd. | • Median KPS score = 80 (range 50 to 100)  
| Countries: 28 institutions in Austria, Czech Republic, France, Germany, Israel, Switzerland, and the United States | • Median 11.4 to 11.8 months since initial GBM diagnosis  
| Risk of Bias: Some concerns (OS, PFS, Safety) to high (QOL) | • Number of recurrences varied at randomization (12% first, 47% second, and 41% third or greater)  
| Intervention: TTF (n=120) | • 80% received prior TMZ therapy  
| Comparator: Best chemotherapy (n=117) | • 19% received prior treatment with bevacizumab |

**Patient Registry Dataset (PRiDe):** Observational cohort with historical comparator groups from EF-11 trial

| Funding: Novocure Ltd. | Intervention group only: |
| Country: United States | • Median age = 55 years  
| Risk of Bias: Some concerns (OS) to high (Safety) | • Median KPS score = 80 (range 10 to 100)  
| Intervention: TTF (n=457) | • Median number of recurrences = 2 (range 1 to 5)  
| Comparator: TTF (n=120) | • Number of recurrences varied at study start for (33% first, 27% second, and 27% third or greater, 13% unknown)  
| Comparator: Best chemotherapy (n=117) | • 78% received prior TMZ therapy  
| | • 55% received prior treatment with bevacizumab |

**GBM = glioblastoma; KPS = Karnofsky Performance Status; OS = overall survival; PFS = progression-free survival; QOL = quality of life; TMZ = temozolomide; TTF = tumor treating fields.**

---

### Recurrent GBM – Included Studies (cont’d)

<table>
<thead>
<tr>
<th>Study Characteristics</th>
<th>Participant Characteristics</th>
</tr>
</thead>
</table>
| **Observational Pilot Study:** Cohort study with historical comparator groups | • Median age = 50.7 to 54 years  
| Funding: Novocure Ltd. | • Median KPS score = 80 to 90 (range 60 to 100)  
| Country: Czech Republic | • Patients receiving TTF were at least 4 weeks from any brain surgery and at least 8 weeks from radiotherapy |
| Risk of Bias: High risk of bias (OS, PFS) | |
| Intervention: TTF (n=10) | |
| Comparator: Gefitinib (n=57) | |
| Comparator: TMZ (n=142) | |
| Comparator: TMZ (n=126) | |
| Comparator: TMZ and procarbazine (n=225) | |
| Comparator: Meta-analyses of multiple chemotherapies (n=225) | |
| **Case series: Post-marketing surveillance program** | • No additional details about the patient population were provided |
| Funding: Novocure Ltd. | |
| Country: United States | |
| Risk of Bias: Not assessed | |
| Intervention: TTF (n=540) | |

**GBM = glioblastoma; KPS = Karnofsky Performance Status; TMZ = temozolomide; TTF = tumor treating fields.**
### Recurrent GBM – EQ1  
#### TTF vs. Second-line Therapy

**Overall Survival (OS)**

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RCT</strong></td>
<td>🟪ΟΟΟΟ VERY LOW</td>
<td>For no benefit with TTF</td>
</tr>
<tr>
<td><strong>Observational Studies</strong></td>
<td>🟪ΟΟΟΟ VERY LOW</td>
<td>For benefit with TTF</td>
</tr>
</tbody>
</table>

**RCT:** Median OS was similar in the intervention (6.6 months) and comparator groups (6.0 months) in the EF-11 trial.

**Observational:** Studies were consistent in direction (but not magnitude of effect) with each other and the RCT. Patients in PRiDe registry reported “significantly longer” OS than EF-11 patients receiving second-line therapy (6.0 months). Median OS in 10 TTF patients (16 months) was “more than double” that of historical controls (range 6 to 10 months) in the observational pilot study.

---

**Progression-free Survival (PFS)**

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RCT</strong></td>
<td>🟪ΟΟΟΟ VERY LOW</td>
<td>For no benefit with TTF</td>
</tr>
<tr>
<td><strong>Observational Pilot</strong></td>
<td>🟪ΟΟΟΟ VERY LOW</td>
<td>For benefit with TTF</td>
</tr>
</tbody>
</table>

**RCT:** Median PFS was 2 months in both the intervention and comparator groups [HR 0.81 (95% CI, 0.60 to 1.09)]; 21% of TTF patients and 15% of second-line therapy patients were progression-free at 6 months (P=0.13).

**Observational:** The historical comparator groups in the observational pilot study reported similar results (9% to 19% were progression-free at 6 months) but a much higher proportion (50%) of the 10 TTF patients were progression-free at 6 months; this is consistent with the RCT in direction but not magnitude of effect. Authors report that the median time to progression was more than double for the TTF than the second-line therapy patients; confidence intervals were very wide in the TTF group.

---

**CI = confidence interval; EQ = efficacy question; GBM = glioblastoma; HR = hazard ratio; RCT = randomized controlled trial; TTF = tumor treating fields.**
### Recurrent GBM – EQ1

**Quality of life (QOL) and Functional Status**

<table>
<thead>
<tr>
<th>Study Type</th>
<th>RCTs</th>
<th>Rating</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 RCT</strong></td>
<td></td>
<td>VERY LOW</td>
<td>After 3 months, TTF participants showed larger improvements on the EORTC-QLQ emotional functioning subscale, less of a decline on the role functioning subscale, and improvement (compared to a decline with chemotherapy) on the cognitive functioning subscale. There were no “meaningful” differences between TTF and second-line therapy with respect to the global health status and social functioning subscales. Patients receiving second-line therapy experienced less of a decline on the physical functioning subscale.</td>
</tr>
</tbody>
</table>

---

### Recurrent GBM – SQ1

**Adverse events (AEs)**

<table>
<thead>
<tr>
<th>Study Type</th>
<th>RCTs</th>
<th>Rating</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 RCT</strong></td>
<td></td>
<td>VERY LOW</td>
<td><strong>RCT:</strong> Mild to moderate contact dermatitis beneath the TTF transducer arrays was reported by 16% of the patients in the TTF group; no severe or disabling dermatologic AEs were reported in either group. Moderate to disabling AEs were reported by 6% of the TTF group and 16% of the second-line therapy group (P=0.022); only 3% of patients overall experienced a severe or disabling AE.</td>
</tr>
<tr>
<td><strong>2 Observational Studies</strong></td>
<td></td>
<td>VERY LOW</td>
<td><strong>Observational:</strong> No serious AEs reported with TTF; 24% to 90% of TTF patients experienced a skin reaction/contact dermatitis with TTF. Other AEs were rare (≤10%) or not attributed to TTF treatment.</td>
</tr>
</tbody>
</table>

In case series of 540 patients receiving TTF treatment, the median time to dermatologic AE onset was 32.5 days (range 2 to 250) and 21.8% of patients had at least one non-serious dermatologic adverse event.
Results

Recurrent GBM: TTF + Second-line Therapy vs. Second-line Therapy

1 observational study

Study Characteristics

<table>
<thead>
<tr>
<th>Post hoc cohort of EF-14 trial participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Funding: Novocure Ltd.</td>
</tr>
<tr>
<td>Country: 83 centers in Austria, Canada, Czech Republic, France, Germany, Israel, Italy, South Korea, Sweden, Switzerland, United States</td>
</tr>
<tr>
<td>Risk of Bias: High risk of bias (OS, safety)</td>
</tr>
<tr>
<td>Intervention: TTF + Second-line therapy (n=144)</td>
</tr>
<tr>
<td>Comparator: Second-line therapy (n=60)</td>
</tr>
</tbody>
</table>

Participant Characteristics

- 144 of 466 patients (31%) randomized to TTF+TMZ in EF-14 trial and 60 of 229 patients (26%) randomized to TMZ alone in EF-14 trial experienced a first recurrence of GBM and continued treatment for this observational study until a second recurrence of GBM or 24 months
- Median age = 57 to 58 years
- Median KPS score = 90 (range 60 to 100)
## Recurrent GBM – EQ1 & SQ1: TTF+Second-line vs. Second-line Therapy

### Overall survival (OS)

1 Cohort

| 🥰 ☐ ☐ ☐ VERY LOW | Median OS was similar in the intervention (11.8 months) and comparator groups (9.2 months); HR=0.70 (95% CI, 0.48 to 1.00) over median 12.6 months of follow up. |

### Adverse events (AEs)

1 Cohort

| 🥰 ☐ ☐ ☐ VERY LOW | Site reactions beneath the TTF transducer arrays were reported by 13% of patients in the intervention group; though 49% of the TTF group experienced at least one grade 3 or 4 AEs, compared to 33% of the second-line therapy group, none were related to TTF treatment. |

---

**CI** = confidence interval; **EQ** = efficacy question; **GBM** = glioblastoma; **HR** = hazard ratio; **SQ** = safety question; **TTF** = tumor treating fields.

---

### Results

#### Other Cancers

3 case series
### Other Cancers – SQ1

<table>
<thead>
<tr>
<th>Study &amp; Patient Characteristics</th>
<th>Results</th>
</tr>
</thead>
</table>
| **Green (2017)**  
Country: United States  
Patients: Male pediatric patients w/high grade gliomas (n=5)  
Intervention: TTF w/chemotherapy and/or radiation | • No serious AEs  
• 1 patient reported a scalp ulceration (grade 2/moderate skin breakdown) |
| **Pless (2013)**  
Country: Switzerland  
Patients: Adults w/advanced NSCLC (n=42)  
Intervention: TTF w/pemetrexed | • None of serious AEs or commonly reported respiratory AEs related to TTF  
• 1 patient reported severe/disabling dermatologic AE (rash/dermatitis/erythema)  
• Mild or moderate dermatologic AEs were more commonly reported |
| **Salzberg (2008)**  
Country: Switzerland  
Patients: Adults w/advanced breast cancer, melanoma, GBM, or pleural mesothelioma (n=6)  
Intervention: TTF | • No serious AEs  
• 3 patients reported grade 1 skin irritations under the transducer arrays |

AE = adverse event; GBM = glioblastoma; TTF = tumor treating fields.
## Clinical Practice Guideline Recommendations

<table>
<thead>
<tr>
<th>Organization (Year)</th>
<th>Quality Rating</th>
<th>New GBM</th>
<th>Recurrent GBM</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Comprehensive Cancer Network (NCCN) (2018)</td>
<td>5/7</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>U.K. National Institute for Health and Care Excellence (NICE) (2018)</td>
<td>7/7</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Medical Oncology Spanish Society (SEOM) (2017)</td>
<td>3/7</td>
<td>---</td>
<td>No</td>
</tr>
<tr>
<td>European Association for Neuro-Oncology (EANO) (2017)</td>
<td>3/7</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>American Association of Neuroscience Nurses (AANN) (2016)</td>
<td>4/7</td>
<td>---</td>
<td>Yes</td>
</tr>
<tr>
<td>European Society for Medical Oncology (ESMO) (2014)</td>
<td>2/7</td>
<td>---</td>
<td>No</td>
</tr>
</tbody>
</table>

GBM = glioblastoma.

### Discussion
### Summary of Strength of Evidence Ratings: New GBM

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Study Design (№ Studies; № Patients)</th>
<th>Certainty Direction of Effect</th>
<th>Summary of Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival (OS)</td>
<td>RCT (1; 695)</td>
<td>⬤⬤⬤◯ LOW For benefit with TTF</td>
<td>Median OS was 20.9 months with TTF+TMZ and 16.0 months with TMZ alone over median 40 months of follow up (difference 4.9 months).</td>
</tr>
<tr>
<td></td>
<td>OBS (1; NR)</td>
<td>⬤⬤⬤◯ VERY LOW For benefit with TTF</td>
<td></td>
</tr>
<tr>
<td>Progression-free Survival (PFS)</td>
<td>RCT (1; 695)</td>
<td>⬤⬤⬤◯ LOW For benefit with TTF</td>
<td>Median PFS was 6.7 months with TTF+TMZ and 4.0 months with TMZ alone over median 40 months of follow up (difference 2.7 months). At 6 months, 56% of TTF+TMZ group and 37% of TMZ alone group were progression-free.</td>
</tr>
<tr>
<td></td>
<td>OBS (1; 42)</td>
<td>⬤⬤⬤◯ VERY LOW For benefit with TTF</td>
<td></td>
</tr>
<tr>
<td>Quality of Life (QOL), Functional Status</td>
<td>RCT (1; 695)</td>
<td>⬤⬤⬤◯ VERY LOW For benefit with TTF</td>
<td>Time to sustained decline longer and more patients with stable or improved QOL subscale domains with TTF+TMZ than TMZ alone.</td>
</tr>
<tr>
<td>Safety</td>
<td>RCT (1; 672)</td>
<td>⬤⬤⬤◯ LOW For minimal harm with TTF</td>
<td>Mild to moderate dermatologic AEs with TTF.</td>
</tr>
<tr>
<td>Cost</td>
<td>OBS (1; 1,000)</td>
<td>⬤⬤⬤◯ LOW TTF not cost-effective</td>
<td>The discounted payor perspective ICER was $817,001 (95% CI, $612,352 to $1,021,651) per life year gained.</td>
</tr>
</tbody>
</table>

**AE = adverse event; GBM = glioblastoma; ICER = incremental cost-effectiveness ratio; OBS = observational; RCT = randomized controlled trials; TMZ = temozolomide; TTF = tumor treating fields.**

### Summary of Strength of Evidence Ratings: Recurrent GBM

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Study Design (№ Studies; № Patients)</th>
<th>Certainty Direction of Effect</th>
<th>Summary of Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival (OS)</td>
<td>RCT (1; 237)</td>
<td>⬤⬤⬤◯ VERY LOW For no benefit with TTF</td>
<td>Median OS was similar in the intervention and comparator groups (6.6 and 6.0 months, respectively) in the EF-11 trial, but significantly longer with TTF in the observational studies.</td>
</tr>
<tr>
<td></td>
<td>OBS (2; 1,479)</td>
<td>⬤⬤⬤◯ VERY LOW For benefit with TTF</td>
<td></td>
</tr>
<tr>
<td>Progression-free Survival (PFS)</td>
<td>RCT (1; 237)</td>
<td>⬤⬤⬤◯ VERY LOW For no benefit with TTF</td>
<td>Median PFS was the same in both the intervention and comparator groups (2 months) in the EF-11 trial, but significantly longer with TTF in the observational study.</td>
</tr>
<tr>
<td></td>
<td>OBS (1; 785)</td>
<td>⬤⬤⬤◯ VERY LOW For benefit with TTF</td>
<td></td>
</tr>
<tr>
<td>Quality of Life (QOL), Functional Status</td>
<td>RCT (1; 63)</td>
<td>⬤⬤⬤◯ VERY LOW For benefit with TTF</td>
<td>Patients receiving TTF showed larger improvements or less of a decline on more QOL subscale domains than patients receiving second-line therapy.</td>
</tr>
<tr>
<td>Safety</td>
<td>RCT (1; 672)</td>
<td>⬤⬤⬤◯ VERY LOW For minimal harm with TTF</td>
<td>Mild to moderate dermatologic AEs with TTF.</td>
</tr>
<tr>
<td></td>
<td>OBS (2; 1,479)</td>
<td>⬤⬤⬤◯ VERY LOW For minimal harm with TTF</td>
<td></td>
</tr>
</tbody>
</table>

**AE = adverse event; GBM = glioblastoma; OBS = observational; RCT = randomized controlled trials; TTF = tumor treating fields.**
## Summary of Strength of Evidence Ratings: Recurrent GBM

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Study Design (№ Studies; № Patients)</th>
<th>Certainty Direction of Effect</th>
<th>Summary of Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival (OS)</td>
<td>OBS (1; 204)</td>
<td>⬇◯◯◯ VERY LOW For no benefit with TTF</td>
<td>Median OS was similar in the intervention and comparator groups (11.8 and 9.2 months, respectively).</td>
</tr>
<tr>
<td>Safety</td>
<td>OBS (1; 204)</td>
<td>⬇◯◯◯ VERY LOW For minimal harm with TTF</td>
<td>Mild to moderate dermatologic AEs with TTF.</td>
</tr>
</tbody>
</table>

AE = adverse event; GBM = glioblastoma; OBS = observational; TTF = tumor treating fields.

## Limitations of the Evidence Base

- Limited number of comparative effectiveness trials
- Risk of bias of included studies
  - Lack of blinding for patient-reported outcomes
  - Attrition, adherence, and crossovers
  - Selection bias in observational studies
- Studies underpowered to determine the clinical effectiveness and safety of TTF for subgroups of interest
- Applicability to current standard of care in U.S.
  - Bevacizumab use and advanced state of disease
  - Lack of U.S. cost studies

TTF = tumor treating fields.
Limitations of this Health Technology Assessment

- **Scope**
  - English-language articles only
  - Excluded studies conducted in countries designated as less than “very high human development” on the United Nations Human Development Report

- **Process**
  - Search limited to 3 databases (PubMed, Cochrane, clinicaltrials.gov)

- **Analysis**
  - Using GRADE with a small evidence base
  - Limitations of AGREE tool for evaluating clinical practice guidelines

Payer Coverage Policies

- Specific criteria vary by payer but often include histologically confirmed supratentorial GBM and prior debulking, radiation, and/or chemotherapy.
- Some payers have an age requirement (minimum 18 or 22 years) or KPS score requirement (>60 or >70).
- For newly diagnosed GBM patients, all payors require the patient is also being treated with TMZ unless contraindicated.

<table>
<thead>
<tr>
<th>Payor</th>
<th>Newly Diagnosed GBM</th>
<th>Recurrent GBM</th>
<th>Other Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicare</td>
<td>No policy identified</td>
<td>No policy identified</td>
<td>No policy identified</td>
</tr>
<tr>
<td>Premera</td>
<td>Covered</td>
<td>Not Covered</td>
<td>Not Covered</td>
</tr>
<tr>
<td>Regence</td>
<td>Covered</td>
<td>Not Covered</td>
<td>Not Covered</td>
</tr>
<tr>
<td>United Healthcare</td>
<td>Covered</td>
<td>Covered</td>
<td>Not Covered</td>
</tr>
<tr>
<td>Aetna</td>
<td>Covered</td>
<td>Covered</td>
<td>Not Covered</td>
</tr>
<tr>
<td>Humana</td>
<td>Covered</td>
<td>Covered</td>
<td>Not Covered</td>
</tr>
<tr>
<td>Kaiser</td>
<td>Covered</td>
<td>Not Covered</td>
<td>Not Covered</td>
</tr>
<tr>
<td>Cigna</td>
<td>Covered</td>
<td>Covered</td>
<td>Not Covered</td>
</tr>
</tbody>
</table>

GBM = glioblastoma; KPS = Karnofsky Performance Status; TMZ = temozolomide; TTF = tumor treating fields.
### Conclusions (Certainty)

#### Newly diagnosed GBM
- Increases OS & PFS (very low to low)
- Increases QOL (very low)
- Minimal harm (low)
- Not cost-effective (low)

#### Recurrent GBM
- May or may not have survival benefits (very low)
- Increases QOL (very low)
- Minimal harm (low)

#### Other cancers
- No evidence

---

GBM = glioblastoma; OS = overall survival; PFS = progression-free survival; QOL = quality of life.

---

**Additional Details**
### SOE Interpretation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, that is, another study would not change the conclusions.</td>
</tr>
<tr>
<td>Moderate</td>
<td>We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.</td>
</tr>
<tr>
<td>Low</td>
<td>We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.</td>
</tr>
<tr>
<td>Very Low</td>
<td>We have very limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has numerous major deficiencies. We believe that substantial additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.</td>
</tr>
</tbody>
</table>

### Subgroup Analyses

**Outcome** | **Study** | **Results**                                                                                                                                                                                                 |
|-------------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| OS          | EF-14 Trial | • Higher among patients who were adherent than among patients who weren’t adherent (HR 0.65, 95% CI, 0.49 to 0.85).  
• No significant differences between groups defined by age, sex, resection history, or KPS score at baseline |
### Subgroup Analyses

#### TTF vs. Second-line Therapy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study</th>
<th>Results</th>
</tr>
</thead>
</table>
| OS      | EF-11 Trial | • When restricted to patients who received at least one cycle of TTF treatment, median OS increased to 7.8 months (HR 0.69, 95% CI, 0.52 to 0.92).  
• Median OS significantly higher in TTF group among the following subgroups: previous failed treatment with bevacizumab, prior low-grade glioma diagnosis, larger tumor size, baseline KPS score ≥80, higher rate of adherence to treatment, lower-dose dexamethasone users.  
• No significant differences between treatment among subgroups defined by age, surgical resection history. |
| OS      | PRIDe Registry | • Median OS was significantly higher among the following subgroups: first recurrence, ≥75 percent daily adherence, KPS scores 90-100, no prior bevacizumab use. |
| PFS     | EF-11 Trial | • Median PFS was higher among responders (n=21) than nonresponders (n=216) within both the TTF (P=0.0007) and second-line therapy (P=0.0222) groups and was numerically higher among patients receiving TTF than patients receiving second-line therapy, regardless of response. |

---

### Subgroup Analyses

#### TTF+Second-line vs. Second-line Therapy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>Post hoc cohort of EF-14 participants</td>
<td>• When comparator group restricted to bevacizumab users, median OS was significantly higher among the intervention group (11.8 months) than the comparator group (9.0 months).</td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; KPS = Karnofsky Performance Status; OS = overall survival; PFS = progression-free survival; TTF = tumor treating fields.
## Clinical Practice Guideline Synthesis

<table>
<thead>
<tr>
<th>Organization, Year (Quality Rating)</th>
<th>Recommendation</th>
<th>Evidence Base; Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Comprehensive Cancer Network (NCCN), 2018 (5 out of 7)</td>
<td>For patients of any age with newly diagnosed GBM and with good performance status (KPS &gt;60), and any MGMT promoter status: Recommend standard brain radiotherapy + concurrent temozolomide and adjuvant temozolomide + <strong>alternating electric field therapy</strong>. For patients with recurrent glioblastoma: consider <strong>alternating electric field therapy</strong>.</td>
<td>2 RCTs; Authors rated the recommendation for newly diagnosed GBM Category 1 and recurring GBM Category 2B</td>
</tr>
<tr>
<td>U.K. National Institute for Health and Care Excellence (NICE) (2018) (7 out of 7)</td>
<td>For patients newly diagnosed glioblastoma: Do not offer <strong>TTFs</strong> as part of management. For patients with recurrent glioblastoma: Do not offer <strong>TTFs</strong> as part of management.</td>
<td>2 RCTs; NICE chooses to reflect the concept of strength in the wording of the recommendation</td>
</tr>
</tbody>
</table>

GBM = glioblastoma; RCT = randomized controlled trial; TTF = tumor treating fields.

## Clinical Practice Guideline Synthesis (cont’d)

<table>
<thead>
<tr>
<th>Organization, Year (Quality Rating)</th>
<th>Recommendation</th>
<th>Evidence Base; Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Association of Neuroscience Nurses (AANN) (2016) (4 out of 7)</td>
<td>Nurses should be aware that use of electrical <strong>TTFs</strong> may be considered a comparable treatment option to chemotherapy for patients with recurrent malignant glioma, particularly when hematologic, infectious, or gastrointestinal toxicities limit treatment options (Level 1 recommendation). When <strong>TTFs</strong> are used, nurses should assess the skin for topical dermatitis (Level 1 recommendation). Nurses should educate patients about measures to improve comfort and compliance with the system (Level 3 recommendation).</td>
<td>1 RCT, 1 narrative expert review; Authors rated two recommendations Level 1 and one recommendation Level 3</td>
</tr>
<tr>
<td>Medical Oncology Spanish Society (SEOM) (2017) (3 out of 7)</td>
<td>For recurrent GBM, <strong>TTFs</strong> failed to prolong survival compared with second-line chemotherapy.</td>
<td>Unclear; Authors rated the evidence level II grade D</td>
</tr>
</tbody>
</table>

GBM = glioblastoma; RCT = randomized controlled trial; TTF = tumor treating fields.
Clinical Practice Guideline Synthesis (cont’d)

<table>
<thead>
<tr>
<th>Organization, Year (Quality Rating)</th>
<th>Recommendation</th>
<th>Evidence Base; Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Association for Neuro-Oncology (EANO) (2017) (5 out of 7 overall, 3 out of 7 for the guidelines handling of TTF)</td>
<td>TTF was not recommended. The following two statements were included in the text: Newly diagnosed GBM: Questions about the mode of action, interpretation of data, and effect on quality of life have been raised, and the role and cost-effectiveness of TTFs in the treatment of newly diagnosed glioblastoma remain to be defined. Recurrent GBM: TTFs were not superior to best physician’s choice in a randomized phase III trial.</td>
<td>2 RCTs; No rating was given when a treatment was not recommended</td>
</tr>
<tr>
<td>European Society for Medical Oncology (ESMO) (2014) (2 out of 7)</td>
<td>TTF was not recommended. The guideline included the following statement for recurrent GBM “TTFs failed to prolong survival compared with second-line chemotherapy.”</td>
<td>1 RCT; Authors rated the TTF evidence level I grade A</td>
</tr>
</tbody>
</table>

GBM = glioblastoma; RCT = randomized controlled trial; TTF = tumor treating fields.

Status of Relevant Clinical Trials

<table>
<thead>
<tr>
<th>Study Status</th>
<th>Newly diagnosed GBM</th>
<th>Recurrent GBM</th>
<th>Other cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not yet recruiting</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Recruiting</td>
<td>9</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Active and not recruiting</td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Completed</td>
<td>1 (EF-14)</td>
<td>1 (EF-11)</td>
<td>1a</td>
</tr>
<tr>
<td>Withdrawn</td>
<td>0</td>
<td>1b</td>
<td>0</td>
</tr>
<tr>
<td>Terminated</td>
<td>0</td>
<td>1c</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>0</td>
<td>2d</td>
</tr>
<tr>
<td>TOTAL</td>
<td>12</td>
<td>12</td>
<td>18</td>
</tr>
</tbody>
</table>

GBM = glioblastoma; NSCLC = non-small cell lung cancer; TTF = tumor treating fields.

a This clinical trial evaluated the efficacy and safety of TTF in NSCLC patients. One case series included in this HTA provides published results.
b Withdrawn due to poor participant accrual.
c Terminated due to amendment of study protocol.
d Both clinical trials were last updated September 21, 2016 and reported as active, not recruiting with a study completion date of July 2017 and December 2016.
### Status of Relevant Clinical Trials: Newly Diagnosed GBM

<table>
<thead>
<tr>
<th>Completion Date</th>
<th>Status</th>
<th>NCT Number</th>
<th>Trial Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>February 2019</td>
<td>Recruiting</td>
<td>NCT03128047</td>
<td>HUMC 1612: Optune® NovoTTF-200A System</td>
</tr>
<tr>
<td>April 2019</td>
<td>Recruiting</td>
<td>NCT03033982</td>
<td>Feasibility Trial of Optune® for Children With Recurrent or Progressive Supratentorial High-Grade Glioma and Ependymoma</td>
</tr>
<tr>
<td>March 2020</td>
<td>Recruiting</td>
<td>NCT03477110</td>
<td>Temozolomide, Radiation Therapy, and Tumor Treating Fields Therapy in Treating Participants With Glioblastoma</td>
</tr>
<tr>
<td>March 2020</td>
<td>Recruiting</td>
<td>NCT03258021</td>
<td>TTFields In Germany in Routine Clinical Care</td>
</tr>
<tr>
<td>May 2020</td>
<td>Active, not recruiting</td>
<td>NCT0323103</td>
<td>Safety and Immunogenicity of Personalized Genomic Vaccine and Tumor Treating Fields (TTFields) to Treat Glioblastoma</td>
</tr>
<tr>
<td>May 2020</td>
<td>Recruiting</td>
<td>NCT02903069</td>
<td>Study of Marizomib With Temozolomide and Radiotherapy in Patients With Newly Diagnosed Brain Cancer</td>
</tr>
<tr>
<td>June 2021</td>
<td>Recruiting</td>
<td>NCT02343549</td>
<td>A Phase II Study of Optune® (NovoTTF) in Combination With Bevacizumab and Temozolomide in Patients With Newly Diagnosed Unresectable Glioblastoma</td>
</tr>
<tr>
<td>June 2022</td>
<td>Active, not recruiting</td>
<td>NCT02152982</td>
<td>Temozolomide With or Without Veliparib in Treating Patients With Newly Diagnosed Glioblastoma Multiforme</td>
</tr>
<tr>
<td>September 2022</td>
<td>Recruiting</td>
<td>NCT03501134</td>
<td>Quality of Life of Patients With Glioblastoma Treated With Tumor-Treating Fields</td>
</tr>
<tr>
<td>February 2023</td>
<td>Recruiting</td>
<td>NCT03405792</td>
<td>Study Testing The Safety and Efficacy of Adjuvant Temozolomide Plus TTFields (Optune®) Plus Pembrolizumab in Patients With Newly Diagnosed Glioblastoma (2-THE-TOP)</td>
</tr>
<tr>
<td>July 2027</td>
<td>Recruiting</td>
<td>NCT03232424</td>
<td>NovoTTF-200A and Temozolomide Chemoradiation for Newly Diagnosed Glioblastoma</td>
</tr>
</tbody>
</table>

### Status of Relevant Clinical Trials: Recurrent GBM

<table>
<thead>
<tr>
<th>Completion Date</th>
<th>Status</th>
<th>NCT Number</th>
<th>Trial Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>December 2018</td>
<td>Recruiting</td>
<td>NCT01894061</td>
<td>NovoTTF-100A With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma</td>
</tr>
<tr>
<td>February 2019</td>
<td>Recruiting</td>
<td>NCT03128047</td>
<td>HUMC 1612: Optune® NovoTTF-200A System</td>
</tr>
<tr>
<td>March 2019</td>
<td>Recruiting</td>
<td>NCT02863271</td>
<td>TTFields and Pulsed Bevacizumab for Recurrent Glioblastoma</td>
</tr>
<tr>
<td>April 2019</td>
<td>Recruiting</td>
<td>NCT03033982</td>
<td>Feasibility Trial of Optune® for Children With Recurrent or Progressive Supratentorial High-Grade Glioma and Ependymoma</td>
</tr>
<tr>
<td>March 2021</td>
<td>Recruiting</td>
<td>NCT01954576</td>
<td>NovoTTF Therapy in Treating Patients With Recurrent Glioblastoma Multiforme</td>
</tr>
<tr>
<td>August 2021</td>
<td>Not yet recruiting</td>
<td>NCT03430791</td>
<td>Trial of Combination TTF (Optune®), Nivolumab Plus/Minus Ipilimumab for Bevacizumab-naive, Recurrent Glioblastoma</td>
</tr>
<tr>
<td>August 2022</td>
<td>Recruiting</td>
<td>NCT02743078</td>
<td>Optune® Plus Bevacizumab in Bevacizumab-Refractory Recurrent Glioblastoma</td>
</tr>
<tr>
<td>September 2022</td>
<td>Recruiting</td>
<td>NCT03501134</td>
<td>Quality of Life of Patients With Glioblastoma Treated With Tumor-Treating Fields</td>
</tr>
<tr>
<td>December 2026</td>
<td>Recruiting</td>
<td>NCT01925573</td>
<td>Optune® (NOVOTT-100A) Bevacizumab+ Hypofractionated Stereotactic Irradiation Bevacizumab-Naive Recurrent Glioblastoma (GCC 1344)</td>
</tr>
</tbody>
</table>
**Background**

In 2018, an estimated 1,735,350 new cancer cases and 609,640 cancer deaths will occur in the United States.\(^1\) Cancer is typically treated by surgery, radiation therapy, or systemic therapy (e.g., chemotherapy). Targeted cancer therapies such as hormone therapy (e.g., tamoxifen for breast cancer) or immunotherapy (e.g., rituximab for non-Hodgkin lymphoma) are systemic therapies that are used to interfere with specific molecules involved in cancer cell growth. Targeted drugs can (a) block or turn off molecular signals that control cell division and proliferation, (b) change proteins within the cancer cells so they are no longer viable, (c) stop making new blood vessels that feed cancer cells, (d) trigger the immune system to kill the cancer cells, or (e) carry toxins to cancer cells to kill them. Radiation therapy is a physical method that uses high-energy beams to kill cancer cells; although it is typically administered from a source outside of the body, it can also be delivered internally (e.g., brachytherapy).

Another physical treatment is a form of electromagnetic field therapy that uses alternating electrical fields to disrupt mitosis (i.e., cell division); cellular proteins are prevented from moving to their correct locations, resulting in cancer cell death. This therapy, also known as tumor treating fields (TTFs), externally delivers alternating electric fields that are very-low intensity and of intermediate frequency (i.e., 100-300 kHz) to an area of proliferating cancer cells. The specific frequency used in treatment is inversely related to the size of the specific cancer cells. Normal cells, which are affected at -50 kHz, remain unaffected by the frequencies used to treat cancer cells. TTFs have been shown to arrest cell proliferation and destroy cancer cells during division in animal models and human cancer cell lines.\(^2\)-\(^6\)

**Policy context**

Optune\(^\circledR\) (formerly the NovoTTF-100A System), a delivery system for TTFs, was approved by the U.S. Food and Drug Administration (FDA) in 2011 for the treatment of recurrent glioblastoma multiforme (GBM) and in 2015 for the treatment of newly diagnosed GBM in combination with temozolomide, an oral chemotherapy drug. The State of Washington’s Health Technology Clinical Committee (HTCC) voted in January 2016 to decline to cover Optune\(^\circledR\). This health technology assessment (HTA) will review the efficacy, safety, and cost-effectiveness of TTFs for treating GBM and other cancers to assist the HTCC in reviewing its existing policy and determining coverage for this medical device.

**Scope of this HTA**

The research questions, analytic framework, and key study selection criteria are listed in this section.

**Efficacy question 1 (EQ 1).** What is the clinical effectiveness of tumor treating fields for the treatment of newly diagnosed glioblastoma multiforme, recurrent glioblastoma multiforme, and other cancers?
Efficacy question 1a (EQ 1a). Does the clinical effectiveness of tumor treating fields vary by clinical history or patient characteristics (e.g., age, sex, Karnofsky performance score, surgical resection)?

Safety question 1 (SQ 1). What are the harms associated with tumor treating fields for the treatment of newly diagnosed glioblastoma multiforme, recurrent glioblastoma multiforme, and other cancers?

Safety question 1a (SQ 1a). Do the harms associated with tumor treating fields vary by clinical history or patient characteristics (e.g., age, sex, Karnofsky performance score, surgical resection)?

Cost question 1 (CQ 1). What are the costs and cost-effectiveness of tumor treating fields?

Figure 1 depicts the framework of the HTA.

Figure 1. Analytic framework depicting scope of this health technology assessment

Population: Adults or children with a histologically confirmed diagnosis of incident or recurrent GBM or other cancer (e.g., non-small cell lung cancer, ovarian cancer, pancreatic cancer)

Intervention: TTFs

Comparator: Chemotherapy; TTFs plus chemotherapy or other adjunctive treatments; placebo; no comparator

Outcomes:

Efficacy: Overall survival; progression-free survival; tumor response and progression; health-related quality of life; functional status (e.g., cognitive function measured by the Karnofsky Performance Scale)

Safety: Serious adverse events; adverse events (e.g., dermatitis, insomnia, headaches)
**Cost/Cost-Effectiveness:** Cost; cost-effectiveness

**Time period:** No time restriction

**Setting:** Countries categorized as “very high human development” according to the United Nations Development Programme’s 2016 Human Development Report

**Other criteria:** English-language publications

**Public comment and response**
No public comments were received.

**References**
HTCC Coverage and Reimbursement Determination

Analytic Tool

HTA’s goal is to achieve better health care outcomes for enrollees and beneficiaries of state programs by paying for proven health technologies that work.

To find best outcomes and value for the state and the patient, the HTA program focuses on three questions:

1. Is it safe?
2. Is it effective?
3. Does it provide value (improve health outcome)?

The principles HTCC uses to review evidence and make determinations are:

**Principle One: Determinations are evidence-based**

HTCC requires scientific evidence that a health technology is safe, effective and cost-effective as expressed by the following standards:

- Persons will experience better health outcomes than if the health technology was not covered and that the benefits outweigh the harms.
- The HTCC emphasizes evidence that directly links the technology with health outcomes. Indirect evidence may be sufficient if it supports the principal links in the analytic framework.
- Although the HTCC acknowledges that subjective judgments do enter into the evaluation of evidence and the weighing of benefits and harms, its recommendations are not based largely on opinion.
- The HTCC is explicit about the scientific evidence relied upon for its determinations.

**Principle Two: Determinations result in health benefit**

The outcomes critical to HTCC in making coverage and reimbursement determinations are health benefits and harms:

- In considering potential benefits, the HTCC focuses on absolute reductions in the risk of outcomes that people can feel or care about.
- In considering potential harms, the HTCC examines harms of all types, including physical, psychological, and non-medical harms that may occur sooner or later as a result of the use of the technology.
- Where possible, the HTCC considers the feasibility of future widespread implementation of the technology in making recommendations.
- The HTCC generally takes a population perspective in weighing the magnitude of benefits against the magnitude of harms. In some situations, it may make a determination for a technology with a large potential benefit for a small proportion of the population.

---

1 Based on Legislative mandate: See RCW 70.14.100(2).
2 The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm
3 The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm
• In assessing net benefits, the HTCC subjectively estimates the indicated population's value for each benefit and harm. When the HTCC judges that the balance of benefits and harms is likely to vary substantially within the population, coverage or reimbursement determinations may be more selective based on the variation.

• The HTCC considers the economic costs of the health technology in making determinations, but costs are the lowest priority.

### Using evidence as the basis for a coverage decision

Arrive at the coverage decision by identifying for Safety, Effectiveness, and Cost whether (1) evidence is available, (2) the confidence in the evidence, and (3) applicability to decision.

1. **Availability of evidence:**

   Committee members identify the factors, often referred to as outcomes of interest, that are at issue around safety, effectiveness, and cost. Those deemed key factors are ones that impact the question of whether the particular technology improves health outcomes. Committee members then identify whether and what evidence is available related to each of the key factors.

2. **Sufficiency of the evidence:**

   Committee members discuss and assess the evidence available and its relevance to the key factors by discussion of the type, quality, and relevance of the evidence using characteristics such as:

   • Type of evidence as reported in the technology assessment or other evidence presented to committee (randomized trials, observational studies, case series, expert opinion);
   • The amount of evidence (sparse to many number of evidence or events or individuals studied);
   • Consistency of evidence (results vary or largely similar);
   • Recency (timeliness of information);
   • Directness of evidence (link between technology and outcome);
   • Relevance of evidence (applicability to agency program and clients);
   • Bias (likelihood of conflict of interest or lack of safeguards).

   Sufficiency or insufficiency of the evidence is a judgment of each clinical committee member and correlates closely to the GRADE confidence decision.

<table>
<thead>
<tr>
<th>Not Confident</th>
<th>Confident</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appreciable uncertainty exists. Further information is needed or further information is likely to change confidence.</td>
<td>Very certain of evidentiary support. Further information is unlikely to change confidence</td>
</tr>
</tbody>
</table>

---

4 Based on GRADE recommendation: [http://www.gradeworkinggroup.org/FAQ/index.htm](http://www.gradeworkinggroup.org/FAQ/index.htm)
Health Technology Evidence Identification

3. Factors for Consideration - Importance

At the end of discussion a vote is taken on whether sufficient evidence exists regarding the technology’s safety, effectiveness, and cost. The committee must weigh the degree of importance that each particular key factor and the evidence that supports it has to the policy and coverage decision. Valuing the level of importance is factor or outcome specific but most often include, for areas of safety, effectiveness, and cost:

- Risk of event occurring;
- The degree of harm associated with risk;
- The number of risks; the burden of the condition;
- Burden untreated or treated with alternatives;
- The importance of the outcome (e.g. treatment prevents death vs. relief of symptom);
- The degree of effect (e.g. relief of all, none, or some symptom, duration, etc.);
- Value variation based on patient preference.

Clinical committee findings and decisions

Efficacy considerations

- What is the evidence that use of the technology results in more beneficial, important health outcomes? Consider:
  - Direct outcome or surrogate measure
  - Short term or long term effect
  - Magnitude of effect
  - Impact on pain, functional restoration, quality of life
  - Disease management
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to no treatment or placebo treatment?
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to alternative treatment?
- What is the evidence of the magnitude of the benefit or the incremental value?
- Does the scientific evidence confirm that use of the technology can effectively replace other technologies or is this additive?
- For diagnostic tests, what is the evidence of a diagnostic tests’ accuracy?
  - Does the use of the technology more accurately identify both those with the condition being evaluated and those without the condition being evaluated?
- Does the use of the technology result in better sensitivity and better specificity?
- Is there a tradeoff in sensitivity and specificity that on balance the diagnostic technology is thought to be more accurate than current diagnostic testing?
- Does use of the test change treatment choices?
Health Technology Evidence Identification

Safety
- What is the evidence of the effect of using the technology on significant morbidity?
  - Frequent adverse effect on health, but unlikely to result in lasting harm or be life-threatening, or;
  - Adverse effect on health that can result in lasting harm or can be life-threatening?
- Other morbidity concerns?
- Short term or direct complication versus long term complications?
- What is the evidence of using the technology on mortality – does it result in fewer adverse non-fatal outcomes?

Cost impact
- Do the cost analyses show that use of the new technology will result in costs that are greater, equivalent or lower than management without use of the technology?

Overall
- What is the evidence about alternatives and comparisons to the alternatives?
- Does scientific evidence confirm that use of the technology results in better health outcomes than management without use of the technology?

Next step: Cover or no cover
If not covered, or covered unconditionally, the chair will instruct staff to write a proposed findings and decision document for review and final adoption at the following meeting.

Next step: Cover with conditions
If covered with conditions, the committee will continue discussion.

1) Does the committee have enough information to identify conditions or criteria?
   - Refer to evidence identification document and discussion.
   - Chair will facilitate discussion, and if enough members agree, conditions and/or criteria will be identified and listed.
   - Chair will instruct staff to write a proposed findings and decision document for review and final adoption at next meeting.

2) If not enough or appropriate information, then Chair will facilitate a discussion on the following:
   - What are the known conditions/criteria and evidence state
   - What issues need to be addressed and evidence state

The chair will delegate investigation and return to group based on information and issues identified. Information known but not available or assembled can be gathered by staff; additional clinical questions may need further research by evidence center or may need ad hoc advisory group; information on agency utilization, similar coverage decisions may need agency or other health plan input; information on current practice in community or beneficiary preference may need further public input. Delegation should include specific instructions on the task, assignment or issue; include a time frame; provide direction on membership or input if a group is to be convened.
Clinical committee evidence votes

First voting question
The HTCC has reviewed and considered the technology assessment and information provided by the administrator, reports and/or testimony from an advisory group, and submissions or comments from the public. The committee has given greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Discussion document: What are the key factors and health outcomes and what evidence is there? (Applies to the population in the PICO for this review)

<table>
<thead>
<tr>
<th>Safety outcomes</th>
<th>Importance of outcome</th>
<th>Safety evidence/ confidence in evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatitis</td>
<td></td>
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<tr>
<td>Insomnia</td>
<td></td>
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<tr>
<td>Headaches</td>
<td></td>
<td></td>
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<tr>
<td>Other serious adverse events</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Efficacy – effectiveness outcomes</th>
<th>Importance of outcome</th>
<th>Efficacy / Effectiveness evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td></td>
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<tr>
<td>Progression-free survival</td>
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<tr>
<td>Tumor response</td>
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<tr>
<td>Quality of life</td>
<td></td>
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<tr>
<td>Functional status</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Cost outcomes</th>
<th>Importance of outcome</th>
<th>Cost evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct costs</td>
<td></td>
<td></td>
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<tr>
<td>Cost-effectiveness</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Special population / Considerations outcomes</th>
<th>Importance of outcome</th>
<th>Special populations/ Considerations evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</table>
### Health Technology Evidence Identification

<table>
<thead>
<tr>
<th>Unproven  (no)</th>
<th>Less  (yes)</th>
<th>Equivalent  (yes)</th>
<th>More in some  (yes)</th>
<th>More in all  (yes)</th>
</tr>
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</table>

**For safety:**
Is there sufficient evidence that the technology is safe for the indications considered?

<table>
<thead>
<tr>
<th>Unproven (no)</th>
<th>Less (yes)</th>
<th>Equivalent (yes)</th>
<th>More in some (yes)</th>
<th>More in all (yes)</th>
</tr>
</thead>
<tbody>
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</table>

**For efficacy/effectiveness:**
Is there sufficient evidence that the technology has a meaningful impact on patients and patient care?

<table>
<thead>
<tr>
<th>Unproven (no)</th>
<th>Less (yes)</th>
<th>Equivalent (yes)</th>
<th>More in some (yes)</th>
<th>More in all (yes)</th>
</tr>
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<tbody>
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</table>

**For cost outcomes/cost-effectiveness:**
Is there sufficient evidence that the technology is cost-effective for the indications considered?

<table>
<thead>
<tr>
<th>Unproven (no)</th>
<th>Less (yes)</th>
<th>Equivalent (yes)</th>
<th>More in some (yes)</th>
<th>More in all (yes)</th>
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</table>
Health Technology Evidence Identification

Discussion

Based on the evidence vote, the committee may be ready to take a vote on coverage or further discussion may be warranted to understand the differences of opinions or to discuss the implications of the vote on a final coverage decision.

- Evidence is insufficient to make a conclusion about whether the health technology is safe, efficacious, and cost-effective;
- Evidence is sufficient to conclude that the health technology is unsafe, ineffectual, or not cost-effective
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for all indicated conditions;
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for some conditions or in some situations

A straw vote may be taken to determine whether, and in what area, further discussion is necessary.

Second Vote

Based on the evidence about the technologies’ safety, efficacy, and cost-effectiveness, it is

_____ Not covered _____ Covered unconditionally _____ Covered under certain conditions

Discussion item

Is the determination consistent with identified Medicare decisions and expert guidelines, and if not, what evidence is relied upon.

Next step: proposed findings and decision and public comment

At the next public meeting the committee will review the proposed findings and decision and consider any public comments as appropriate prior to a vote for final adoption of the determination.

1) Based on public comment was evidence overlooked in the process that should be considered?
2) Does the proposed findings and decision document clearly convey the intended coverage determination based on review and consideration of the evidence?

Next step: final determination

Following review of the proposed findings and decision document and public comments:

Final vote

Does the committee approve the Findings and Decisions document with any changes noted in discussion?

If yes, the process is concluded.

If no, or an unclear (i.e., tie) outcome chair will lead discussion to determine next steps.
Medicare Coverage and Guidelines

[From page 37 of the Final Evidence Report]

The Centers for Medicare and Medicaid Services (CMS) does not have a national coverage determination related to TTF. Table 11 provides an overview of other payer coverage policies, and Table 12 summarizes excerpts from these policies that are relevant to TTF.

Guidelines

[From page 31 of the Final Evidence Report]

Table 9. Clinical practice guidelines that include TTF treatments

<table>
<thead>
<tr>
<th>Organization</th>
<th>Guideline Title (Year)</th>
<th>Evidence Base</th>
<th>Recommendation</th>
<th>Rating/Strength of Evidence Narrative Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Comprehensive Cancer Network (NCCN)</td>
<td>NCCN Clinical Practice Guidelines in Oncology. Central Nervous System Cancers Version 1.2018 (2018)</td>
<td>2 RCTs</td>
<td>For patients of any age with newly diagnosed GBM and with good performance status (KPS &gt;60), and any MGMT promoter status: Recommend standard brain radiotherapy + concurrent temozolomide and adjuvant temozolomide + alternating electric field therapy. For patients with recurrent glioblastoma: consider alternating electric field therapy.</td>
<td>Authors rated the recommendation for newly diagnosed GBM Category 1 and recurring GBM Category 2B</td>
</tr>
<tr>
<td>U.K. National Institute for Health and Care Excellence (NICE)</td>
<td>Brain tumours (primary) and brain metastases in adults (2018)</td>
<td>2 RCTs</td>
<td>For patients newly diagnosed glioblastoma: Do not offer TTF as part of management. For patients with recurrent glioblastoma: Do not offer TTF as part of management.</td>
<td>NICE chooses to reflect the concept of strength in the wording of the recommendation</td>
</tr>
<tr>
<td>American Association of Neuroscience Nurses (AANN)</td>
<td>Care of the Adult Patient with a Brain Tumor (2014) (Revised 2016)</td>
<td>1 RCT, 1 Narrative Expert Review</td>
<td>Nurses should be aware that use of electrical TTF may be considered a comparable treatment option to chemotherapy for patients with recurrent malignant glioma, particularly when hematologic, infectious, or gastrointestinal toxicities limit treatment options (Level 1 recommendation). When TTF are used, nurses should assess the skin for topical dermatitis (Level 1 recommendation). Nurses should educate patients about measures to improve comfort and compliance with the system (Level 3 recommendation).</td>
<td>Authors rated two recommendations Level 1 and one recommendation Level 3</td>
</tr>
<tr>
<td>Medical Oncology Spanish Society (SEOM)</td>
<td>SEOM clinical guidelines for diagnosis and treatment of glioblastoma (2017)</td>
<td>Unclear</td>
<td>For recurrent GBM, TTF failed to prolong survival compared with second-line chemotherapy.</td>
<td>Authors rated the evidence level II grade D</td>
</tr>
</tbody>
</table>
## Table 9. Clinical practice guidelines that include TTF (continued)

<table>
<thead>
<tr>
<th>Organization</th>
<th>Guideline Title (Year)</th>
<th>Evidence Base</th>
<th>Recommendation</th>
<th>Rating/Strength of Evidence Narrative Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Association for Neuro-Oncology (EANO)</td>
<td>EANO guideline on the diagnosis and treatment of adult astrocytic and oligodendrogial gliomas (2017)</td>
<td>2 RCTs</td>
<td>TTF was not recommended. The following two statements were included in the text:</td>
<td>No rating was given when a treatment was not recommended</td>
</tr>
<tr>
<td></td>
<td>Quality Rating: 5 out of 7 overall. 3 out of 7 for the guidelines handling of TTF</td>
<td></td>
<td>Newly diagnosed GBM: Questions about the mode of action, interpretation of data, and effect on quality of life have been raised, and the role and cost-effectiveness of TTF in the treatment of newly diagnosed glioblastoma remain to be defined.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Recurrent GBM: TTF were not superior to best physician’s choice in a randomized phase III trial.</td>
<td></td>
</tr>
<tr>
<td>European Society for Medical Oncology (ESMO)</td>
<td>High-grade glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2014)</td>
<td>1 RCT</td>
<td>TTF was not recommended. The guideline included the following statement for recurrent GBM “TTF failed to prolong survival compared with second-line chemotherapy.”</td>
<td>Authors rated the TTF evidence level I grade A</td>
</tr>
<tr>
<td></td>
<td>Quality Rating: 2 out of 7</td>
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</tbody>
</table>

**Abbreviations:** AGREE II = Appraisal of Guidelines for Research & Evaluation II; CT = controlled trial; GBM = glioblastoma; KPS = Karnofsky Performance Score; MGMT = 06-methylguanine-DNA Methyltransferase; RCT = randomized controlled trial; SR = systematic review; TTF = tumor treating fields; U.K. = United Kingdom.

*a* Results of our independent quality assessment using the AGREE II tool (version 2017.21). Unless otherwise noted, the Rating refers to the quality of the overall guideline including the guidelines handling of the TTF evidence. A score of 1 indicates the lowest quality possible, a score of 7 indicated the highest quality possible.

*b* Only recommendations from the guideline pertinent to TTF for the treatment of GBM are summarized.

*c* Refers to the quality rating/ strength of the recommendation as described in the guideline by the authors of the CPG.

*d* Alternating electric field therapy is only an option for patients with supratentorial disease.

*e* Category 1 evidence: based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. Note the recommendation for newly diagnosed GBM was changed from category 2A (based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate) to category 1 in a flash update to the 2018 guideline.

*f* Level 1 recommendations are supported by Class 1 evidence. Class I = Randomized controlled trials without significant limitations or meta-analysis. Level 3 recommendations are supported by Class III and IV evidence. Class III = Qualitative study, case study, or series Class IV = Evidence from expert committee reports and expert opinion of the AANN guideline panel; standards of care and clinical protocols that have been identified.

*g* Level 2 Evidence = Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity. Grade D = Moderate evidence against efficacy or for adverse outcome, generally not recommended.

*h* Level 1 = Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity, Grade A= Strong evidence for efficacy with a substantial clinical benefit, strongly recommended.