Washington State Health Care Authority

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:

Title	Business Name & Address	Business Type
Click here to enter text.	Click here to enter text.	Click here to enter text.
Click here to enter text.	Click here to enter text.	Click here to enter text.
Click here to enter text.	Click here to enter text.	Click here to enter text.

(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:

Business Name	Business Address	Business Type
Click here to enter text.	Click here to enter text.	Click here to enter text.
Click here to enter text.	Click here to enter text.	Click here to enter text.
Click here to enter text.	Click here to enter text.	Click here to enter text.
Click here to enter text.	Click here to enter text.	Click here to enter text.

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:

Received From	Organization Address	Service Performed
Click here to enter text.	Click here to enter text.	Click here to enter text.
Click here to enter text.	Click here to enter text.	Click here to enter text.
Click here to enter text.	Click here to enter text.	Click here to enter text.

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.

Source Name & Address	Received By	Source Type
University of Washington	Jason Rockhill	salary
UWP	Jason Rockhill	salary
University of Washington	wife	salary
Click here to enter text.	Click here to enter text.	Click here to enter text.

(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

If "yes", describe: The University of Washington Medical Center provides care for patients shoes coverage can be determined by the HTCC

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.)

Lobbyist Name	Business Name	Type Business Shared
Click here to enter text.	Click here to enter text.	Click here to enter text.
Click here to enter text.	Click here to enter text.	Click here to enter text.
Click here to enter text.	Click here to enter text.	Click here to enter text.

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:

Income Source	Address	Description of Income Source
Click here to enter text.	Click here to enter text.	Click here to enter text.
Click here to enter text.	Click here to enter text.	Click here to enter text.

Click here to enter text.	Click here to enter text.	Click here to enter text.

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:

Business Name	Business Address	Description of Business
Click here to enter text.	Click here to enter text.	Click here to enter text.
Click here to enter text.	Click here to enter text.	Click here to enter text.
Click here to enter text.	Click here to enter text.	Click here to enter text.

7. Service Fee of More Than $1,000

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

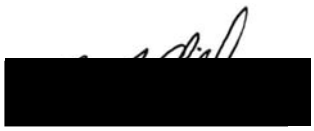
List each ***person for whom you performed a service for a fee of more than $1,000*** in the immediate preceding calendar year or the current year to date.

Name	Description of Service
Click here to enter text.	Click here to enter text.
Click here to enter text.	Click here to enter text.
Click here to enter text.	Click here to enter text.

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

[redacted]

jkrock@uw.edu (profesional)
[redacted]

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).

Graduate - Doctor of Philosophy (PhD), 1997. University of Illinois – Urbana/Champaign, Dr. Richard Gumport, Thesis Advisor. Thesis Title: The Role of Water-Adenine Complexes in Protein-DNA Interactions.

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.

Post-Doctoral Studies - University of Illinois – Urbana/Champaign, Dr. Richard Gumport's Lab. Interest – Water-mediated protein/DNA interactions with guanosine nucleoside analogues. Oct 1998 – 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.

Co-Director of UW Medicine Clinical Neuro-Oncology. April 2013 – Dec 2014.

Neuro Oncology Radiation Therapy Enhancement Committee (NORTEC), Chair. Responsible for the development of clinical treatment protocols and efficiencies for brain tumor patients in a patient centric manner. Jan 2012 – Dec 2014.

UWP Retirement & Benefits Committee. March 2013 – March 2016.

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

Member of the Solid Tumor Scientific Review Committee. Aug 2008 – Jun 2010.

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 2018.

Seattle Magazine and Castle Connelly, Top Doctor in Seattle, March 2018.

Seattle Metropolitan Magazine "Top Doc". August 2017.

Seattle Metropolitan Magazine "Top Doc". August 2016.

Seattle Metropolitan Magazine "Top Doc". August 2015.

Seattle Magazine and Castle Connelly, Top Doctor in Seattle, February 2015.

Seattle Metropolitan Magazine "Top Doc". August 2014.

Seattle Metropolitan Magazine "Top Doc". August 2013.

Department of Radiation Oncology Excellence in Teaching Award. July 2007 – Jun 2008.

Contributions to the University of Illinois at Urbana/Champaign College of Medicine Award. Co-Recipient with Dr. Carol Rockhill, Oct 2006.

Drs. Charles and Patricia O'Morchoe Leadership Fellow - 1st recipient. 1998 - 1999.

University of Illinois Fellow 1997-98, 1998-1999.

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:

Washington, Active Full licensure, #MD00040775. Jun 2004 – current.

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:
Supervisor of Undergraduate Medical Research for Theo Sottero. Jan 2012 – Jun 2012.
Supervisor of Undergraduate Medical School Research for Michelle Lin. Sept 2009 – Jun 2010.
Supervisor of Undergraduate Medical School Research for Kenneth Foerster. Jun 2008 – June 2010.
Lecture for Bellevue College Radiation Therapy Program – Lecture on Radiosurgery. May 2008 – current. Provide lectures to radiation therapy students on radiosurgery.
Attending for Chronic Care Clerkship – Palliative Care. Supervising 4th year Medical Students one afternoon a week about talking to patients with potentially life-threatening brain tumors and end-of-life issues. University of Washington Medical School, Seattle, WA Jul 2005 – Jun 2009.

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 Neurology 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 - currrent.
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.

Didactics in Ophthalmology on Radiation and the Optic Pathways, University of Washington School of Medicine. July 2004 – June 2012.
Didactics in Anesthesiology on Radiation and Cancer Pain, University of Washington School of Medicine. July 2004 – June 2005.

Doctoral Education:
Ph.D. committee Russ Rockne "Mathematical Modeling of Radiation Therapy in Highly Diffuse Tumors." August 2013.

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. "Gamma Knife Stereotactic Radiosurgery for AVM'S: Dose Staged versus Volume Staged" Leksell Gamma Knife Society Meeting, Dubai, March 2018.
Rockhill JK. "Fundamentals of Radiation Oncology Imaging for Skull Base Tumors, RSNA Chicago IL, Nov 2015.
Rockhill JK. "Protons vs SRS for CNS Malignancies: Strengths and Limitations." CNS/Skull Base Symposium. New York NY, April 2015.
Rockhill JK. "Imaging Evaluation of Post-Radiation Therapy Normal Tissue Effects" RSNA Chicago IL, Nov 2014.
Rockhill JK. "Benign Tumors and the Role of Radiation Therapy for Them. Including Gamma Knife and Proton Therapy." AAMD 39th Annual Meeting, Seattle, WA. June 2014.
Rockhill JK. "Brain Metastasis." Columbia Basin Medical Conference, Moses Lake WA. November 2013.
Rockhill JK. "The Role of Stereotactic Radiosurgery/Radiotherapy for Brain Metastases." 2013 AAMD Region I Meeting, Anchorage AK. August 2013.
Rockhill JK. "Benign Brain Tumors and the Role of Radiation Therapy – Radiosurgery and Protons." 2013 AAMD Region I Meeting, Anchorage AK. August 2013.
Rockhill JK. "Irradiating CNS Tumors – We've Personalized Targeting, Can We Personalize Dose." Society for Brain Mapping and Therapeutics. Baltimore, MD. May 2013.
Rockhill JK. "Clinical Issues in the Treatment of Gliomas." Recent Advances in Biologically Guided Radiation Therapy, UW Medicine, Seattle, WA. Aug 5, 2011.
Rockhill JK and Sandison G. "Radiobiological Rationale for High LET Radiotherapy." British Columbia Cancer Agency. Vancouver, BC, July 2011.
Rockhill JK. "Extend™ Your Possibilities with Perfexion." Elekta Gamma Knife Users Meeting. Florida, Jun 7, 2011.
Rockhill JK. "Post Therapeutic Brain: Radiation, Radiosurgery, and Chemotherapy" RSNA Annual Meeting. Vancouver, BC. June 2009.
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, "Update on the treatment of gliomas." Hawaii State Oncology Society Meeting, Honolulu HI. Jan 2017

Rockhill JK, Silbergeld DL, Chamberlain MC. "The latest treatments, staging, research and clinical trials available for brain cancers." Skagit Valley Hospital. Mt. Vernon WA. Oct 2014.

Rockhill JK, Silbergeld DL, Chamberlain MC. "The latest treatments, staging, research and clinical trials available for brain cancers." Olympic Medical Center. Sequim WA. Sept 2014.

Rockhill JK, Silbergeld DL, Chamberlain MC. "The latest treatments, staging, research and clinical trials available for brain cancers." Multicare. Tacoma WA. Aug 2014.

Rockhill JK, Silbergeld DL, Mrugala MM. "Brain Cancer Updates" NCCN Continuing Education Breakthrough in Solid Tumor Oncology, Seattle WA Jun 19-20, 2014.

Rockhill, JK. "Multi-Session Gamma Knife." Northwest Association of Medical Physicist Annual Meeting. Seattle, WA. Sept. 2011.

Rockhill, JK. "Brain Metastases: ? " Seattle Cancer Care Alliance Monthly Meeting for Advanced Nurse Practioners. Seattle, WA. May 2011.

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

Rockhill JK. "Glioblastoma Multiforme - Where are we from a Radiation Oncology Perspective." Oral presentation to Harrison Hospital Oncology. Bremerton, WA. Sept 29, 2009.

Rockhill JK, Mrugala M. "Team Approach to CNS Disease in Metastatic Breast Cancer: Part 1." Oral presentation for the University of Washington Continuing Medical Education Course: Challenges and Controversies in Breast Cancer. Seattle, WA Oct 25-26, 2007.

Rockhill JK. "Stereotactic Radiosurgery for AVM's." Oral presentation for University of Washington Continuing Medical Education Course: Advances in Stroke and Cerebrovascular Disease Management. Seattle, WA. March 23-24, 2007.

Rockhill JK. "Radiation Consideration for Anterior Visual Pathway Tumors." Oral presentation at the Northwest Neuro-Ophthalmology Updates, Seattle, WA, Nov. 13, 2004.

Grand Rounds:

Rockhill JK. "Stereotactic Radiotherapy: What's Fractionation Got To Do With It." University of Washington Department of Neurology Grand Rounds, Nov 16, 2017.

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.

Rockhill JK. "XRT for Spine Metastases: It Shouldn't Be an Emergency." Combined University of Washington Neurological Surgery and Orthopedics Grand Rounds, Sept 21, 2005.

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:

1. Ene CI, Macomber MW, Gao W, Falcone J, Barber J, Rostomily R, Ferreira M, Ellenbogen R, Holland E, Rockhill J, Silbergeld D, Halasz L. Patterns of failure after stereotactic radiosurgery for recurrent high grade glioma: A single institution experience of 10 years. Neurosurgery (Accepted Sept 2018.)
2. Nabors LB, Portnow J, Ammirati M, Baehring J, Brem H, Butowski N, Fenstermaker RA, Forsyth P, Hattangadi-Gluth J, Holdhoff M, Howard S, Junck L, Kaley T, Kumthekar P, Loeffler JS, Moots PL, Mrugala MM, Nagpal S, Pandey M, Parney I, Peters K, Puduvalli VK, Ragsdale J 3rd, Rockhill J, Rogers L, Rusthoven C, Shonka N, Shrieve DC, Sills AK Jr, Swinnen LJ, Tsien C, Weiss S, Wen PY, Willmarth N, Bergman MA, Engh A. NCCN Guidelines Insights: Central Nervous System Cancers, Version 1.2017. J Natl Compr Canc Netw. 2017 Nov;15(11):1331-1345.
3. Nerva JD, Barber J, Levitt MR, Rockhill JK, Hallam DK, Ghodke BV, Sekhar LN, Kim LJ. Onyx embolization prior to stereotactic radiosurgery for brain arteriovenous malformations: a single-center treatment algorithm. J Neurointerv Surg. 2018 Mar;10(3):258-267 (Epub 2017 Jul 14).
4. Smith WP, Young LA, Phillips MH, Cheung M, Halasz LM, Rockhill JK. Clinical Positioning Accuracy for Multisession Stereotactic Radiotherapy with the Gamma Knife Perfexion. Technol Cancer Res Treat. 2017 Dec 16(6): 893–899.
5. Kim M, Kotas J, Rockhill JK, Phillips M. A Feasibility Study of Personalized Prescription Schemes for Glioblastoma Patients Using a Proliferation and Invasion Glioma Model. Cancers (Basel). 2017 May 13;9(5) 51.
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

brain arteriovenous malformations: the Pediatric Quality of Life Inventory.J Neurosurg Pediatr. 2016 Nov;18(5):611-622.
7. Nerva JD, Kim LJ, Barber J, Rockhill JK, Hallam DK, Ghodke BV, Sekhar LN. Outcomes of Multimodality Therapy in Pediatric Patients With Ruptured and Unruptured Brain Arteriovenous Malformations. Neurosurgery. 2016 May;78(5):695-707.
8. Ly KI, Hamilton SR, Rostomily RC, Rockhill JK, Mrugala MM. Improvement in Visual Fields After Treatment of Intracranial Meningioma With Bevacizumab. J Neuroophthalmol. 2015 Dec;35(4):382-6.
9. Brachman DG, Pugh SL, Ashby LS, Thomas TA, Dunbar EM, Narayan S, Robins HI, Bovi JA, Rockhill JK, Won M, Curran WP. Phase 1/2 Trials of Temozolomide, Motexafin Gadolinium, and 60-Gy Fractionated Radiation for Newly Diagnosed Supratentorial Glioblastoma Multiforme: Final Results of RTOG 0513. Int J Radiat Oncol Bio Phys. 2015 Apr 1; 91(5):961-7.
10. Cho E, Rubinstein L, Stevenson P, Gooley T, Philips M, Halasz LM, Gensheimer MF, Linden HM, Rockhill JK, Gadi VK. The use of stereotactic radiosurgery for brain metastases from breast cancer: Who benefits most? Breast Cancer Res Treatment. 2015 Feb; 149(3):743-9.
11. Nerva JD, Mantovani A, Barber J, Kim LJ, Rockhill JK, Hallam DK, Ghodke BV, Sekhar LN. Treatment Outcomes of Unruptured Arteriovenous Malformations With a Subgroup Analysis of ARUBA (A Randomized Trial of Unruptured Brain Arteriovenous Malformations)-Eligible Patients. Neurosurgery 76.5 (2015): 563-570.
12. Rockne RC, Trister AD, Jacobs J, Hawkins-Daarud AJ, Neal ML, Hendrickson K, Mrugala MM, Rockhill JK, Kinahan P, Krohn KA, Swanson KR. A patient-specific computational model of hypoxia-modulated radiation resistance in glioblastoma using 18F-FMISO-PET. J R Soc Interface. 2015 Feb 6;12(103).
13. Baldock AL, Yagle K, Born DE, Ahn S, Trister AD, Neal M, Johnston SK, Bridge CA, Basanta D, Scott J, Malone H, Sonabend AM, Canoll P, Mrugala MM, Rockhill JK, Rockne RC, Swanson KR. Invasion and proliferation kinetics in enhancing gliomas predict IDH1 mutation status. Neuro Oncol. 2014 Jun; 6: 779-786.
14. Ramakrishna R, Rostomily R, Sekhar L, Rockhill K, Ferreira M. Hemangiopericytoma: Radical resection remains the cornerstone of therapy. J Clin Neurosci. 2014 Apr;21:612-615.
15. Adair, JE., Johnson SK, Mrugala MM, Beard BC, Guyman LA, Baldock AL, Bridge CA, Hawkins-Daarud AH, Gori JL, Born DE, Gonzalez-Cuvar LF, Silbergeld DL, Rockne RC, Storer BE, Rockhill JK, Swanson KR, Liem HP. Gene therapy enhances chemotherapy tolerance and efficacy in glioblastoma patients. The Journal of clinical investigation 124.9 (2014): 4082-4092.J Clin Invest. 2014;124(9):4082–4092.
16. Halasz L, Rockhill J. Stereotactic radiosurgery and stereotactic radiotherapy for brain metastases. Surgical Neurology International. 2013 Oct 1;4:S185-S191.
17. Baldock AL, Rockne RC, Boone AD, Neal ML, Hawkins-Daarud A, Corwin DM, Bridge CA, Guyman LA, Trister AD, Mrugala MM, Rockhill JK, Swanson KR. From patient-specific mathematical neuro-oncology to precision medicine. Front Oncol. 2013;3:62
18. Neal ML, Trister AD, Ahn S, Baldock A, Bridge CA, Guyman L, Lange J, Sodt R, Cloke T, Lai A, Cloughesy TF, Mrugala MM, Rockhill JK, Rockne RC, Swanson KR. Response classification based on a minimal model of glioblastoma growth is prognostic for clinical outcomes and distinguishes progression from pseudoprogression. Cancer Res. 2013 May 15;73(10):2976-86.
19. Halasz LH, Rockhill JK. Stereotactic radiosurgery and stereotactic radiotherapy for brain metastases. Surg Neurol Int. 2013 May 2:4(Suppl 4):S185-91.
20. Neal ML, Trister AD, Cloke T, Sodt R, Ahn S, Anne L. Baldock, Bridge CA, Lai A, Timothy F. Cloughesy TF, Mrugala MM, Rockhill JK, Rockne RC, Swanson KR. (2013)

Discriminating Survival Outcomes in Patients with Glioblastoma Using a Simulation-Based, Patient-Specific Response Metric. PLoS ONE 8(1): e51951. doi:10.1371/journal.pone.0051951

21. Ramakrishna R, Rostomily R, Rockhill J. A rare case of gamma knife-induced smoking cessation in a patient with a vestibular schwannoma. Br J Neurosurg. 2012 Sep 28. [Epub ahead of print]
22. Mikheev AM, Ramakrishna R, Stoll EA, Mikheeva SA, Beyer RP, Plotnik DA, Schwartz JL, Rockhill JK, Silber JR, Born DE, Kosai Y, Horner PJ, Rostomily RC. Increased age of transformed mouse neural progenitor/stem cells recapitulates age-dependent clinical features of human glioma malignancy. Aging Cell. 2012 Dec;11(6):1027-35
23. Adair JE , Beard BC, Trobridge GD, Neff T, Rockhill JK, Silbergeld DL, Mrugala MM, Kiem H.-P. Extended Survival of Glioblastoma Patients After Chemoprotective HSC Gene Therapy. Sci. Transl. Med. 4, 133ra57 (2012).
24. Chowdhary A, Spence AM, Sales L, Rostomily RC, Rockhill JK, Silbergeld DL. Radiation associated tumors following therapeutic cranial radiation. Surg Neurol Int 2012;3:48.
25. Fink JR, Carr RB, Matsusue E, Iyer RS, Rockhill JK, Haynor DR, Maravilla KR. Comparison of 3 Tesla proton MR spectroscopy, MR perfusion and MR diffusion for distinguishing glioma recurrence from posttreatment effects. *J Magn Reson Imaging.* 2012 Jan;35(1):56-63. doi: 10.1002/jmri.22801. Epub 2011 Oct 14.
26. Sales L, Rockhill JK. Cancer pain emergencies: is there a role for radiation therapy? *Curr Pain Headache Rep.* 2010 Dec;14(6):483-8.
27. Keene C, Chang R, Lopez-Yglesias A, Shalloway B, Sokal I, Reed P, Keene L, Montine K, Breyer R, Rockhill JK, Montine T. Suppressed accumulation of cerebral amyloid β peptides in aged transgenic Alzheimer's disease mice by transplantation with wild type or PGE2 receptor subtype 2-null bone marrow. *Am J Pathol*. 2010 Jul; 177(1):346-54.
28. Rockne R, Rockhill JK, Mrugala M, Spence AM, Kalet I, Hendrickson K, Lai A, Cloughesy T, Alvord EC Jr, Swanson KR. Predicting the efficacy of radiotherapy in individual glioblastoma patients in vivo: a mathematical modeling approach. *Phys Med Biol*. 2010 Jun 21;55(12):3271-85.
29. Yang T, Rockhill JK, Sekhar L. A case of high grade undifferentiated sarcoma after surgical resection and stereotactic radiosurgery of a vestibular schwannoma. *Skull Base*. 2010 May;20(3):179-83.
30. Wang CH, Rockhill JK, Mrugala M, Peacock DL, Lai A, Jusenius K, Wardlaw JM, Cloughesy T, Spence AM, Rockne R, Alvord, Jr. EC, Swanson KR. Prognostic Significance of Growth Kinetics in Newly Diagnosed Glioblastomas Revealed by Combining Serial Imaging with a Novel Bio-mathematical Model. *Cancer Res*. 2009 Dec 1;69(23):9133-40.
31. Matsusue E, Fink JR, Rockhill JK, Ogawa T, Maravilla KR. Distinction between glioma progression and post-radiation change by combined physiologic MR imaging. *Neuroradiology* 2009:Oct 16.
32. Loiselle C, Rockhill JK. Radiation, chemotherapy, and symptom management in cancer-related cognitive dysfunction. *Curr Pain Headache Rep* 2009:Aug;13(4):271-6.
33. Rockne R, Alvord EC, Rockhill JK, Swanson KR. A Mathematical Model for Brain Tumor Response to Radiation Therapy. *J Math Biol* 2008:Sep 25.
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Rockhill JK. "Model Tumor Systems and Tumor Growth Kinetics." Oral presentation for the Annual Northwest Radiobiology Conference, May 15, 2009.
Rockhill JK. "CNS Lymphoma." Oral presentation to University of Washington Radiation Oncology Residents, April 10, 2009.
Rockhill JK. "Radiation Consideration for Anterior Visual Pathway Tumors." Oral presentation to the University of Washington Ophthalmology Residents, Mar 13, 2008.
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Rockhill JK. "Radiation Therapy for Cancer Pain." Oral presentation to the University of Washington Anesthesiology residents, UWMC , Jan 29, 2007.
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Rockhill JK. "Radiosurgery for AVMs." Oral presentation to the University of Washington Neurosurgery Residents, Supper Club, Oct 25, 2005.

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Rockhill JK. "Biology of Radiation Therapy." Oral presentation to the University of Washington Neurosurgery residents, Supper Club, Jun 14, 2005.

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Rockhill JK. "Radiation Chemistry – Gone in 60 Seconds." Oral presentation at the Annual Northwest Radiobiology Conference, Seattle, WA. May 2003.

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Notable Meeting Participation:

James S. McDonnell Foundation**,** "The Mathematical Biology of Human Brain Cancer." Babson Park, MA April 20-22, 2009.

Washington State Health Care Authority

Agency medical director comments

Tumor Treating Fields – Re-review

Shana Johnson, MD
Clinical Quality Care Transformation
Health Care Authority

November 16, 2018

Washington State Health Care Authority

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.hca.wa.gov/hta/meetingmaterials/Forms/ExtMeetingMaterials.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

2

Factors Prompting TTF Re-review

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

3

Tumor Treating Fields (TTF)

Medical Director Concerns

Safety	Low
Efficacy	High
Cost	High

4

State Agency Coverage Policy

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

5

Other Insurers' Coverage Policies

Tumor Treating Field Coverage	New Diagnosis	Recurrent
National Coverage Determination	None	None
Local Coverage Determination	None	None
Regence	Yes	No
Aetna	Yes	Yes
Kaiser	Yes	No

6

Washington State Health Care Authority

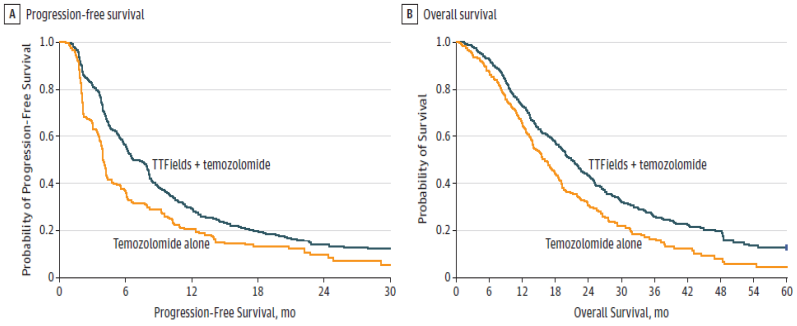
Guideline recommendations

- **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 a adjunct (Category 2B)
- **UK National Institute for Health Care and Excellence (NICE) 2018**
  - Does not recommend
  - Not an efficient use of resources

7

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



No. at risk

TTFields	466	229	100	62	30	18	466	424	333	256	174	107	65	45	30	19	16
Temozolomide	229	66	35	18	9	2	229	191	144	95	60	33	22	13	7	5	2

A, Median progression-free survival from randomization for the tumor-treating fields (TTFields) 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; $P < .001$). B, Median survival from randomization was 20.9 for the TTFields plus temozolomide group vs 16.0 months for the temozolomide-alone group (HR, 0.63; 95% CI, 0.53-0.76; $P < .001$). Median follow up was 44 months (range, 25-91 months) in both groups.

Stupp R, Taillibert S, Kanner A, et al. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. *JAMA*. 2017;318(23):2306-2316.

8

Washington State Health Care Authority

Annual Survival Rates

Table 2. Summary of Study End Points[a]

	TTFields + Temozolomide (n = 466)	Temozolomide Alone (n = 229)	Between-Group Differences
Progression-free survival			
Primary end point, median (95% CI), mo	6.7 (6.1-8.1)	4.0 (3.8-4.4)	2.7 (2.1-4.2)
Overall survival			
Secondary end point, median (95% CI), mo	20.9 (19.3-22.7)	16.0 (14.0-18.4)	4.9 (2.3-7.9)
Exploratory end points, % (95% CI			
Progression-free 6-mo survival rate	56 (51-61)	37 (30-44)	19 (15-23)
Annual survival rates, y			
1	73 (69-77)	65 (59-72)	18 (10-25)
2	43 (39-48)	31 (25-38)	12 (4-18)
3	26 (22-31)	16 (12-23)	10 (3-17)
4	20 (16-25)	8 (4-14)	12 (5-19)
5	13 (9-18)	5 (2-11)	8 (2-14)

Abbreviation:
TTFields, tumor-treating fields.

[a] Survival rates are actuarial estimates according to the Kaplan-Meier method.

Stupp 2017, JAMAStupp R, Taillibert S, Kanner A, et al. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. *JAMA*. 2017;318(23):2306-2316.

9

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- 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)

10

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

11

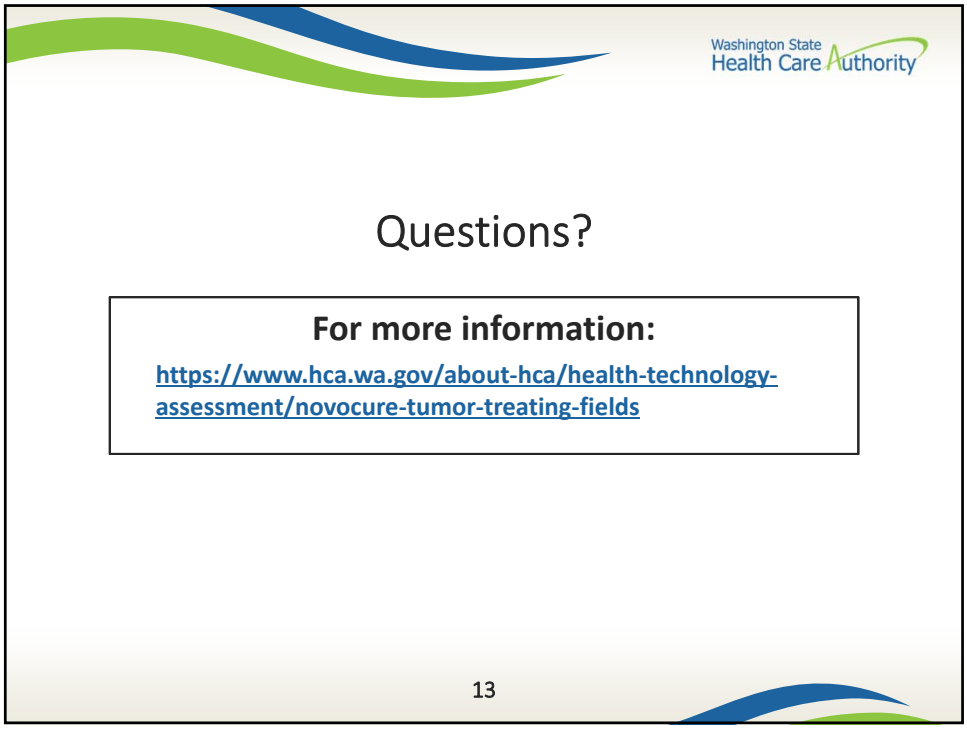
Agency Recommendations

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

12


Washington State Health Care Authority
Questions?
For more information:
https://www.hca.wa.gov/about-hca/health-technology-assessment/novocure-tumor-treating-fields
13

Washington State Health Care Authority

Order of scheduled presentations:

Tumor treating fields, (Optune®)

	Name
1	Justin Kelly, RN, BSN, Novocure

RTI INTERNATIONAL

UNC | THE CECIL G. SHEPS CENTER FOR HEALTH SERVICES RESEARCH

RTI-University of North Carolina Evidence-based Practice Center

Tumor Treating Fields (Optune®)

Health Technology Assessment
State of Washington Health Care Authority

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Presented by:
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November 16, 2018
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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

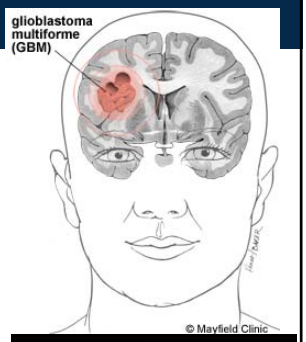
2 Page in Report N/A

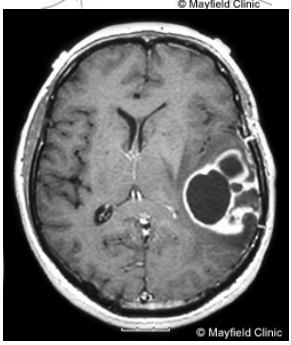
Background

3 Pages 3-7

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





GBM = glioblastoma.

4 Pages 3 & 4

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

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

5 Pages 4 & 5

GBM = glioblastoma; TMZ = temozolomide.

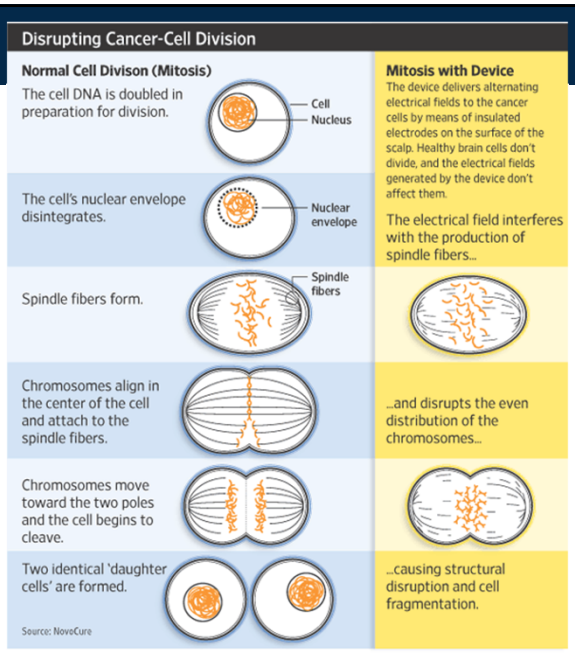
Technology Description

Alternating electric fields enter the cancer cell and **<u>disrupt mitotic spindle microtubule assembly</u>** 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

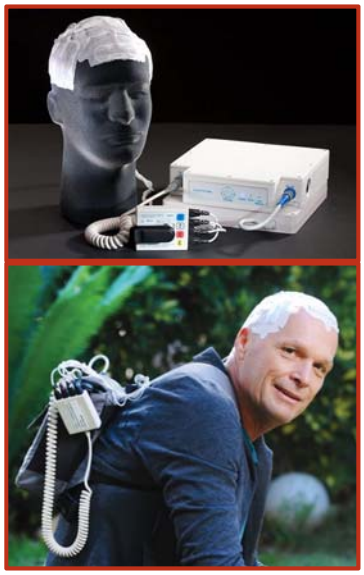
GBM = glioblastoma.



6 Pages 5 & 6

Image obtained from: Dooreen, JC (2010) 'A New Way to Treat Brain Cancer,' *The Wall Street Journal*, 8 June 2010, available online at https://www.wsj.com/articles/SB10001424052748703303904575292691538647642

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

7 Page 6

Images obtained from: https://consultqd.clevelandclinic.org/new-studies-assess-promise-of-tumor-treating-fields/ and https://newsroom.uw.edu/postscript/normalcy-vs-time-brain-cancer-patients-choice

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

Regulatory Status

	Recurrent GBM	Newly Diagnosed GBM
FDA Approval	April 2011	October 2015
Indications	• Age 22 years or older • GBM in supratentorial location • Confirmed recurrent GBM after chemotherapy • **To be used as monotherapy** • As alternative to standard medical therapy after surgical and radiation options exhausted	• Age 22 years or older • GBM in supratentorial location • Confirmed newly diagnosed GBM following maximal debulking surgery and completion of radiation therapy with concomitant standard-of-care chemotherapy • **To be used with TMZ**
Contraindications	• Active implanted medical device present (brain, spinal cord, or vagus nerve stimulators, pacemaking, defibrillators, programmable shunts) • Skull defect present • Known sensitivity to conductive hydrogels	

8 Pages 6 & 7

GBM = glioblastoma; TMZ = temozolomide.

Policy Context for Washington

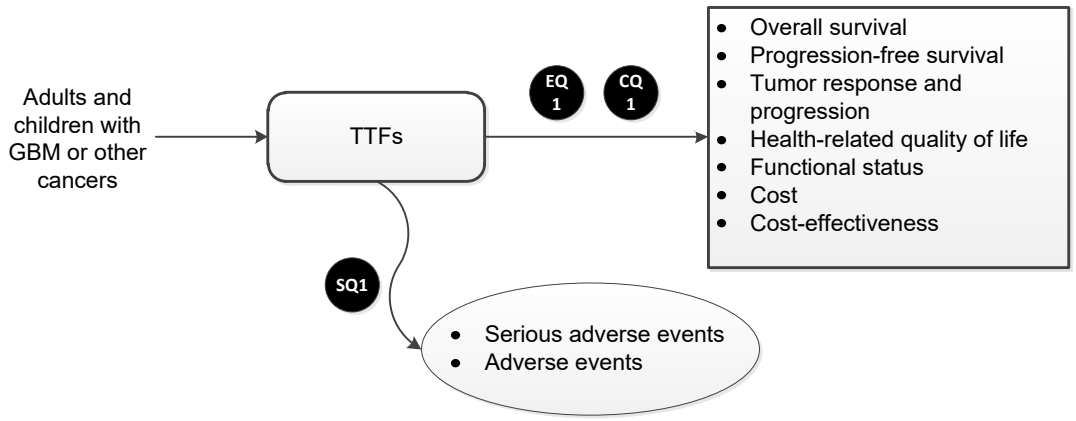
- Based on the prior 2015 report, the State of Washington's Health Technology Clinical Committee voted in January 2016 to not cover Optune®
- This topic was selected for re-review based on newly available published evidence and rated:
  - Low concerns for safety
  - High concerns for efficacy
  - High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

9 Page 7

Methods

10 Pages 7-13

Analytic Framework



11 Page 8

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

Study Selection for Primary Research Review

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

12 Pages 9-11

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

13 Page 11

CEA = cost-effectiveness analysis; RCT = randomized controlled trial.

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

14 Page 12

RCT = randomized controlled trial; SOE = strength of evidence.

Results

15 Pages 13-32

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		Recurrent GBM		Other Cancer	
EQ1:	2 (3)	EQ1:	4 (7)	EQ1:	0 (0)
SQ1:	2 (2)	SQ1:	5 (5)	SQ1:	3 (3)
CQ1:	1 (1)	CQ1:	0 (0)	CQ1:	0 (0)

- Clinical Practice Guidelines: **6**

16 Page 13

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

17 Page N/A

GBM = glioblastoma; TTF = tumor treating fields.

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

18 Page N/A

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

19 Pages 14-20

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

Newly Diagnosed GBM – Included Studies

TTF+TMZ vs. TMZ

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

20 Pages 14-19

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)

TTF+TMZ vs. TMZ

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

21 Pages 19 & 20

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

Newly Diagnosed GBM – EQ1

TTF+TMZ vs. TMZ

Overall Survival (OS)

1 RCT ⊕⊕◯◯ LOW For benefit with TTF **1 Observational Pilot** ⊕◯◯◯ VERY 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 **1 Observational Pilot** ⊕◯◯◯ VERY 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.

22 Pages 15-17

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

TTF+TMZ vs. TMZ

Quality of Life (QOL) and Functional Status

1 RCT ⊕◯◯◯ VERY LOW For benefit with TTF	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.

23 Pages 17 & 18

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

TTF+TMZ vs. TMZ

Adverse events (AEs)

1 RCT ⊕⊕◯◯ LOW For minimal harm with TTF	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

24 Pages 18 & 19

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

Newly Diagnosed GBM – CQ1

TTF+TMZ vs. TMZ

Cost-effectiveness

1 Cost-effectiveness analysis ⊕⊕◯◯ LOW Not cost-effective	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.

25 Page 20

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

Results

Recurrent GBM: TTF vs. Second-line Therapy

1 trial, 2 observational studies, 1 case series

26 Pages 20-28

GBM = glioblastoma; TTF = tumor treating fields.

Recurrent GBM – Included Studies

TTF vs. Second-line Therapy

Study Characteristics	Participant Characteristics
EF-11 Trial **Funding:** Novocure Ltd. **Countries:** 28 institutions in Austria, Czech Republic, France, Germany, Israel, Switzerland, and the United States **Risk of Bias:** Some concerns (OS, PFS, Safety) to high (QOL) **Intervention:** TTF (n=120) **Comparator:** Best chemotherapy (n=117)	• Median age = 54 years • Median KPS score = 80 (range 50 to 100) • Median 11.4 to 11.8 months since initial GBM diagnosis • Number of recurrences varied at randomization (12% first, 47% second, and 41% third or greater) • 80% received prior TMZ therapy • 19% received prior treatment with bevacizumab
Patient Registry Dataset (PRiDe): Observational cohort with historical comparator groups from EF-11 trial **Funding:** Novocure Ltd. **Country:** United States **Risk of Bias:** Some concerns (OS) to high (Safety) **Intervention:** TTF (n=457) **Comparator:** TTF (n=120) **Comparator:** Best chemotherapy (n=117)	Intervention group only: • Median age = 55 years • Median KPS score = 80 (range 10 to 100) • Median number of recurrences = 2 (range 1 to 5) • Number of recurrences varied at study start for (33% first, 27% second, and 27% third or greater, 13% unknown) • 78% received prior TMZ therapy • 55% received prior treatment with bevacizumab

27 Pages 20-28

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)

TTF vs. Second-line Therapy

Study Characteristics	Participant Characteristics
Observational Pilot Study: Cohort study with historical comparator groups **Funding:** Novocure Ltd. **Country:** Czech Republic **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)	• Median age = 50.7 to 54 years • Median KPS score = 80 to 90 (range 60 to 100) • Patients receiving TTF were at least 4 weeks from any brain surgery and at least 8 weeks from radiotherapy
Case series: Post-marketing surveillance program **Funding:** Novocure Ltd. **Country**: United States **Risk of Bias**: Not assessed **Intervention:** TTF (n=540)	• No additional details about the patient population were provided

28 Pages 20-28

GBM = glioblastoma; KPS = Karnofsky Performance Status; TMZ = temozolomide; TTF = tumor treating fields.

Recurrent GBM – EQ1

TTF vs. Second-line Therapy

Overall Survival (OS)

1 RCT ⨁◯◯◯ VERY LOW For no benefit with TTF **2 Observational Studies** ⨁◯◯◯ VERY LOW For benefit with TTF	**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.

29 Pages 22-25

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

Recurrent GBM – EQ1

TTF vs. Second-line Therapy

Progression-free Survival (PFS)

1 RCT ⨁◯◯◯ VERY LOW For no benefit with TTF **1 Observational Pilot** ⨁◯◯◯ VERY LOW For benefit with TTF	**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.

30 Pages 22-26

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

Recurrent GBM – EQ1

TTF vs. Second-line Therapy

Quality of life (QOL) and Functional Status

1 RCT ⨁◯◯◯ VERY LOW For benefit with TTF	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.

31 Pages 22-26

EORTC-QLQ = European Organization for Research and Treatment Quality of Life Questionnaire; EQ = efficacy question; GBM = glioblastoma; RCT = randomized controlled trial; TTF = tumor treating fields.

Recurrent GBM – SQ1

TTF vs. Second-line Therapy

Adverse events (AEs)

1 RCT ⨁◯◯◯ VERY LOW For minimal harm with TTF **2 Observational Studies** ⨁◯◯◯ VERY LOW For minimal harm with TTF	**RCT**: 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. **Observational**: 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.

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.

32 Pages 26-28

GBM = glioblastoma; RCT = randomized controlled trial; SQ = safety question; TTF = tumor treating fields

Results

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

1 observational study

33 Pages 20-28

GBM = glioblastoma; TTF = tumor treating fields.

Recurrent GBM – Included Study

TTF+Second-line vs. Second-line Therapy

Study Characteristics	Participant Characteristics
Post hoc cohort of EF-14 trial participants **Funding**: Novocure Ltd. **Country:** 83 centers in Austria, Canada, Czech Republic, France, Germany, Israel, Italy, South Korea, Sweden, Switzerland, United States **Risk of Bias:** High risk of bias (OS, safety) **Intervention:** TTF + Second-line therapy (n=144) **Comparator:** Second-line therapy (n=60)	• 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)

34 Pages 20-28

GBM = glioblastoma; KPS = Karnofsky Performance Status; TMZ = temozolomide; TTF = tumor treating fields.

Recurrent GBM – EQ1 & SQ1

TTF+Second-line vs. Second-line Therapy

Overall survival (OS)

1 Cohort ⨁◯◯◯ VERY LOW For no benefit with TTF	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 For minimal harm with TTF	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.

35 Pages 22-28

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

Results

Other Cancers

3 case series

36 Pages 29 & 30

Other Cancers – SQ1

Study & Patient Characteristics	Results
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

37 Pages 29 & 30

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

Results

Clinical Practice Guidelines

38 Pages 30-32

Clinical Practice Guideline Recommendations

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

39 Pages 30-32

GBM = glioblastoma.

Discussion

40 Pages 33-44

Summary of Strength of Evidence Ratings: New GBM

Outcomes	TTF + TMZ vs. TMZ		
	Study Design (№ Studies; № Patients)	**Certainty Direction of Effect**	**Summary of Main Findings**
Overall Survival (OS)	RCT (1; 695) OBS (1; NR)	⊕⊕◯◯ LOW For **benefit** with TTF ⊕◯◯◯ VERY LOW For **benefit** with TTF	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).
Progression-free Survival (PFS)	RCT (1; 695) OBS (1; 42)	⊕⊕◯◯ LOW For **benefit** with TTF ⊕◯◯◯ VERY LOW For **benefit** with TTF	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.
Quality of Life (QOL), Functional Status	RCT (1; 695)	⊕◯◯◯ VERY LOW For **benefit** with TTF	Time to sustained decline longer and more patients with stable or improved QOL subscale domains with TTF+TMZ than TMZ alone.
Safety	RCT (1; 672)	⊕⊕◯◯ LOW For **minimal harm** with TTF	Mild to moderate dermatologic AEs with TTF.
Cost	OBS (1; 1,000)	⊕⊕◯◯ LOW TTF **not cost-effective**	The discounted payor perspective ICER was $817,001 (95% CI, $612,352 to $1,021,651) per life year gained.

41 Page 34

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

Outcomes	TTF vs. Second-line Therapy		
	Study Design (№ Studies; № Patients)	**Certainty Direction of Effect**	**Summary of Main Findings**
Overall Survival (OS)	RCT (1; 237) OBS (2; 1,479)	⊕◯◯◯ VERY LOW For **no benefit** with TTF ⊕◯◯◯ VERY LOW For **benefit** with TTF	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.
Progression-free Survival (PFS)	RCT (1; 237) OBS (1; 785)	⊕◯◯◯ VERY LOW For **no benefit** with TTF ⊕◯◯◯ VERY LOW For **benefit** with TTF	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.
Quality of Life (QOL), Functional Status	RCT (1; 63)	⊕◯◯◯ VERY LOW For **benefit** with TTF	Patients receiving TTF showed larger improvements or less of a decline on more QOL subscale domains than patients receiving second-line therapy.
Safety	RCT (1; 672) OBS (2; 1,479)	⊕◯◯◯ VERY LOW For **minimal harm** with TTF ⊕◯◯◯ VERY LOW For **minimal harm** with TTF	Mild to moderate dermatologic AEs with TTF.

42 Page 34

AE = adverse event; GBM = glioblastoma; OBS = observational; RCT = randomized controlled trials; TTF = tumor treating fields.

Summary of Strength of Evidence Ratings: Recurrent GBM

Outcomes	TTF + Second-line Therapy vs. Second-line Therapy		
	Study Design (№ Studies; № Patients)	**Certainty Direction of Effect**	**Summary of Main Findings**
Overall Survival (OS)	OBS (1; 204)	⊕◯◯◯ VERY LOW For **no benefit** with TTF	Median OS was similar in the intervention and comparator groups (11.8 and 9.2 months, respectively).
Safety	OBS (1; 204)	⊕◯◯◯ VERY LOW For **minimal harm** with TTF	Mild to moderate dermatologic AEs with TTF.

43 Page 34

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

44 Pages 34-36

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

45 Page 41

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.

Payor	Newly Diagnosed GBM	Recurrent GBM	Other Cancers
Medicare	No policy identified	No policy identified	No policy identified
Premera	Covered	Not Covered	Not Covered
Regence	Covered	Not Covered	Not Covered
United Healthcare	Covered	Covered	Not Covered
Aetna	Covered	Covered	Not Covered
Humana	Covered	Covered	Not Covered
Kaiser	Covered	Not Covered	Not Covered
Cigna	Covered	Covered	Not Covered

46 Pages 37-40

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

We have very limited to limited confidence that the estimate of effect lies close to the true effect for these outcomes.

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.

47 Page 44

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

Additional Details

54 Page N/A

SOE interpretation

Grade	Definition
High	**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.
Moderate	**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.
Low	**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.
Very Low	**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.

49 Page 12

Subgroup Analyses

TTF+TMZ vs. TMZ

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

50 Page 17

CI = confidence interval; HR = hazard ratio; KPS = Karnofsky Performance Status; OS = overall survival; TMZ = temozolomide; TTF = tumor treating fields.

Subgroup Analyses

TTF vs. Second-line Therapy

Outcome	Study	Results
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.

51 Pages 25 & 26

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

Subgroup Analyses

TTF+Second-line vs. Second-line Therapy

Outcome	Study	Results
OS	Post hoc cohort of EF-14 participants	• 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).

52 Page 25

OS = overall survival; TTF = tumor treating fields.

Clinical Practice Guideline Synthesis

Organization, Year (Quality Rating)	Recommendation	Evidence Base; Strength of Evidence
National Comprehensive Cancer Network (NCCN), 2018 (5 out of 7)	For patients of any age with newly diagnosed GBM and with good performance status (KPS >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.**	2 RCTs; Authors rated the recommendation for newly diagnosed GBM Category 1 and recurring GBM Category 2B
U.K. National Institute for Health and Care Excellence (NICE) (2018) (7 out of 7)	For patients newly diagnosed glioblastoma: Do not offer **TTFs** as part of management. For patients with recurrent glioblastoma: Do not offer **TTFs** as part of management.	2 RCTs; NICE chooses to reflect the concept of strength in the wording of the recommendation

53 Pages 31 & 32

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

Clinical Practice Guideline Synthesis (cont'd)

Organization, Year (Quality Rating)	Recommendation	Evidence Base; Strength of Evidence
American Association of Neuroscience Nurses (AANN) (2016) (4 out of 7)	Nurses should be aware that use of electrical **TTFs** 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 **TTFs** 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).	1 RCT, 1 narrative expert review; Authors rated two recommendations Level 1 and one recommendation Level 3
Medical Oncology Spanish Society (SEOM) (2017) (3 out of 7)	For recurrent GBM, **TTFs** failed to prolong survival compared with second-line chemotherapy.	Unclear; Authors rated the evidence level II grade D

54 Pages 31 & 32

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

Clinical Practice Guideline Synthesis (cont'd)

Organization, Year (Quality Rating)	Recommendation	Evidence Base; Strength of Evidence
European Association for Neuro-Oncology (EANO) (2017) (5 out of 7 overall, 3 out of 7 for the guidelines handling of TTF)	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.	2 RCTs; No rating was given when a treatment was not recommended
European Society for Medical Oncology (ESMO) (2014) (2 out of 7)	TTF was not recommended. The guideline included the following statement for recurrent GBM "**TTFs** failed to prolong survival compared with second-line chemotherapy."	1 RCT; Authors rated the TTF evidence level I grade A

55 Pages 31 & 32

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

Status of Relevant Clinical Trials

Study Status	Newly diagnosed GBM	Recurrent GBM	Other cancers
Not yet recruiting	0	1	4
Recruiting	9	8	8
Active and not recruiting	2	0	3
Completed	1 (EF-14)	1 (EF-11)	1[a]
Withdrawn	0	1[b]	0
Terminated	0	1[c]	0
Unknown	0	0	2[d]
TOTAL	12	12	18

[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.*

56 Page 42

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

Status of Relevant Clinical Trials: Newly Diagnosed GBM

Completion Date	Status	NCT Number	Trial Name
February 2019	Recruiting	NCT03128047	HUMC 1612: Optune® NovoTTF-200A System
April 2019	Recruiting	NCT03033992	Feasibility Trial of Optune® for Children With Recurrent or Progressive Supratentorial High-Grade Glioma and Ependymoma
March 2020	Recruiting	NCT03477110	Temozolomide, Radiation Therapy, and Tumor Treating Fields Therapy in Treating Participants With Glioblastoma
March 2020	Recruiting	NCT03258021	TTFields In Germany in Routine Clinical Care
May 2020	Active, not recruiting	NCT03223103	Safety and Immunogenicity of Personalized Genomic Vaccine and Tumor Treating Fields (TTFields) to Treat Glioblastoma
May 2020	Recruiting	NCT02903069	Study of Marizomib With Temozolomide and Radiotherapy in Patients With Newly Diagnosed Brain Cancer
June 2021	Recruiting	NCT02343549	A Phase II Study of Optune® (NovoTTF) in Combination With Bevacizumab and Temozolomide in Patients With Newly Diagnosed Unresectable Glioblastoma
June 2022	Active, not recruiting	NCT02152982	Temozolomide With or Without Veliparib in Treating Patients With Newly Diagnosed Glioblastoma Multiforme
September 2022	Recruiting	NCT03501134	Quality of Life of Patients With Glioblastoma Treated With Tumor-Treating Fields
February 2023	Recruiting	NCT03405792	Study Testing The Safety and Efficacy of Adjuvant Temozolomide Plus TTFields (Optune®) Plus Pembrolizumab in Patients With Newly Diagnosed Glioblastoma (2-THE-TOP)
July 2027	Recruiting	NCT03232424	NovoTTF-200A and Temozolomide Chemoradiation for Newly Diagnosed Glioblastoma

57 Page 43

GBM = glioblastoma; NCT = National Clinical Trial; TTF = tumor treating fields.

Status of Relevant Clinical Trials: Recurrent GBM

Completion Date	Status	NCT Number	Trial Name
December 2018	Recruiting	NCT01894061	NovoTTF-100A With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma
February 2019	Recruiting	NCT03128047	HUMC 1612: Optune® NovoTTF-200A System
March 2019	Recruiting	NCT02663271	TTFields and Pulsed Bevacizumab for Recurrent Glioblastoma
April 2019	Recruiting	NCT03033992	Feasibility Trial of Optune® for Children With Recurrent or Progressive Supratentorial High-Grade Glioma and Ependymoma
March 2021	Recruiting	NCT01954576	NovoTTF Therapy in Treating Patients With Recurrent Glioblastoma Multiforme
August 2021	Not yet recruiting	NCT03430791	Trial of Combination TTF (Optune®), Nivolumab Plus/Minus Ipilimumab for Bevacizumab-naive, Recurrent Glioblastoma
August 2022	Recruiting	NCT02743078	Optune® Plus Bevacizumab in Bevacizumab-Refractory Recurrent Glioblastoma
September 2022	Recruiting	NCT03501134	Quality of Life of Patients With Glioblastoma Treated With Tumor-Treating Fields
December 2026	Recruiting	NCT01925573	Optune® (NOVOTTF-100A)+ Bevacizumab+ Hypofractionated Stereotactic Irradiation Bevacizumab-Naive Recurrent Glioblastoma (GCC 1344)

58 Page 43

GBM = glioblastoma; NCT = National Clinical Trial; TTF = tumor treating fields.

Washington State Health Care Authority

FINAL Key Questions and Background

Tumor treating fields

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® (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®. 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)?

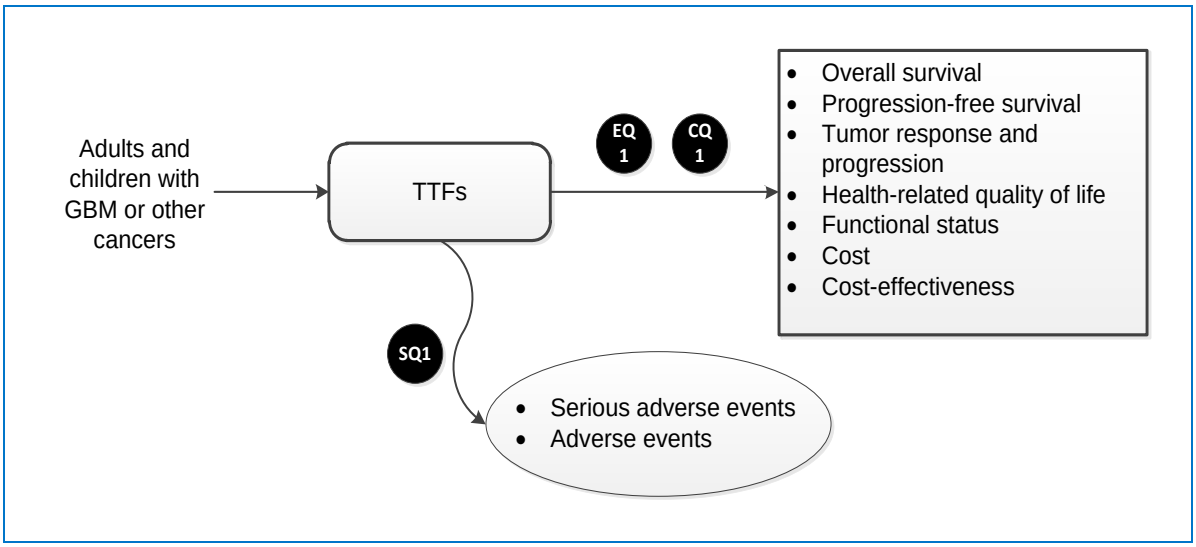
Safety question 1 (SQ 1). What are the harms associated with tumor treating fields for the treatment of newly diagnosed glioblastoma multiforme, recurrent glioblastoma multiforme, and other cancers?

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)

Final

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[7]

Other criteria: English-language publications

Public comment and response

No public comments were received.

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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[1] as expressed by the following standards[2]:

- 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[3]:

- 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[4] 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.

Not Confident	Confident
Appreciable uncertainty exists. Further information is needed or further information is likely to change confidence.	Very certain of evidentiary support. Further information is unlikely to change confidence

[4] Based on GRADE recommendation: http://www.gradeworkinggroup.org/FAQ/index.htm

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?

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)

Safety outcomes	Importance of outcome	Safety evidence/ confidence in evidence
Dermatitis		
Insomnia		
Headaches		
Other serious adverse events		

Efficacy – effectiveness outcomes	Importance of outcome	Efficacy / Effectiveness evidence
Overall survival		
Progression-free survival		
Tumor response		
Quality of life		
Functional status		

Cost outcomes	Importance of outcome	Cost evidence
Direct costs		
Cost-effectiveness		

Special population / Considerations outcomes	Importance of outcome	Special populations/ Considerations evidence

For safety:

Is there sufficient evidence that the technology is safe for the indications considered?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all (yes)

For efficacy/ effectiveness:

Is there sufficient evidence that the technology has a meaningful impact on patients and patient care?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all (yes)

For cost outcomes/ cost-effectiveness:

Is there sufficient evidence that the technology is cost-effective for the indications considered?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all (yes)

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

Organization ***Guideline Title (Year)*** **Guideline Quality Rating[a]**	**Evidence Base**	**Recommendation[b]**	**Rating/Strength of Evidence Narrative Assessment[c]**
National Comprehensive Cancer Network (NCCN) *NCCN Clinical Practice Guidelines in Oncology. Central Nervous System Cancers Version 1.2018 (2018)*[38] Quality Rating: 5 out of 7	2 RCTs	For patients of any age with newly diagnosed GBM and with good performance status (KPS >60), and any MGMT promoter status: Recommend standard brain radiotherapy + concurrent temozolomide and adjuvant temozolomide + **alternating electric field therapy.**[d] For patients with recurrent glioblastoma: consider **alternating electric field therapy.**[d]	Authors rated the recommendation for newly diagnosed GBM Category 1 and recurring GBM Category 2B[e]
U.K. National Institute for Health and Care Excellence (NICE) *Brain tumours (primary) and brain metastases in adults (2018)*[43] Quality Rating: 7 out of 7	2 RCTs	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.	NICE chooses to reflect the concept of strength in the wording of the recommendation
American Association of Neuroscience Nurses (AANN) *Care of the Adult Patient with a Brain Tumor (2014)*[39] *(Revised 2016)* Quality Rating: 4 out of 7	1 RCT, 1 Narrative Expert Review	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).	Authors rated two recommendations Level 1 and one recommendation Level 3[f]
Medical Oncology Spanish Society (SEOM) *SEOM clinical guidelines for diagnosis and treatment of glioblastoma (2017)*[40] Quality Rating: 3 out of 7	Unclear	For recurrent GBM, **TTF** failed to prolong survival compared with second-line chemotherapy.	Authors rated the evidence level II grade D[g]

Table 9. Clinical practice guidelines that include TTF (continued)

Organization *Guideline Title (Year)* Guideline Quality Rating[a]	Evidence Base	Recommendation[b]	Rating/Strength of Evidence Narrative Assessment[c]
European Association for Neuro-Oncology (EANO) *EANO guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas (2017)*[41] Quality Rating: 5 out of 7 overall. 3 out of 7 for the guidelines handling of TTF	2 RCTs	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 **TTF** in the treatment of newly diagnosed glioblastoma remain to be defined. Recurrent GBM: **TTF** were not superior to best physician's choice in a randomized phase III trial.	No rating was given when a treatment was not recommended
European Society for Medical Oncology (ESMO) *High-grade glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2014)*[42] Quality Rating: 2 out of 7	1 RCT	TTF was not recommended. The guideline included the following statement for recurrent GBM "**TTF** failed to prolong survival compared with second-line chemotherapy."	Authors rated the TTF evidence level I grade A[h]

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.