Washington State Health Care Authority

Agency Medical Director Comments

Novocure (Tumor Treating Fields)

January 15, 2016

Daniel Lessler, MD
Chief Medical Officer
Washington Health Care Authority

"Bio-Electromagnetics"

- Application of alternating electric fields (AEMs) to kill tumor cells
  - AEMs referred to as "Tumor Treating Fields" (TTFs)
- Putative mechanism of action is through disruption of mitosis; other modes of action also hypothesized
- April 2011: FDA approved first bio-electromagnetic device for the treatment of recurrent glioblastoma

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Novocure

"Novocure"

- Utilizing portable, battery operated device, TTFs are transmitted to the tumor via disposable surface electrodes
- Electrodes placed after "head mapping" (in the case of glioblastoma) with serial MR images
- Continuously applied for an extended period (at least 4 weeks)

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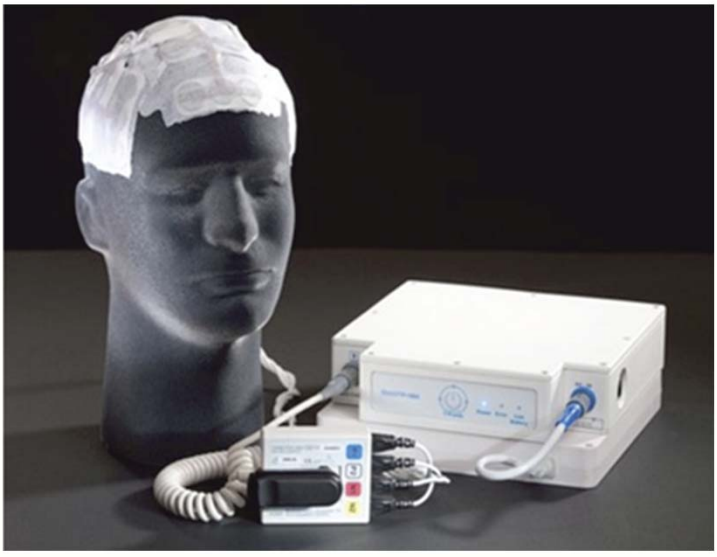
NovoTTF - 100A System



Novocure

Key Questions

1. What is the clinical effectiveness of Novocure for the treatment of glioblastoma?
2. What is the clinical effectiveness of Novocure for the treatment of other cancers?
3. What are the harms associated with Novocure?
4. Does the effectiveness of Novocure or incidence of adverse events vary by clinical history or patient characteristics?
5. What are the cost implications and cost-effectiveness of Novocure?

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Agency Medical Director Concerns

- **Safety = Low**
- **Efficacy = High**
- **Cost = High**

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State Agency Policies and Utilization

- **Agency Policies**
  - **Uniform Medical Plan:** Not covered (consistent with Regence medical policy)
  - **Medicaid:** No policy
  - **Labor & Industries:** No policy
- **Emerging Technology**
  - Very limited utilization data to date

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Novocure for Treatment of Glioblastoma: Evidence Prior to December, 2015

- Single RCT of Novocure vs. chemotherapy for recurrent glioblastoma
  - 80% of patients had failed 2 or more prior chemotherapies
  - Active control group received additional chemotherapy, regimens varied (at discretion of treating physician)
  - No difference in survival; fewer adverse effects in Novocure group
- Methodologic flaws noted:
  - Unclear that "active control" (salvage chemotherapy) in fact better than placebo with respect to survival, which was study's primary endpoint
  - "The management of patients with recurrent or progressive 'high grade glioma' is difficult, and active re-intervention has not been proven to prolong survival." Batchelor T, et al. Management of Recurrent High Grade Gliomas. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA (Accessed on December 29, 2015)
- Other studies demonstrating survival advantage with Novocure of poor or very poor quality

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Novocure

Maintenance Therapy with Tumor Treating Fields: December, 2015 Publication

- Stupp, et al. JAMA. 2015: RCT of TTFs for treatment of supratentorial glioblastoma in patients with no evidence of progression after standard chemoradiotherapy (unblinded; no sham treatment)
- Interim analysis showed benefit; study terminated early
  - Median progression free survival 7.1 months in TTF+temozolomide vs 4.0 months in temozolomide alone (p=0.001) *(ITT analysis)*
  - Median survival 20.5 months in TTF+temozolomide vs 15.6 months in temozolomide alone *(in "per protocol" analysis but "ITT" analysis not substantially different)*
- No significant increase in adverse systemic effects; higher incidence of scalp irritation, anxiety, confusion and HAs in those treated with TTFs

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Novocure for Treatment of Cancers Other Than Glioblastoma

- Very limited data
- Overall, inadequate evidence to evaluate safety and effectiveness of Novocure in the treatment of cancers other than glioblastoma

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Novocure: Cost-Effectiveness

- Cost ranges between $10,907 and $21,429 per month
- No data on cost-effectiveness

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Guidelines and Payer Policies*

- No **CMS** national coverage determination (NCD)
- **National Comprehensive Cancer Network (NCCN):** Novocure is a treatment option in patients with recurrent glioblastoma
- **Group Health**: Not covered (insufficient evidence)
- **Regence:** Not covered (investigational)
- **Aetna:** Medically necessary as monotherapy for persons with histologically or radiologically confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy

*Prior to December 2015 publication: JAMA. 2015; 314(23): 2535-2543.

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Agency Medical Directors' Recommendations

- Novocure is covered for treatment of supratentorial glioblastoma when provided in conjunction with temozolomide in patients with no evidence of progression after standard chemoradiotherapy
- Novocure is not covered for re-current glioblastoma
- Novocure is not covered for cancers other than glioblastoma

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Questions?

More Information

www.hca.wa.gov/hta/Pages/novocure.aspx

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Health Technology Assessment

Order of Scheduled Presentations:

Novocure (Tumor Treating Fields)

	Name
1	
2	
3	
4	
5	
6	

No requests to provide public comment on the technology review were received.

Washington State Health Care Authority
Health Technology Assessment

Novocure (Tumor Treating Fields)

Clinical Expert

Lynne P. Taylor, MD, FAAN, FANA

Neuro-Oncologist
Hematology- Oncology
Virginia Mason Medical Center, Seattle, WA

Adjunct Associate Professor of Medicine/Neurology
Tufts School of Medicine, Boston, MA

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.		X
2.	Equity interests such as stocks, stock options or other ownership interests.		X
3.	Status or position as an officer, board member, trustee, owner.		X
4.	Loan or intellectual property rights.		X
5.	Research funding.		X
6.	Any other relationship, including travel arrangements.		X

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		X

If yes to #7, provide name and funding Sources:

*If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.*

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

X [redacted] 1/04/2016 LYNNE TAYLOR MD

Signature *Date* *Print Name*

So we may contact you regarding this information, please provide the following:

Email Address: LYNNE.TAYLOR@VIRGINIAMASON.ORG

Phone Number: 206.799.6414 (personal cell)

CURRICULUM VITAE
Lynne P. Taylor, MD, FAAN, FANA

DATE: 9/21/2015

FULL NAME AND DEGREE/S:
Lynne P. Taylor, MD, FAAN, FANA

CITIZENSHIP: Born in Birmingham, England
Naturalized US Citizen, 1971

CURRENT ADMINISTRATIVE TITLE:
Neuro-Oncologist
Hematology-Oncology
Virginia Mason Medical Center

Adjunct Associate Professor of Medicine/Neurology
Tufts School of Medicine
Boston, MA

OFFICE ADDRESS:
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Seattle, WA 98101

OFFICE PHONE NUMBER:
206-223-6193

E-MAIL ADDRESS:
Lynne.Taylor@vmmc.org

FAX ADDRESS:
206-223-2382

EDUCATION

Undergraduate

1970-71		Northwestern University, Evanston, IL
1971-74	BA	University of Illinois, Chicago, IL (Ed)
1976-78		Northwestern University, Evanston, IL (Returned to obtain pre-med courses)

Medical School and/or Graduate School

1978-79		Northwestern University, Chicago, IL
1979-82	MD	Washington University, St. Louis, MO (Transferred because of marriage)

CURRICULUM VITAE
Lynne P. Taylor, MD, FAAN, FANA

POSTDOCTORAL TRAINING

Internship and Residencies:

1982-83	Medicine	Barnes-Jewish Hospital, St. Louis, MO
1983-86	Neurology	Hospital University Pennsylvania, Phil, PA

Fellowships:

1986-88	Neuro-Oncology	Memorial Sloan-Kettering Cancer Center, NY

Additional training:

2009	Multi-disciplinary Palliative Care Week, St. Christopher's Hospice London, England
2010	Clinical Scholar, American Association of Hospice and Palliative Care Medicine, Stanford Hospital, Palo Alto, California

LICENSURE AND CERTIFICATION

Board Certification:

1987	American Board of Psychiatry and Neurology (Neurology) #29900
2011	American Board of Psychiatry and Neurology (Hospice and Palliative Medicine) #46
2011	United Council of Neurologic Sub-specialties (Neuro-Oncology) #NO287-11

State Licensure:

1982	Missouri
1983	Pennsylvania
1986	New York
1988	Washington, AT25833
2011	Massachusetts, Registration #249706

ACADEMIC APPOINTMENTS

1990-1992	Clinical Instructor, Neurology, University of Washington, Seattle
1992-2005	Clinical Assistant Professor, Neurology, University of Washington, Seattle
2005-2011	Clinical Associate Professor, Neurology, University of Washington, Seattle
2011-2013	Lecturer, Tufts University School of Medicine, Boston, MA
7/13-7/14	Associate Professor, Department of Medicine, Tufts University School of Medicine, Boston, MA
7/13-7/14	Associate Professor, Department of Neurology (secondary), TUSM
3/01/15-	Clinical Associate Professor, Neurology, University of Washington, Seattle

CURRICULUM VITAE
Lynne P. Taylor, MD, FAAN, FANA

HOSPITAL APPOINTMENTS

1988-2011	Virginia Mason Medical Center (VMMC), Seattle, Washington Neurologist and Director of Neuro-Oncology
2014-	VMMC, Seattle, Washington Director of Neuro-Oncology, Cancer Center
2001-2007	Seattle Cancer Care Alliance, Seattle, WA
1993-2007	Harborview Hospital, Seattle, WA
2011-	Tufts Medical Center, Boston, Massachusetts
2011-2013	New England Sinai Hospital, Boston, Massachusetts
2014	Virginia Mason Medical Center, Seattle, WA
2014	Evergreen Hospital, Kirkland, WA

GRANTS

2013	Innovations in Education Grant "Integrating end-of-life care across the curriculum: Starting the conversation" Tufts Medical School, $9,200.00

AWARDS AND HONORS

1993	Medicine **Teacher of the Month**, VMMC
1996	**Fellow**, American Academy of Neurology
1997	Medicine **Teacher of the quarter**, VMMC
2003	American Medical Women's Association "Local legends" nominee
2005	Palatucci Advocacy Leadership Forum Advocate, AAN
2007-11	Seattle Magazine, Top Doctors
2009	Palatucci Advocacy Leadership Forum, Advocate, AAN
2009	Huff-Hegstrom Medicine **Teacher of the Year**, VMMC
2009-2010	Best Doctors Seattle Metropolitan Magazine
2010-11	Seattle Magazine Top Doctor
2010	VMMC Internal Medicine Resident's **Top 50 Teachers**
2010-13	America's Top Doctor
2011-12	Castle Connolly, Top 1% Neurologists
2010-15	Castle Connolly America's Top Doctors for Cancer
2012	Palatucci Advocacy Leadership Forum, Advisor, AAN
2011-2012	Patients choice awards
2012-13	Boston Magazine "Top Doctors"
2013	Boston Super Doctors (Top 5% in the Boston metro area)
2013	**Fellow,** American Neurologic Association (ANA)
2014	Castle Connolly, Top Doctors (Neurology)

HOSPITAL, MEDICAL SCHOOL, OR UNIVERSITY COMMITTEE ASSIGNMENTS:

Virginia Mason Medical Center, Seattle, WA

1994	Executive committee, VMMC, member
1996	Utilization review committee, VMMC, member

1998-2001 At-large member, Executive committee (elected by peers)
2007-2009 Bailey-Boushay AIDs Hospice, Board of Directors, member
2009-2011 End-of-life Guiding Team, member
2001-2011 Cancer Center Steering Committee, member
2003-2009 CARSCOG committees, Stroke care, **Director**
1990-2011 **Director** of Neuro-Oncology
1990-2011 **Chair**, Neuro-Oncology Tumor Board
2015- Member, Cancer Committee, Palliative care representative

Tufts Medical Center, Boston, MA
2013- **Chair**, Working Group in Palliative Care at the request of Dr. Dan Weiner, Curriculum Committee Chair and Scott Epstein, Dean for Educational Affairs
2013- Neurology Chair Search Committee, member
2012 Cancer Care Committee, Palliative Care member

OTHER MAJOR COMMITEE ASSIGNMENTS:

1996-97 **President**, Puget Sound Neurologic Association
2010-2011 **Chair**, Data Safety Monitoring Board
Dr. Marc Chamberlain Bendamustine study
2013 ACGME Milestone Development for Shared Subspecialties (Hospice and Palliative Medicine), **RRC representative**
2014-2016 American Association of Hospice and Palliative Medicine (AAHPM)
Ethics Committee
2014-2017 American Society of Clinical Oncology (ASCO)
Ethics Committee

TRAINING OF GRADUATE STUDENTS/POST DOCTORAL

2011-12 Mayanka Tickoo, MD
MS-PREP Candidate, TUSM
Palliative Care Utilization project

2012-13 Jennifer Harkey, Masters in Biological Science candidate,
TUSM, Quality of life in adult survivors of pediatric brain tumors

TRAINING OF FELLOW POST FELLOWSHIP

2012-2013 Marvin Duque, MD
Wednesday Neuro-Oncology Clinic
24 hours/month for the academic year (216 hours)

TEACHING RESPONSIBILITIES (present and past) chronological

University of Washington, Seattle, WA

Organized Neurology education at VMMC for University of Washington School of Medicine, Dr. Eric Kraus, Clerkship Director

1990-2002 Introduction to Clinical Medicine
Preceptor

Second year medical students, 2 students
8 hours per year

2003-2010 Neurology Clerkship
Preceptor
4 week course
12 students per year

Virginia Mason Medical Center, Seattle, WA

1998-2011 Outpatient Neurology Elective
Internal Medicine Residents
Preceptor
12 Residents per year

1998-2011 Ward Attending
Internal Medicine Residents
2 months per year

2009-2012 Weekly Neurology Conference
Didactic
Four hours/monthly

American Academy of Neurology

1995	AAN Annual Meeting, Seattle, WA. Organized and led a 300 student/teacher symposium in neuroscience.
2000-2002	**Course Director,** Case Studies in Neuro-Oncology
2005	Case Studies in Neuro-Oncology, **Faculty**
2012	Course: Neurologic Palliative Care, **Faculty**
	Annual Meeting, New Orleans, LA
2013	Course: Neurologic Palliative Care
	Annual Meeting, San Diego, **Faculty**
2014	Course: Neurologic Palliative Care

Annual Meeting, Philadelphia, PA, **Faculty**

2014 Half Day Course: "Core Concepts in Pain Management"
Course Director: Philadelphia, PA

2015 Half Day Course: "Core concepts in pain management"
Course Director: Washington, DC

Tufts Medical Center, Boston, MA

2011-2014 Weekly rotating Neuro-Oncology Clinic
Heme-Onc Fellows
1 Fellow, 1 day per week

6/2012-2014 Established combined Neuro-Path/Neuro-Onc rotation
Tufts Neurology Residents
1 Resident Monthly throughout the year

1/2012-2014 Added Palliative Care consults to consult rotation
Tufts Heme-Onc Fellows
1 Fellow Monthly throughout the year

6/2013-2014 Introduced Clinical Selective in Palliative Care
Introduced Clinical Elective in Palliative Care for 3rd year medical students (2 week blocks)

6/2013-2014 Introduced Clinical Elective in Palliative Care for 4th year medical students
(1 month blocks)

PROFESSIONAL SOCIETIES

1988- American Academy of Neurology (AAN)
1996 **Fellow**, AAN
2013- American Neurologic Association (ANA)
2013 **Fellow**, ANA
1988- American Society of Clinical Oncology (ASCO)
2008- American Association of Neurological Surgeons, Section on Tumors
1998-2009 Southwest Oncology Group
1998- Radiation Therapy Oncology Group
1996- Society for Neuro-Oncology
2000-2011 Puget Sound Oncology Consortium
2001-2010 Undersea and Hyperbaric Medical Society
2008- American Association of Hospice and Palliative Care Medicine (AAHPM)

OFFICE AND COMMITTEE ASSIGNMENTS IN PROFESSIONAL SOCIETIES

American Academy of Neurology

1992-1996	Subcommittee on Education for Non-Neurologists (SENN), member
1996-2001	SENN, **Chairman**
1997-2001	Education Committee, member
1996-2001	A.B. Baker Subcommittee, member
2001-2005	**Board of Directors, Director**
2003-2005	Ad-hoc Committee, Formation of a Neuro-PAC, member
2001-2005	Neuroscience Prize Committee, member
2005-2009	**Chairman**, Neuroscience Prize Committee
2005-2007	**Chairman**, Leadership Task Force
2007-2013	Membership Committee, member
2007-2009	Leadership Development Program Committee, **Chairman**
2011-2013	Leadership Work Group, **Chairman**
2011-	Ethics, Law and Humanities Committee, member
2013-	Fellow Application Review Workgroup, member

American Society of Clinical Oncology:

2013-	Ethics Committee, member

American Academy of Hospice and Palliative Medicine

2013-	Ethics Committee, member
2015-	External Awareness committee

American Board of Psychiatry and Neurology

1996-2004	**Board Examiner**
2000-2002	Committee on Recertification in Neurology

Southwest Oncology Group

1998-1990	Brain Tumor Committee

United Council for Neurologic Subspecialties

2006-	Neuro-Oncology Certifying exam, question writing committee

Washington State Neurologic Society

2015-	Sergeant at arms

MAJOR RESEARCH INTERESTS

1. Treatment of primary brain tumor patients
2. Quality of life for neuro-oncology patients
3. Palliative care in cancer patients

RESEARCH SUPPORT

1993-1998 Grant Title: *Alteplase ThromboLysis for Acute Non-Interventional Therapy in Ischemic Stroke (ATLANTIS)*
Funding Agency: Genentech
Amount: $100,000.00
Role: **Principal Investigator**

1996-1999 Grant Title: *A Randomized controlled trial comparing intra-thecal sustained release cytarabine (DepoCyt)to intra-thecal methotrexate in patients with neoplastic meningitis from solid tumors.*
Funding Agency: Skye Pharma
Amount: $32,000.00
Role: **Principal Investigator**

2005-2006 Grant Title: *Phase III randomized evaluation of convection enhanced delivery of IL 13-PE38QQR compared with Gliadel wafer for recurrent glioblastoma.*
Funding Agency: NeoPharm
Amount: $126,000.00
Role: **Principal Investigator**

2005-2009 Grant Title: *Xerecept (hCRF) for patients requiring dexamethasone to treat edema associated with brain tumors.*
Funding Agency: Neurobiologicals
Role: **Principal Investigator**

2008-2011 Grant Title: *Efficacy and Safety of AP12009 in adult patients with recurrent or refractory astrocytoma or secondary glioblastoma as compared to standard chemotherapy treatment. A randomized, actively controlled, open label, clinical Phase III study.*
Funding Agency: Antisense Pharma
Role: **Principal Investigator**

2008-2011 Grant Title: *Phase I Trial of BIBW 2992 (Afatinib) in treating patients with recurrent glioblastoma multiforme*
Funding Agency: Boehringer Ingelheim
Amount: $12,000.00
Role: **Principal Investigator**

2011-2014 Grant Title*: A Prospective, Multi-center Trial of NovoTTF-100A Together With Temozolomide Compared to Temozolomide Alone in Patients with Newly Diagnosed GBM*
Funding Agency: Novocure

Role: **Principal Investigator**

2012-2014 Grant Title: *DC Vax A Phase III Clinical Trial Evaluating DCVax-L, Autologous Dendritic Cells Pulsed with Tumor Lysate Antigen for the Treatment of Glioblastoma Multiforme.*
Funding Agency: Northwest Biotherapeutics
Role: **Principal Investigator**

2012-2014 *A Phase III Trial of Post-Surgical Stereotactic Radiosurgery (SRS) Compared with Whole Brain Radiotherapy (WBRT) for Resected Metastatic Brain Disease*
Granting Agency: North Cancer Center Treatment Group
Role: **Principal Investigator**

EDITORIAL BOARDS AND ACTIVITY

1992-2005	Continuum (AAN)	**Board member**
2000-	Neurology	Reviewer
2004-	Annals of Neurology	Reviewer
2005-	Neurology Now (AAN)	**Board member**
2011-2012	AAN.com	Reviewer
2011-	Journal Clinical Oncology	Reviewer
2011-	Journal of Neuro-Oncology	Reviewer
2014-	Cephalalgia	Reviewer
2014-	Neurology: Neuroimmunology & Neuroinflammation	Reviewer

BIBLIOGRAPHY

Papers

1. **Taylor LP**, Posner JB. Phenobarbital rheumatism in primary brain tumor patients. Ann Neurol 1989; 25:92-94.
2. DeAngelis LM, Gnecco C, **Taylor LP**, Warrell RP. Evolution of neuropathy and myopathy during intensive vincristine/corticosteroid chemotherapy for non-Hodgkin's lymphoma. Cancer 1991; 67:2241-2246.
3. Eisenberg B, Coates GG, Gass MA, Sicuro PL, Lee ME, **Taylor LP**. In-111 DTPA cisternographic demonstration of magna cisterna magna. Clinical Nuclear Medicine 1994; 19(10):915-916,
4. Aboulafia DM, **Taylor LP**, Crane RD, Yon JL, Rudolph RH. Carcinomatous meningitis complicating cervical cancer: a clinicopathologic study and literature review. Gyn Onc 1996; 60:313-318,
5. Batchelor TT, **Taylor LP**, Thaler HT, Posner JB, DeAngelis LM. Steroid myopathy in cancer patients. Neurology 1997; 48:1234-1238.
6. Elliott M, **Taylor LP.** Shiatsu sympathectomy. Neurology 2002; 58:1302-1304.

7. Aboulafia DM, **Taylor LP**. Vacuolar myelopathy and vacuolar cerebellar leukoencephalopathy: A late complication of AIDs after highly active antiretroviral therapy-induced immune reconstitution. AIDS Patient Care and STDs 2002; 16:579-584.
8. **Taylor LP**. A team approach to the management of vestibular schwannoma. Virginia Mason Medical Center Bulletin, Spring, 2009; 37-43.
9. **Taylor LP**. Diagnosis, treatment, and prognosis of glioma: Five new things. Neurology Clinical Practice 2010; 75 Suppl 1:1-5. (Invited by Dr. John Corboy, Ed)
10. DeVito N, Pilichowska M, **Taylor LP,** Mui K, Jassam Y, Cossor F. Small lymphocytic lymphoma (SLL) presenting as a Paraneoplastic syndrome with acute central nervous system (CNS) demyelination. Clinical Lymphoma, Myeloma and Leukemia. 2014; 14(4): e131-e-135.
11. Nelson SE, Jassam YN, **Taylor LP.** A case of refractory Hashimoto's encephalopathy demonstrating improvement with plasmapharesis. Case Report in Internal Medicine. Apr 2014;1(2):83-88.
12. Stupp R, Taillibert S, Kanner A, Kesari S, Steinberg D, Toms S, **Taylor LP**, et al. A Phase 3 trial comparing tumor-treating fields therapy plus Temozolomide alone maintenance therapy for newly diagnosed glioblastoma. JAMA. 2015;314(23):2535-2543.

Invited Papers:

1. Nelson S, **Taylor LP**. Headaches in brain tumor patients: Primary or Secondary? Headache 2014 Apr; 54(4): 776-785.
2. **Taylor, LP.** Mechanism of headache in brain tumor patients. Headache 2014 Apr; 54(4): 772-775.
3. **Taylor, LP.** Comment. Chemoradiotherapy for glioblastoma patients—The double-edged sword. Neurology 2015;85:689.

Book Chapters

1. **Taylor LP**. Cerebrovascular disease. In: Finn SD, McGee SR, editors. Outpatient Medicine. Seattle: WB Saunders; 1992. p. 449-453.
2. **Taylor LP**. Neurologic disorders. In: Agostini RA, editor. Medical and Orthopedic Issues of Active and Athletic Women. Philadelphia: Hanley & Belfus; 1994. p. 251-259.
3. **Taylor LP**. Neurological complications of leukemia. In: Wiley RG, editor. Neurological complications of cancer. New York: Marcel Dekker; 1995. p. 449-464.
4. American Academy of Neurology. **LP Taylor**. Neck and back pain. In: Family practice curriculum in Neurology. Second edition, 2008. Available at: http://www.aan.com/go/education/curricula/family/toc Accessed July 30, 2012.
5. **Taylor LP**. Neurologic complications of leukemia and lymphoma. In: Newton H and Malkin M, editors. Neurological complications of systemic cancer and anti-neoplastic therapy. Switzerland: Informa Health Care: 2010. p. 265-280.

CURRICULUM VITAE
Lynne P. Taylor, MD, FAAN, FANA

Book authored/edited

1. American Academy of Neurology. NeuroTriage Telephone. Editors, Selwa L, Ozuna J, **Taylor LP**, Goldman S, Stewart S, Good J, Forrest-Smith, M. MA: Butterworth-Heinemann, 2002.
2. **Taylor LP**, Umphrey-Porter A, Richards D. Navigating life with a brain tumor. New York: Oxford University Press; 2012.

Other media

1. American Brain Tumor Association Webinar, 9/27/2013 "Advanced Care Planning and Palliative Care" https://www.youtube.com/watch?v=RSD_ymDxaxs#t=1016

Published abstracts

1. **Taylor LP**, Rorke LB, Packer R: PAS-positive granules in childhood ependymoma. Ann Neurol 1986; 20:397-398.
2. **Taylor LP**, Posner JB: Steroid myopathy in cancer patients treated with dexamethasone. Neurology 1989; 39 Suppl 1:129.
3. Flowers M, Tapscott SJ, Emerson J, Emerson MV, Reagan T, **Taylor LP**, et al: Incidence of peripheral neuropathy (PN) prior to thalidomide treatment for chronic graft-versus-host disease (GVHD). ASH, 1996.
4. **Taylor LP**, Wade J: The varied faces of cyclosporine A neurotoxicity. Neurology 2000;54 Suppl 3:A40.
5. Ready JR, **Taylor LP**, Gross KM: Susac syndrome: A case report of this rare disease of microangiopathy of the retina, cochlea and brain, Society of General Internal Medicine, 2001.
6. **Taylor LP**, Yau E, Lacrampe M: Primary spinal melanoma: A case report and review of the literature. Neurology 2006; 66:A340.
7. **Taylor LP**: Complete bilateral third nerve palsies as the initial manifestation of anti-HU Paraneoplastic encephalomyelitis. Neuro-Oncology 2007; 515:MA-03.
8. **Taylor LP**: Multiple sclerosis mimics: Prolonged relapses and remissions and leukoencephalopathy in two case reports of primary CNS lymphoma. Neuro-Oncology 2010;12 Suppl 4:NO-89.
9. **Taylor LP**, Otero H: Sustained quality of life in a patient with Leptomeningeal lymphoma treated with quarterly intra-thecal rituximab. Neuro-Oncology, 2011:13 Suppl 3:QL-05.
10. **Taylor LP**, Stewart M: Prolonged one year symptomatic interval prior to diagnosis of Leptomeningeal carcinomatosis in a breast cancer patient. Neuro-Oncology, 2011:13 Suppl 3:NO56.

Invited lectures (last 5 years only)

2010	Neurology Grand Rounds "Lymphoma in the nervous system" Madigan Army Medical Center, Tacoma, WA

2010	Alaska Academy of Family Physicians "Diagnosis and early treatment of Brain tumors. Homer, Alaska
2010	Washington State Nursing Association "Brain Tumors" Seattle, WA
2010	Course: Clinical Best Practices in Dementia Care "Rapidly progressive dementias" Virginia Mason Medical Center, Seattle, WA
2011	Course: Primary CNS Lymphoma Yakima Valley Medical Conference, Yakima, WA
2011	Neurology Grand Rounds "Central nervous system lymphoma" North Shore University Health System, Evanston, IL
2012	Course: Neurologic Palliative Care Annual Meeting, AAN, New Orleans, LA
2012	Surgical Grand Rounds "Surgical Palliative Care" Tufts Medical Center, Boston, MA
2012	Cancer Center Grand Rounds, Jordan Hospital "Palliative Care", Plymouth, MA
2012	Cancer Center Grand Rounds, Jordan Hospital "Neuro-Oncology", Plymouth, MA
2012	Neuroscience Grand Rounds "Neuro-Oncology and classic localization", Tufts, Boston, MA
2012	Neurology Grand Rounds, Baystate Medical Center "Primary CNS Lymphoma", Springfield, MA
2012	Last Resort Options Brockton Hospital Grand Rounds, Brockton, MA
2012	UMass Neurology Grand Rounds "Lymphoma and the Nervous System"
2012	Risk Management in the Neurosciences, Tufts CME course, Boston, MA
2012	Cancer Center Grand Rounds, Tufts Medical Center "Neurophysiology of Pain"
2012	"Talking with the Severely Ill and Dying Patient". Medical Interviewing and the Doctor Patient Relationship, Tufts Medical School

2013	Course: Neurologic Palliative Care Annual Meeting, AAN, San Diego, CA
2013	Metrowest Medical Center, Natick, MA "Updates on brain metastases"
2013	"ALS and Palliative Care" didactic, Tufts PMR department
06/19/13	St. Luke's Hospital, New Bedford, MA. Last Resort Options
09/27/13	Winchester Hospital, Winchester, MA "Palliative Care"
10/03/13	"Palliative Care in Neurology: The art of prognostication" Neurology Grand Rounds, University of Washington, Seattle, WA
10/23/13	"Neuro-Palliative Care" Palliative Care Grand Rounds, Massachusetts General Hospital
02/13/14	Pseudo-progression or pseudo-response? How to make sense of treatment related changes in the brain. Loma Linda School of Medicine: kukuna-o-ka-la Radiation Oncology Conference, Big Island, Hawaii
02/14/14	Neuro-cognitive and endocrine changes in patients with primary and metastatic brain tumors. Loma Linda School of Medicine: kukuna-o-ka-la Radiation Oncology Conference, Big Island, Hawaii
4/14/14	"Disturbances of consciousness" Tufts Medical School Neuroscience course
4/27/14	Overview of Core Pain Management Concepts. AAN Annual meeting, Philadelphia, PA
4/27/14	Review of the evidence for non-opioid medications for chronic and neuropathic pain AAN Annual meeting, Philadelphia, PA
09/25/14	Neuro-Oncology St. Patrick Hospital Missoula, MT
10/28/14	Brain Tumor headaches in children Children's Hospital of Philadelphia Philadelphia, PA

12/05/14	"When Cancer meets the brain" Grand Rounds, Virginia Mason Medical Center Seattle, WA
1/16/15	"Mechanisms of brain tumor headache" Headache Cooperative of the Pacific San Francisco, CA
2/12/15	"The Art of Prognostication" Grand Rounds, Kadlec Hospital Richland, WA
2/21/15	"Being mortal" End of life choices 9th Annual Women's Wellness forum Bainbridge Island, WA
5/13/15	Headache in brain tumor patients Neurology Grand Rounds, Tufts Medical Center Boston, MA
07/17/15	"The art of prognostication and why it matters" Grand Rounds, Virginia Mason Medical Center Seattle, WA
09/13/15	Prognostication Alaska Family Medicine Summit Talkeetna, Alaska
10/02/15	Course Director Update in Neurology for Primary Care, VMMC "Critical diagnoses you can't afford to miss" Seattle, WA
11/.13/2015	"Medical prognostication" Columbia Basin Medical Conference Moses Lake, WA
11/18/15	Palliative care for Neuro-oncology Neuro-Oncology Review Course, Society for Neuro-Oncology San Antonio, TX

Novocure
(Tumor Treating Fields)

Natalie R. Slezak, PhD
Hayes, Inc.
January 15, 2016

Shorthand and abbreviations

- **AEs** – adverse events
- **chemotx** – chemotherapy
- **dx'd** – diagnosed
- **FQ** – fair-quality
- **fxn** – function
- **GBM** – glioblastoma
- **grp(s)** – group(s)
- **HR** – hazard ratio
- **KPS** – Karnofsky Performance Status
- **KQ** – Key Question
- **n** – number of patients
- **NS** – not statistically significant
- **NR** – not reported
- **NSCLC** – non-small cell lung cancer
- **OS** – overall survival
- **PFS** – progression-free survival
- **PQ** – poor-quality
- **pt(s)** – patient(s)
- **QOL** – quality of life
- **RCT** – randomized controlled trial
- **RT** – radiation therapy
- **sx** – symptom(s)
- **TMZ** – temozolomide
- **TTF** – tumor treating fields
- **tx** – treatment/treat
- **tx'd** – treated
- **VPQ** – very-poor-quality

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Presentation overview

- Background
- Scope, Methods, and Search Results
- Findings
- Practice Guidelines and Payer Policies
- Overall Summary and Discussion

3

Background

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Glioblastoma (GBM)

- Fast-growing glioma that develops from glial cells in the brain
- Prevalence in Americans
  - 2 to 3 per 100,000 adults per year (National Cancer Institute, 2015)
  - Increases with age; more common in men
- Overall prognosis poor
  - Median survival: 10-14 months (Rulseh et al., 2012)
  - Recurrent GBM: 5-7 months (Rulseh et al., 2012)
  - Better outcomes: Younger age, better functional scores

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Current Therapies for GBM

- Newly dx'd GBM
  - Surgery, followed by combination RT and chemotx using TMZ
  - Median time to recurrence: ~7 months (Mrugala et al., 2014)
- Recurrent GBM
  - ~20% of patients may undergo repeat surgery
    - Carmustine polymer wafers
  - Most patients undergo chemotx
    - Combination tx w/ bevacizumab
- Additional tx options needed
  - Reduced toxicity

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Novocure (Tumor Treating Fields)

- NovoTTF-100A System (Novocure / Optune)
  - Device that emits alternating electric fields that disrupt rapid cell division
  - Requires continuous application to be effective
    - Worn 18 hrs per day/4-wk tx cycle
    - 2-3 days off tx at end of each 4-wk cycle
    - Tx continued until disease progression
- FDA approval
  - Recurrent GBM (April 2011)
    - RCT (n=237) (Stupp et al., 2012)
  - Newly dx'd GBM (October 2015)
    - RCT (n=315) (Stupp et al., 2015)

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Novocure (Optune)

- Device comprises:
  - Electrical field generator
  - 4 insulated transducer arrays
  - Connector cable
  - Power source (battery or electrical outlet)
- Tx parameters
  - 200 kHz; minimal field intensity of 0.7 V/cm

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Novocure tx for cancers other than GBM

- Ongoing clinical trials currently investigating Novocure in other conditions
  - Non-small cell lung cancer (NSCLC)
    - 1 published case series
  - Mesothelioma
  - Ovarian carcinoma
  - Pancreatic adenocarcinoma
  - Meningioma
  - Low-grade gliomas

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Scope, Methods, and Search Results

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PICO

- **Population:** Adults dx'd with recurrent GBM or other forms of cancer (e.g., NSCLC, ovarian carcinoma, non-recurrent GBM)
- **Interventions:** Novocure (TTF)
- **Comparisons:** Chemotx; Novocure alone vs Novocure plus adjunctive txs; placebo; no comparator
- **Outcomes:** OS; tumor response and progression; other health outcomes (e.g., QOL); AEs; cost and cost-effectiveness

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Key Questions

1. What is the **clinical effectiveness** of Novocure for treatment of the following conditions?
   1a. What is the clinical effectiveness of Novocure for **treatment of GBM**?
   1b. What is the clinical effectiveness of Novocure for t**reatment of other cancers**?

2. What are the **harms** associated with Novocure?

3. Does the effectiveness of Novocure or incidence of adverse events **vary by clinical history or patient characteristics** (e.g., age, sex, prior treatments)?

4. What are the **cost implications and cost-effectiveness** of Novocure?

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Search Strategy

- Primary studies
  - No time limit
  - PubMed and OVID: May 28, 2015
  - Inclusion criteria
    - Assessed efficacy/safety of Novocure in pts with cancer
    - English-language journals
  - Exclusion criteria for all KQs
    - No quantitative data
    - Conference abstracts
    - Case reports/series of case reports
- Final update searches
  - November 20, 2015

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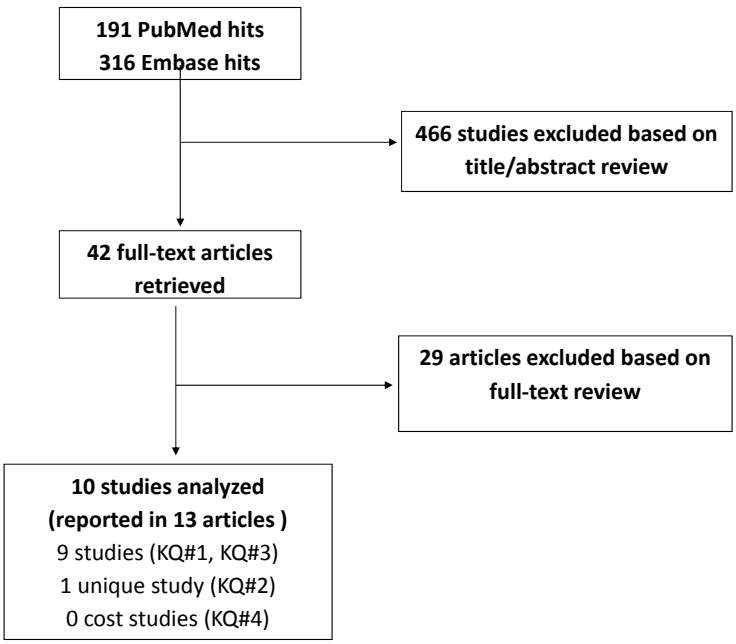

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Quality assessment aligns with GRADE system (Appendix II)

- Individual **study** appraisal
  - *Are the study findings valid?*
    - Study design, execution, and analysis (checklist)
    - *Good — Fair — Poor — Very Poor*
- Evaluation of **body of evidence** for each outcome
  - *How confident are we that this evidence answers the KQs?*
    - –Applicability to PICO
    - –Quantity/Precision of data
    - –Consistency of findings across studies
    - –Publication bias
    - *High — Moderate — Low — Very Low*

Quality of the Body of Evidence

High
- Reliable evidence reflecting the true effect
- Unlikely to change with future studies

Moderate
- Reasonable confidence that the results represent the true direction of effect
- The effect estimate might change with future studies

Low
- Little confidence due to poor quality and/or mixed results and/or a paucity of studies
- Future studies are likely to change the estimates and possibly the direction

Very Low
- No confidence in any result found (e.g., paucity of data)
- Data are such that we cannot make a statement on the findings

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Findings

(See Summary of Findings Tables and Appendix IV for further detail)

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Overview: Studies evaluating the effectiveness of Novocure

Indication	Findings for KQ#1	# Studies, Overall Quality
GBM	**Recurrent GBM** (n=873) • Novocure is at least comparable with chemotx	5, low (1 FQ RCT, 1 VPQ trial with historical controls, 1 VPQ cohort study, 1 PQ multicenter registry study with historical controls, and 1 PQ subgroup analysis)
	Newly dx'd GBM (n=325) • Novocure superior to chemotx	2, very low (1 FQ RCT, VPQ cohort study)
NSCLC	• n=41 • 15% of pts exhibited a **partial response** to tx	1, very low (1 VPQ case series)
Various solid tumors	• n=6 • 17% of pts exhibited a **partial response** to tx	1, very low (1 VPQ case series)

KQ#1a: Effectiveness of Novocure for Recurrent GBM

Evidence	Study results
5 studies (n=873) **Kirson 2007** (n=12; trial with historical controls, VPQ) **Stupp 2012** (n=237; RCT, FQ) **Mrugala 2014** (n=457; Registry study with historical controls, PQ) **Vymazal and Wong 2014** (n=130; subgroup analysis, PQ) **Wong 2015** (n=37; retrospective cohort, VPQ) **Low Overall Quality** (few studies, some with small sample sizes)	**Median OS (Novocure grp, chemotx grp):** Kirson 2007: 14.3 months, 6.7 months (*P*=NR) Mrugala 2014: 9.6 months, 6.0 months (*P*=0.0003) Vymazal and Wong 2014: 6.6 months, NR **Median PFS at 6 months (Novocure grp, chemotx grp):** Kirson 2007: 50%, 15% (*P*=NR) Stupp 2012: 21%, 15% (NS) **Percentage OS at 6 months, 1 yr, 2 yrs (Novocure grp, chemotx grp):** Stupp 2012: 53%, 48%; 20%, 19%; 8%, 3% (*P*=NR) Mrugala 2014: NR, NR; 44%, 24%; 30%, 7%

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KQ#1a: Effectiveness of Novocure for Recurrent GBM

Evidence	Study results
5 studies (n=873) **Kirson 2007** (n=12; trial with historical controls, VPQ) **Stupp 2012** (n=237; RCT, FQ) **Mrugala 2014** (n=457; registry study with historical controls, PQ) **Vymazal and Wong 2014** (n=130; subgroup analysis, PQ) **Wong 2015** (n=37; retrospective cohort, VPQ) **Low Overall Quality** (few studies, some with small sample sizes)	**Percentage of pts with partial or complete radiological response to tx (Novocure grp, chemotx grp):** Stupp 2012: 14%, 10% (NS) Vymazal and Wong 2014: 15%, NR **Median OS (Novocure plus bevacizumab plus TCCC* grp, Novocure plus bevacizumab only grp):** Wong 2015: 10.3 months, 4.1 months (NS) **Median PFS (Novocure plus bevacizumab plus TCCC* grp, Novocure plus bevacizumab only grp):** Wong 2015: 8.1 months, 2.8 months (NS)

***TCCC = 6-thioguanine, lomustine, capecitabine, and celecoxib**

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KQ#1a: Effectiveness of Novocure for Recurrent GBM

Evidence	Study results
5 studies (n=873) **Kirson 2007** (n=12; trial with historical controls, VPQ) **Stupp 2012** (n=237; RCT, FQ) **Mrugala 2014** (n=457; Registry study with historical controls, PQ) **Vymazal and Wong 2014** (n=130; subgroup analysis, PQ) **Wong 2015** (n=37; retrospective cohort, VPQ) **Low Overall Quality** (few studies, some with small sample sizes)	**Quality of Life** Stupp 2012 (n=63): • No meaningful differences were observed in global health and social fxn between grps. • Cognitive fxn, role fxn, and emotional fxn favored Novocure. • Physical fxn was slightly worse with Novocure • Worse sx scale (increased pain and fatigue) in chemotx grp

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KQ#1a: Effectiveness of Novocure for Newly Dx'd GBM

Evidence	Study results
2 studies (n=325) Stupp 2015 (RCT, fair) Kirson 2009 (cohort study, very poor) **Very Low Overall Quality** (very few studies available)	**Stupp 2015 (Novocure plus TMZ grp, TMZ only grp):** **Median PFS:** 7.1 mos, 4.0 mos (*P*=0.001), HR 0.62 (98.7% CI, 0.43–0.89) **Median OS:** 20.5 mos, 15.6 mos (*P*=0.004), HR 0.64 (98.7% CI, 0.43 –0.89) **Kirson 2009 (Novocure grp, chemotherapy grp):** **Median PFS:** 35.6 mos, 7.1 mos (*P*=0.0002), HR 3.32 (95% CI, 1.9–5.9) **Median OS:** 39 mos, 4.7 months (*P*=0.0018)

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KQ#1b: Effectiveness of Novocure for NSCLC

Evidence	Study results
1 study (n=41) Pless 2013 (case series, very poor) **Very Low Overall Quality** (single study available)	15% of NSCLC pts exhibited a **partial response** to Novocure tx **Median PFS:** 22.2 wks **Median OS:** 13.8 months **1-Yr Survival:** 57%

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KQ#1b: Effectiveness of Novocure for Solid Tumors from Breast Cancer, Melanoma, and Mesothelioma

Evidence	Study results
1 study (n=6) Salzberg 2008 (case series, very poor) **Very Low Overall Quality** (single study available)	1 breast cancer pt (17%) showed a **partial response** to tx. 3 pts (50%) with skin lesions due to breast cancer or melanoma had **stable disease**. 1 pt (17%) with GBM* exhibited **progressive disease.** 1 mesothelioma pt (17%) had a **mixed response**.

*This pt was not included in the GBM literature review as it is a case report.

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KQ #2: What harms are associated with Novocure?

- 7 studies reported on AEs during Novocure tx
- Dermatologic AEs
  - Most common complication reported was mild to moderate dermatitis under the transducer arrays
    - 16% to 90%
  - Improve with topical corticosteroids, repositioning of electrodes
  - Skin ulcers in 1% to 7% of pts (2 studies)

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KQ #2: What harms are associated with Novocure?

- Other commonly reported AEs
  - Fatigue (3%–24%)
  - Pain/discomfort (5%–12%)
  - Gastrointestinal disorders (3%–12%)
  - Nervous system disorders (10%–30%)
  - Infections (1%–4%)
- Stupp et al. (2012): Significantly more gastrointestinal, hematological, and infectious AEs observed in the chemotx grp than in the Novocure grp.
- Stupp et al. (2015): Mild anxiety, confusion, insomnia, and headaches more frequent in Novocure plus TMZ pts; mainly occurred at the time of tx initiation.

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KQ #3: Differential performance or impact according to clinical hx, pt characteristics?

- Post-hoc analysis found that pts tx'd at their 1st GBM recurrence had significantly longer OS (20 months) compared with pts tx'd at 2nd recurrence (8.5 months) or ≥3rd recurrence (4.9 months) (P=0.0271) (Mrugala et al., 2014)
- 5 of the 8 studies analyzed for KQ #1 reported the number of previous GBM episodes
  - OS and PFS tended to be longer in studies that enrolled more pts in their 1st or 2nd GBM episode

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Overall Survival and Number of Previous GBM Episodes

Study author (year)	Previous episodes of GBM	Study results
Kirson (2009) n=10	0 previous episodes	OS (Novocure grp): 39 mos OS (Chemotx grp): 14.7 mos
Stupp (2015) n=315	0 previous episodes	OS (Novocure grp): 20.5 mos OS (Chemotx grp): 15.6 mos
Kirson (2007) n=12	50% -1st recurrence	OS (Novocure grp): 14.3 mos OS (Chemotx grp): 6.7 mos
Mrugala (2014) n=457	33% -1st recurrence 27% - 2nd recurrence	OS (Novocure grp): 9.6 mos OS (Chemotx grp): 6.0 mos
Wong (2015) n=37	18% - 1st recurrence 26% - 2nd recurrence	OS (Novocure grp): 4.1 mos
Mrugala (2014) n=457	33% -1st recurrence 27% - 2nd recurrence	% pts OS (1 yr, 2 yrs): 44%, 30%
Stupp (2012) n=237	9% -1st recurrence	% pts OS (1 yr, 2 yrs): 20%, 7.5%

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Progression-Free Survival and Number of Previous GBM Episodes

Study author (year)	Number of previous episodes of GBM	Study results
Kirson (2007) n=12	50% -1st recurrence	PFS at 6 mos (Novocure grp): 50% PFS at 6 mos (Chemotx grp): 15%
Stupp (2012) n=237	9% -1st recurrence	PFS at 6 mos (Novocure grp): 21% PFS at 6 mos (Chemotx grp): 15%
Stupp (2015) n=315	0 previous episodes	PFS (Novocure grp): 7.1 mos PFS (Chemotx grp): 4.0 mos
Kirson (2009) n=10	0 previous episodes	PFS (Novocure grp): 35.6 mos PFS (Chemotx grp): 7.1 mos
Wong (2015) n=37	18% - 1st recurrence 26% - 2nd recurrence	PFS (Novocure grp): 2.8 mos

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KQ #3: Differential performance or impact according to clinical hx, pt characteristics?

- Other prognostic variables that affected clinical outcomes
  - Lower daily doses of dexamethasone exhibited longer OS (Wong et al., 2014)
  - More favorable KPS score had significantly longer OS (Mrugala et al., 2014; Vymazal and Wong, 2014)
  - Not exposed to bevacizumab tx prior to Novocure tx more likely to respond to tx (Mrugala et al., 2014; Vymazal and Wong, 2014)
  - Secondary GBM upgraded from low-grade gliomas more likely to respond to tx (Vymazal and Wong, 2014)
  - Smaller tumor size more likely to respond to tx (Vymazal and Wong, 2014)

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KQ #3: Differential performance or impact according to clinical hx, pt characteristics?

- Compliance with Novocure device an important factor
  - 2 studies found that median OS was significantly longer in Novocure pts with a monthly compliance rate ≥75% (≥18 hrs per day) than in pts with a compliance <75%
    - OS 7.7 months vs 4.5 months **(*P*=0.042)** (Stupp et al., 2012)
    - OS 13.5 months vs 4.0 months **(*P*<0.0001)** (Mrugala et al., 2014)
  - 1 study found that response to tx was correlated with compliance **(*P*<0.001)** (Vymazal and Wong, 2014)
    - Average compliance 92% in partial and complete responders
    - Average compliance 85% in pts with stable disease
    - Average compliance 79% in pts with progressive disease

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KQ #4: Cost implications

- Cost-effectiveness
  - No published studies evaluating the cost of Novocure per unit of clinical benefit were available in the reviewed literature
- Cost of Novocure device
  - Estimate of the cost of the device to be $10,907.81 to $21,429.96 per month (Randall, 2010; Kotz, 2014)

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Practice Guidelines and Payer Policies

Payer policies

- No Centers for Medicare & Medicaid Services (CMS) National Coverage Determination (NCD) was identified
- Aetna:
  - TTFs are medically necessary for persons with recurrent GBM after receiving chemotx.
  - TTFs are experimental and investigational for the tx of other malignant tumors and for all other indications.
- These payers consider TTFs to be experimental:
  - GroupHealth
  - Regence Group

Practice Guidelines: GBM

Quantity/quality of guidelines	Tx recommendations
6 guidelines (3 fair, 3 poor) **AANN**, Association of Neuroscience Nurses **AANS**, American Association of Neurological Surgeons **CNS**, Congress of Neurological Surgeons **EANO**, European Association of Neuro-Oncology **ESMO**, European Society for Medical Oncology **NCCN**, National Comprehensive Cancer Network	Newly dx'd GBM: • Surgery → by RT + concurrent TMZ → adjuvant TMZ • Carmustine polymer wafers (Gliadel Wafers) may prolong survival
	Recurrent GBM: Options include repeat surgery, irradiation, chemotx, or bevacizumab
	Progressive GBM: Enroll in an appropriate clinical trial
	Novocure tx: • Should only be administered in the context of clinical trials (EANO, 2014; no level of recommendation stated) • May be considered a comparable tx option to chemotx in recurrent GBM pts (AANN, 2014; Level 1) • Novocure failed to prolong survival compared with chemotx (ESMO, 2013; IA: Strong recommendation) • Novocure is an option in the tx algorithm for recurrent GBM (NCCN, 2015; Category 2B [consensus that tx is appropriate based on low-level evidence])

Overall Summary and Discussion

Final Summary

- Overall, results for Novocure for treating recurrent GBM are positive and suggest that Novocure is at least comparable with chemotx in increasing OS and PFS
  - Low-quality evidence (small quantity of data, small sample sizes, and lack of concurrent control or comparator grps in most studies)
- 2 studies suggest that Novocure increases OS and PFS compared with chemotx in pts with newly diagnosed GBM
  - Very-low-quality evidence (very small quantity of data for this indication)

Final Summary

- Novocure for NSCLC
  - 1 small case series (n=41) found that 15% of pts exhibited a partial response
  - Relatively short tx duration (12 hrs per day)
  - Very low quality (very small quantity of data, lack of comparator grp)
- Novocure for solid tumors of various etiologies
  - 1 very small case series (n=6) found that 1 breast cancer pt (17%) showed a partial response
  - Other pts had stable or progressive disease
  - Very low quality (very small quantity of data, lack of comparator grp)
- Novocure for all other indications insufficient due to the lack of studies

Final Summary

- Current evidence suggests Novocure does not pose major safety concerns
  - Evidence of safety is of low quality (because of the quality of individual studies and lack of statistical comparisons with a control grp)
- Several studies provided data suggesting that compliance with Novocure tx was an important factor related to tx outcome
  - ≥18 hrs per day
- Very little direct evidence for QOL or functional states during Novocure tx
  - 1 study suggested that cognitive and emotional fxn favored Novocure
  - Physical fxn worse with Novocure
  - Sx scale worse in the chemotx grp (increased pain and fatigue)

Additional research needed for all Key Questions

- RCTs and cohort studies of sufficient size and design to further investigate the safety and efficacy of Novocure in pts with recurrent or newly dx'd GBM, NSCLC, or other cancers, compared with chemotx or other txs.
- Studies designed to systematically investigate differential effectiveness and safety according to pt characteristics and previous tx hx.
- Studies investigating the impact of Novocure on QOL and functional status.
- Economic evaluations on the cost-effectiveness of Novocure.

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Thank you!

QUESTIONS?

Extra Slides

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.

[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

- 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.
- 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

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

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

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.

Health Technology Evidence Identification

Discussion Document:

What are the key factors and health outcomes and what evidence is there?

Safety Outcomes	Safety Evidence
Adverse events	
Dermatologic complications	
Skin ulcers	
Fatigue	
Pain/discomfort	
Gastrointestinal disorders	
Nervous system disorders	
Infections	
Other	

Efficacy – Effectiveness Outcomes	Efficacy / Effectiveness Evidence
Overall survival	
Progression free survival	
Tumor response/progression	
Partial response	
Complete response	
Quality of life	
Special Population / Considerations Outcomes	**Special Populations/ Considerations Evidence**
Age	
Sex	
Ethnicity	
Race	
Karnofsky Performance Status (KPS)	
Steroid dose levels	
Tumor grade	
Compliance	
Cost Outcomes	**Cost Evidence**
Costs	
Cost-effectiveness	

Medicare Coverage and Guidelines

[From Page 13 of the Updated Final Evidence Report]
No Centers for Medicare & Medicaid Services (CMS) National Coverage Determination (NCD) was identified for Novocure/Optune.

[From Page 12 of the Updated Final Evidence Report]

Table 3. Summary of Practice Guideline Recommendations

Key: AANN, Association of Neuroscience Nurses; AANS, American Association of Neurological Surgeons; ACCP, American College of Chest Physicians; ASTRO, American Society for Radiation Oncology; CNS, Congress of Neurological Surgeons; EANO, European Association of Neuro-Oncology; ESMO, European Society for Medical Oncology; GBM, glioblastoma; GL, guideline; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; pt(s), patient(s); RT, radiotherapy; TMZ, temozolomide; tx, treatment

Quantity of Individual GLs	Individual GL Quality	Recommendations
Tx of GBM		
6 (AANN, AANS/CNS, EANO, ESMO, NCCN)	3 Fair 3 Poor	Newly diagnosed GBM: Resection or biopsy, followed by RT plus concurrent TMZ, followed by adjuvant TMZ. Carmustine polymer wafers (Gliadel Wafers) may prolong survival when implanted into the resection cavity at the time of surgery. Recurrent GBM: Options include re-resection, reirradiation, rechallenge chemotherapy, or bevacizumab. Progressive GBM: Pts w/ progressive GBM should be enrolled in an appropriate clinical trial. Novocure: Novocure should only be administered in the context of clinical trials (EANO); nurses should be aware that Novocure may be considered a comparable tx option to chemotherapy in recurrent GBM pts (AANN); GBM failed to prolong survival compared w/ chemotherapy (ESMO); Novocure is an option in the tx algorithm for recurrent GBM (NCCN).
Tx of NSCLC		
5 (ACCP, ASTRO, ESMO, NCCN)	2 Good 1 Fair 2 poor	Surgery: Optimal surgical management involves complete resection. RT and Chemotherapy: Options include induction chemotherapy followed by surgery, induction chemoradiotherapy followed by surgery, or concurrent definitive chemoradiotherapy. Pts that have a planned lobectomy (as opposed to pneumonectomy) are the best candidates for preoperative chemoradiotherapy. The 2 most common concurrent chemotherapy regimens are cisplatin/etoposide and carboplatin/paclitaxel. If pts are evaluated as unresectable, 2 to 4 cycles of concurrent chemoradiotherapy is the standard of care. Platinum-based chemotherapy yields the best outcomes. Bevacizumab: Bevacizumab plus chemotherapy or chemotherapy alone is

Quantity of Individual GLs	Individual GL Quality	Recommendations
		indicated in pts with poor performance status and with advanced or recurrent NSCLC (NCCN). Stage IV NSCLC: The standard first-line chemotherapy is platinum-based chemotherapy. Chemotherapy should be initiated while the pt has a good performance status. Systemic tx should be offered to all stage IV pts w/ poor performance status. 4 to 6 tx cycles of chemotherapy are recommended (ESMO). None of the guidelines mentioned the use of Novocure for treating NSCLC.

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.

Is there sufficient evidence under some or all situations that the technology is:

	Unproven (no)	Equivalent (yes)	Less (yes)	More (yes)
Effective				
Safe				
Cost-effective				

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.