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
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)

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?

Novocure

Agency Medical Director Concerns

- Safety = Low
- Efficacy = High
- Cost = High
Novocure

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

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
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

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
Novocure

**Novocure: Cost-Effectiveness**

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

**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

Novocure

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

Questions?

More Information
www.hca.wa.gov/hta/Pages/novocure.aspx
**Order of Scheduled Presentations:**

**Novocure (Tumor Treating Fields)**

<table>
<thead>
<tr>
<th>Name</th>
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<tr>
<td>1</td>
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No requests to provide public comment on the technology review were received.
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"

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

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

________________________________________________________________________________________
________________________________________________________________________________________

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<th>Potential Conflict Type</th>
<th>Yes</th>
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<tbody>
<tr>
<td>7. Representation: if representing a person or organization, include the name and fund</td>
<td></td>
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</tbody>
</table>

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  Signature: ___________________________ Date: 1/04/2016  Print Name: LYNNE TAYLOR M.D.

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

Email Address: LYNNE.TAYLOR@VIRGINI.AMAZON.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:
1100 9th Avenue, C2-HEME
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

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

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  CARSCOOG 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 COMMITTEE 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**


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

Annual Meeting, Philadelphia, PA, Faculty
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- Fellow Application Review Workgroup, member
2013- Ethics, Law and Humanities Committee, member
2013- Ethics Committee, 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
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Lynne P. Taylor, MD, FAAN, FANA

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**

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<th>Journal/Board</th>
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<td>1992-2005</td>
<td>Continuum (AAN)</td>
<td>Board member</td>
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<td>2000-</td>
<td>Neurology</td>
<td>Reviewer</td>
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<td>2004-</td>
<td>Annals of Neurology</td>
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<td>2005-</td>
<td>Neurology Now (AAN)</td>
<td>Board member</td>
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<td>2011-2012</td>
<td>AAN.com</td>
<td>Reviewer</td>
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<tr>
<td>2011-</td>
<td>Journal Clinical Oncology</td>
<td>Reviewer</td>
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<td>2011-</td>
<td>Journal of Neuro-Oncology</td>
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<tr>
<td>2014-</td>
<td>Cephalalgia</td>
<td>Reviewer</td>
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<td>2014-</td>
<td>Neurology: Neuroimmunology &amp; Neuroinflammation</td>
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**BIBLIOGRAPHY**

*Papers*


**Invited Papers:**


**Book Chapters**


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

Book authored/edited


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


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

         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
Presentation overview

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

Background
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

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
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)

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
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

Scope, Methods, and Search Results
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

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 treatment 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?
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

191 PubMed hits
316 Embase hits

466 studies excluded based on title/abstract review

42 full-text articles retrieved

29 articles excluded based on full-text review

10 studies analyzed (reported in 13 articles)
  9 studies (KQ#1, KQ#3)
  1 unique study (KQ#2)
  0 cost studies (KQ#4)
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
Findings

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

Overview: Studies evaluating the effectiveness of Novocure

<table>
<thead>
<tr>
<th>Indication</th>
<th>Findings for KQ#1</th>
<th># Studies, Overall Quality</th>
</tr>
</thead>
</table>
| GBM              | **Recurrent GBM** *(n=873)*  
• Novocure is at least comparable with chemotx  
**Newly dx’d GBM** *(n=325)*  
• Novocure superior to 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)  
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

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

#### 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*
### KQ#1a: Effectiveness of Novocure for Recurrent GBM

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

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

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Study results</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 studies (n=325)</td>
<td><strong>Stupp 2015 (Novocure plus TMZ grp, TMZ only grp):</strong>&lt;br&gt;Median PFS: 7.1 mos, 4.0 mos (P=0.001), HR 0.62 (98.7% CI, 0.43–0.89)&lt;br&gt;Median OS: 20.5 mos, 15.6 mos (P=0.004), HR 0.64 (98.7% CI, 0.43–0.89)</td>
</tr>
<tr>
<td>Stupp 2015 (RCT, fair)&lt;br&gt;Kirson 2009 (cohort study, very poor)</td>
<td><strong>Very Low Overall Quality</strong>&lt;br&gt;(very few studies available)</td>
</tr>
<tr>
<td>Kirson 2009 (Novocure grp, chemotherapy grp):&lt;br&gt;Median PFS: 35.6 mos, 7.1 mos (P=0.0002), HR 3.32 (95% CI, 1.9–5.9)&lt;br&gt;Median OS: 39 mos, 4.7 months (P=0.0018)</td>
<td></td>
</tr>
</tbody>
</table>
KQ#1b: Effectiveness of Novocure for NSCLC

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

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

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

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

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.
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

---

**Overall Survival and Number of Previous GBM Episodes**

<table>
<thead>
<tr>
<th>Study author (year)</th>
<th>Previous episodes of GBM</th>
<th>Study results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kirson (2009) n=10</td>
<td>0 previous episodes</td>
<td>OS (Novocure grp): 39 mos OS (Chemotx grp): 14.7 mos</td>
</tr>
<tr>
<td>Stupp (2015) n=315</td>
<td>0 previous episodes</td>
<td>OS (Novocure grp): 20.5 mos OS (Chemotx grp): 15.6 mos</td>
</tr>
<tr>
<td>Kirson (2007) n=12</td>
<td>50% – 1st recurrence</td>
<td>OS (Novocure grp): 14.3 mos OS (Chemotx grp): 6.7 mos</td>
</tr>
<tr>
<td>Mrugala (2014) n=457</td>
<td>33% – 1st recurrence 27% – 2nd recurrence</td>
<td>OS (Novocure grp): 9.6 mos OS (Chemotx grp): 6.0 mos</td>
</tr>
<tr>
<td>Wong (2015) n=37</td>
<td>18% – 1st recurrence 26% – 2nd recurrence</td>
<td>OS (Novocure grp): 4.1 mos</td>
</tr>
<tr>
<td>Mrugala (2014) n=457</td>
<td>33% – 1st recurrence 27% – 2nd recurrence</td>
<td>% pts OS (1 yr, 2 yrs): 44%, 30%</td>
</tr>
<tr>
<td>Stupp (2012) n=237</td>
<td>9% – 1st recurrence</td>
<td>% pts OS (1 yr, 2 yrs): 20%, 7.5%</td>
</tr>
</tbody>
</table>
Progression–Free Survival and Number of Previous GBM Episodes

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

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)
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 $\geq 75\%$ ($\geq 18$ 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

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)
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

<table>
<thead>
<tr>
<th>Quantity/quality of guidelines</th>
<th>Tx recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 guidelines</td>
<td></td>
</tr>
<tr>
<td>(3 fair, 3 poor)</td>
<td></td>
</tr>
</tbody>
</table>

**Newly dx’d GBM:**
- Surgery \(\rightarrow\) by RT + concurrent TMZ \(\rightarrow\) 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)

- 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 fnn favored Novocure
  - Physical fnn 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.
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 using characteristics such as:

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

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

<table>
<thead>
<tr>
<th>Not Confident</th>
<th>Confident</th>
</tr>
</thead>
</table>

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

<table>
<thead>
<tr>
<th>Safety Outcomes</th>
<th>Safety Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
<td></td>
</tr>
<tr>
<td>Dermatologic complications</td>
<td></td>
</tr>
<tr>
<td>Skin ulcers</td>
<td></td>
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<tr>
<td>Fatigue</td>
<td></td>
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<tr>
<td>Pain/discomfort</td>
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<tr>
<td>Gastrointestinal disorders</td>
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</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
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</tbody>
</table>
# Efficacy – Effectiveness Outcomes

<table>
<thead>
<tr>
<th>Efficacy – Effectiveness Outcomes</th>
<th>Efficacy / Effectiveness Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td></td>
</tr>
<tr>
<td>Progression free survival</td>
<td></td>
</tr>
<tr>
<td>Tumor response/progression</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td></td>
</tr>
<tr>
<td>Quality of life</td>
<td></td>
</tr>
</tbody>
</table>

# Special Population / Considerations Outcomes

<table>
<thead>
<tr>
<th>Special Population / Considerations Outcomes</th>
<th>Special Populations/ Considerations Evidence</th>
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<td>Age</td>
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<td>Sex</td>
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<td>Ethnicity</td>
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<tr>
<td>Race</td>
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<tr>
<td>Karnofsky Performance Status (KPS)</td>
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<tr>
<td>Steroid dose levels</td>
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<td>Tumor grade</td>
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<td>Compliance</td>
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# Cost Outcomes

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<th>Cost Outcomes</th>
<th>Cost Evidence</th>
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<td>Costs</td>
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<td>Cost-effectiveness</td>
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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

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<thead>
<tr>
<th>Quantity of Individual GLs</th>
<th>Individual GL Quality</th>
<th>Recommendations</th>
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<tr>
<td><strong>Tx of GBM</strong></td>
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<tr>
<td>6 (AANN, AANS/CNS, EANO, ESMO, NCCN)</td>
<td>3 Fair 3 Poor</td>
<td>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).</td>
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<p>| <strong>Tx of NSCLC</strong>            |                       |                 |
| 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 |</p>
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<tr>
<th>Quantity of Individual GLs</th>
<th>Individual GL Quality</th>
<th>Recommendations</th>
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<tr>
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<td>indicated in pts with poor performance status and with advanced or recurrent NSCLC (NCCN).</td>
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<td><em>Stage IV NSCLC</em>: 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).</td>
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<td>None of the guidelines mentioned the use of Novocure for treating NSCLC.</td>
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**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:

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<tr>
<th></th>
<th>Unproven (no)</th>
<th>Equivalent (yes)</th>
<th>Less (yes)</th>
<th>More (yes)</th>
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<tbody>
<tr>
<td>Effective</td>
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<tr>
<td>Safe</td>
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<tr>
<td>Cost-effective</td>
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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.