Washington State Health Care Authority

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

Peer review and public comment on draft evidence report

October 17, 2018

Health Technology Assessment Program (HTA)

Washington State Health Care Authority

PO Box 42712
Olympia, WA 98504-2712
(360) 725-5126
www.hca.wa.gov/hta
shtap@hca.wa.gov

Prepared by:
RTI International–University of North Carolina Evidence-based Practice Center
Research Triangle Park, NC 27709
www.rti.org

This document was created in response to peer review and public comments on a Draft Health Technology Assessment (HTA) report prepared by the RTI-UNC Evidence-based Practice Center through a contract to RTI International from the State of Washington Health Care Authority (HCA). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the State of Washington HCA and no statement in this document should be construed as an official position of the State of Washington HCA.

The information in the document is intended to help the State of Washington's independent Health Technology Clinical Committee make well-informed coverage determinations. This document and its associated Evidence Report are not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this document and the associated Evidence Report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

Acknowledgments

The following individuals from the RTI-UNC Evidence-based Practice Center contributed to this report:

Lead Investigator: Rachel Palmieri Weber, PhD
Co-Investigator: Karen Crotty, PhD, MPH
Clinical Advisor: Simon Khagi, MD
Analyst: Rachel Clark, BA
Scientific Reviewer: Leila Kahwati, MD, MPH
Library/Document Preparation: Mark Howell, MLS; Loraine Monroe; Laura Small, BA

Contents

List of Tables

Peer Review Comments and Responses

Two independent, external peer reviewers were invited to provide comments on the Draft Evidence Report. These individuals did not receive any compensation in exchange for their review. Their names, affiliations, and conflicts of interest reported are summarized in ***Table 1***.

Table 1. External Peer Reviewers of the Draft Evidence Report

Name	Title/Affiliation	Conflicts of Interest Reported
Glenn J. Lesser, MD, FACP	Louise McMichael Miracle Professor in Oncology, Associate Chief, Section on Hematology and Oncology, Principal Investigator, Wake Forest NCORP Research Base, Director of Medical Neuro-Oncology, Co-Leader, Neuro-Oncology Research Program, Wake Forest Baptist Comprehensive Cancer Center	Financial conflicts: Research Support for Brain Tumor Clinical Trials from the following companies: Vascular Biogenics, New Link Genetics, Incyte, Pfizer, Orbus therapeutics, Novartis. Data Safety Monitoring Board Chair – Stemline Therapeutics. Invited member: Monteris: NeuroBlate Oncology Concepts & Innovation Forum. Non-financial conflicts: Primary clinical specialty is medical oncology, neuro-oncology. Prescribes TTF for select patients with brain tumors.
Savvas C. Pavlides, PhD	Research Analyst, Emerging Technologies, Health Technology Assessment Information Service, ECRI Institute	Financial conflicts: None. Non-financial conflicts: None.

Peer reviewers did not identify any missing studies and did not identify any studies that should have been excluded from the report. Peer reviewers offered thoughtful suggestions for clarifying background information on tumor treating fields and the Optune® device. Finally, peer reviewers identified additional considerations related to limitations of the evidence that were not fully addressed. We addressed most comments submitted by peer reviewers in the Final Evidence Report. We considered most revisions made based on peer review comments as minor revisions. Specific peer review comments and responses are provided in ***Table 2***.

Table 2. Peer Reviewer Comments on Draft Evidence Report and Response

Item	Comment	Response
Introduction		
Are there any additional issues you think we should cover in the introduction?	Not clear from table of contents what is considered the "introduction". I do believe some additional information regarding the paucity of effective treatment options for patients with both newly diagnosed and recurrent GBM as well as the limited progress and few therapies approved over the past few decades could be added.	We have added additional text in section 1.1.3 to describe the paucity of effective treatment options.
	A brief description and discussion of the optional associated planning software, NovoTAL, can be included in the "Technology Description" section. The NovoTAL software enables the development of an array plan for planning optimal array placement, specific to each patient based on the patient's most recent MRIs. The reader may also benefit from a brief description of patient flow and the different scenarios for patients who are starting treatment with the Optune. The description is particularly relevant for providing context for the workflow and the staffing/ care process and infrastructure needs associated with this treatment modality (TTF). Briefly, after a physician prescribes Optune: 1. The paperwork may be forwarded to the company. A Novocure device specialist will set-up the Optune kit at the patient's home and apply the leads. This approach does not require any additional physician office visits or resources. Or 2. The patient may return to the physician's office for array placement.	We have added text in section 1.2 that describes the NovoTAL software. Thank you for the suggestion to add additional details about the workflow of treatment with TTF. We have cited Novocure's instructions for use in the report should the reader desire more specific details about Optune®.
Do you see anything inaccurate, superfluous, or unclear?	No.	Thank you.
	I would refrain from using the term "multiforme" throughout the report as it is not included in WHO's most recent classification system. However, I do believe the abbreviation GBM is most appropriate as it most commonly used in conversation and in the literature. In the "Technology Description" section, the term "electromagnetic field therapy" is used to describe the noninvasive alternating electric field intended to disrupt malignant cell mitosis. Instead of an "electromagnetic field," Optune more accurately creates alternating electric fields intended to interfere with and disrupt mitotic spindle microtubule assembly and to disrupt completion of cell division by creating dielectrophoretic dislocation of charged intracellular constituents associated with these processes.	Glioblastoma and glioblastoma multiforme are used interchangeably in the literature. The term 'multiforme' is included in the both the Washington State Agency Utilization Data report and the FDA's pre-market approval letter. To maintain consistency in terminology, we will retain the term 'multiforme' in the final report. We have removed the term "electromagnetic field therapy" from the report and added additional text to section 1.2 in an effort to more accurately describe tumor treating fields.
Any additional comments?	As per above.	Thank you.
	The introduction is very comprehensive and provides adequate information for the reader to follow the report.	Thank you.

Item	Comment	Response
Methods		
Do you see any problems with our methods?	No.	Thank you.
	The research questions have the appropriate focus for the stated purpose of this health technology assessment. Additionally, study design selection and the effectiveness outcomes, safety outcomes and cost outcomes are appropriate for the report's scope. In the "Methods" section, Table 2 lists "TTF plus chemotherapy or other adjunctive treatments" as a comparator. For newly diagnosed glioblastoma (GBM), TTF therapy is indicated as an adjuvant to maintenance temozolomide; for recurrent GBM, TTF is intended as a monotherapy. Therefore, the reader can benefit from an explanation of the rationale for the selection of TTF plus chemotherapy as a comparator.	Thank you. We have added additional text to section 2.1.2.2 to remind readers of the FDA-approved indications for TTF in patients with new and recurrent GBM.
Any additional comments about the Methods section?	No.	Thank you.
	As stated above, research question selection is appropriate and focused. A small comment for the safety questions (SQ1 and SQ1a) regarding use of the word "harms." The use of the word "harms" in the safety questions negatively predisposes the user to expect TTF to harm patients. Consider using "adverse events" as the phrase has a more balanced connotation.	We use the term 'harms' to be consistent with the prior report but describe these outcomes as adverse events throughout the body of the report.
Results		
Are there any studies you believe we may have missed?	No.	Thank you.
	Studies included for assessing newly diagnosed GBM and recurrent GBM are appropriate.	Thank you.
Are there studies that you believe we should have excluded?	No.	Thank you.
	No.	Thank you.
Do you believe we have inaccurately described any studies?	No.	Thank you.
	No.	Thank you.
Any additional comments about the Results?	No.	Thank you.
	I agree with the efficacy and safety risk of bias (ROB) and strength of evidence (SOE) assessment of outcomes for newly diagnosed GBM. The stratification of ROB and SOE by treatment comparison is appropriate.	We have added a rationale for the overall quality rating of "some concerns" for the EF-11 trial to Table F-1. With respect to the OS and PFS outcomes, we agree with your comments on completeness of data, the use of intention-to-treat analyses, and the objective ascertainment of the outcomes data (i.e.,

Item	Comment	Response
	Some clarification would be helpful for the risk of bias (ROB) assessment of the outcomes overall survival (OS) and progression free survival (PFS) for the EF-11 randomized controlled trial reported in Stupp et al., 2012. For these outcomes, Table F1 does not provide a rationale for the "overall rationale for quality rating." However, the reader can benefit from a description of the rationale that led to "some concerns" for the ROB assessment for OS and PFS because the reasons for downgrade are not immediately evident. OS data reported in Stupp et al., 2012 are quite complete (less than 5% not reported for each treatment group) and bias for this domain (missing outcome data) is low. Regarding the ROB domains deviations from intended interventions and measurement of outcome, we agree that patients and care givers were not blinded to patient treatment allocations. However, OS is an objective outcome that was objectively reported and not likely influenced by knowledge of group allocation. Similarly, despite lack of patient and care giver blinding, PFS survival was assessed by blinded assessors. Regarding relatively high treatment discontinuation in the TTF group, OS and PFS analyses included the intention to treat population, thereby mitigating concerns of lack of adherence having a clinically meaningful effect. In light of this context, the user could benefit from an explanation of the rational for judging OS and PFS ROB as "some concerns" and an explanation/ description of the primary concerns leading to ROB downgrade.	objective OS outcome, masked PFS outcome assessor). We do note, however, the imbalance of the groups at baseline with respect to prior treatments and number of recurrences, as well as differential adherence to assigned treatment. There were additional concerns related to the safety outcomes data, primarily due to a lack of it from the active control group and the potential for the patient-reported data to be influenced by knowledge of the treatment.
	Given the terminal nature of recurrent GBM and that an intended benefit of Optune is to improve patient QOL, I believe a more granular comparison of serious adverse events (AEs) between chemotherapy and TTF monotherapy would be useful to the HTA report. The user may benefit by a more granular presentation of serious AEs and the direction of effect of each. Grouping of AEs masks the burden of chemotherapy-related AEs in relation to TTF and vice versa. Some of the serious AEs reported require very different treatment than others and carry varied implications to patient health. The user may benefit from knowing AEs for which TTF is worse and AEs for which chemotherapy is worse.	We have added additional text to section 3.3.2.2 to describe chemotherapy-related adverse events for the recurrent GBM patient populations in both the EF-11 trial and the prospective follow-up from patients in the EF-14 trial who experienced a recurrence. Additional data are available in Table D-11.
Discussion		
Do you think we missed any important points?	It appears that the main reason for the conclusions regarding very low to low certainty that the addition of TTF to usual care increases overall and progression-free survival as well as the very low certainty that TTF improves quality of life and functional status in newly diagnosed GBM patients stems from bias concerns from the only relevant study – Stupp 2017. The reviewers accurately	We agree with your comments about blinding with respect to the survival outcomes and have added text to section 4.2.2 in the discussion section to clarify the risk of bias concerns related to this issue.

Item	Comment	Response
	point out a number of potential concerns about bias (table F) however I am not sure (also discussed in the review) that a better study could be ethically or cost-effectively done. The lack of blinding is a concern but for a variety of reasons – ethical concerns, inability to produce an exact placebo device that also heated up the skin a bit, etc. – couldn't be done. Clearly crossover and nonblinding may also have affected some of the QOL data. However, I am not certain (albeit I am not a statistician) that these biases are likely to have significantly affected a survival endpoint (easy to measure) and in the absence of clear data supporting an imbalance of accepted prognostic factors in both arms, wonder why the almost 5 month survival difference was minimized. This is particularly important in a disease where there are almost no effective therapies and where the median survival is only about 16 months in all comers. Saying that the obvious biases result in a conclusion that the addition of TTF to usual care "may or may not" provide a survival benefit seems like a very strong statement to me. The major problem with this whole review is, of course, that there are few relevant peer-reviewed datasets that can be used to determine outcome/effectiveness.	For newly diagnosed GBM, we rated the strength of evidence as low for benefit with TTF, based on the EF-14 trial results (HR=0.63; 95% CI 0.53 to 0.76 for OS and HR=0.63; 95% CI 0.52 to 0.76 for PFS). Results from one observational study were consistent with the EF-14 trial (strength of evidence: very low). As we state in the conclusion section of the report, we conclude with very low to low certainty that the addition of TTF to usual care with TMZ increases overall and progression-free survival among patients with newly diagnosed GBM. Our conclusion that TTF 'may or may not' result in survival benefits was with respect to patients receiving TTF with or without second-line treatment for recurrent GBM. There was a mix of benefit and no benefit with TTF among 1 trial and 3 observational studies (very low strength of evidence).
	I think the "Discussion" section should include discussion on the control arm of the EF-11 clinical trial. As stated in the report, in the EF-11 trial, investigators compare TTF with best standard chemotherapy in patients with recurrent GBM. However, the choice of control arm chemotherapy does not reflect optimal treatment. Since FDA approved bevacizumab for treating recurrent GBM, it has been used (alone or with lomustine) as the standard of care. Only 31% of patients reported in Stupp et al. 2012 were treated with bevacizumab. The low percentage of patients in the control arm who were treated with bevacizumab is likely because Stupp et al enrolled patients between 2006 and May 2009 and bevacizumab was approved in the U.S. in May 2009. I believe this is important context to provide the reader. Another important limitation of the Stupp et al. 2012 trial that should be discussed is that the study may have had uneven distribution of patients harboring MGMT (O6-methylguanine DNA-methyltransferase) promoter methylation. MGMT promoter methylation is considered a prognostic factor for temozolomide response. Because some patients enrolled in the trial were treated with temozolomide, an uneven distribution of these patients into treatment groups may have affected outcomes. The EF-11 authors did not report consideration of MGMT promoter methylation.	Thank you for your comments. We agree that both of these potential limitations provide important context and as such, have added text to section 4.2.3 of the report's discussion.

Item	Comment	Response
Do you disagree with any of the discussion items?	As per above.	Thank you.
	No.	Thank you.
Any additional comments about the Discussion?	My concern voiced above is that this review will/might prevent patients from accessing this device for a disease for which there are really no good other options. In particular, newly diagnosed GBM patients without MGMT promotor methylation have a very poor prognosis with standard therapy yet they seem to derive the 5 month survival benefit in this trial based on subgroup analysis. This is a very "clinician centric" argument and may not apply to an "objective" analysis…but, it is the real-world outcome of this type of analysis.	Thank you for sharing your clinical perspective. We have shared your comment with the State of Washington; the independent Health Technology Clinical Committee is tasked with determining coverage for tumor treating fields.
	An additional comment regarding Stupp et al. 2012 is that patients with several recurrences were allowed to participate in the study. Approximately 85% of patients enrolled in the study after a second or third recurrence. Typically patients with multiple recurrences are excluded from GBM trials because they have tumors that have acquired resistance to several treatments.	We have added additional text to section 4.2.3 in the discussion section to highlight the heterogeneity of patients with respect to number of recurrences and prior treatment.
Other Sections		
Any comments on the structured abstract, conclusion, figures, tables and appendices?	Appropriate.	Thank you.
	These sections are easy to read and clear.	Thank you.
General Comments		
Is the report clearly written, adequately detailed and of an appropriate length?	Somewhat lengthy given the small number of studies discussed but very complete.	Thank you.
	Overall, this is a well-written and very thorough report.	Thank you.
Please make any additional comments you feel would help us improve the report.	None.	Thank you.
	None.	Thank you.

Abbreviations: AE = adverse events; CI = confidence interval; FDA = United States Food and Drug Administration; GBM = glioblastoma multiforme; HR = hazard ratio; HTA = health technology assessment; ITT = intent to treat; MGMT = O6-methylguanine DNA-methyltransferase; OS = overall survival; PFS = progression free survival; QOL = quality of life; RCT = randomized controlled trial; ROB = risk of bias; SOE = strength of evidence; SQ = safety question; TMZ = temozolomide; TTF = tumor treating fields.

Public Comments and Responses

The Draft Evidence Report was posted for public comment from August 31, 2018 to October 1, 2018. Two individuals provided public comments. Their names and affiliations are summarized in ***Table 3.***

Table 3. Individuals Submitting Public Comments on the Draft Evidence Report

Name	Title/Affiliation
Justin M. Kelly, RN, BSN	Regional Vice President, Health Policy, Novocure
Lynne P. Taylor, MD	Attending Physician, University of Washington Medical Center, Seattle Cancer Alliance Clinical Professor, Department of Neurology Neuro-Oncologist, Co-Director Alvord Brain Tumor Center

Public comments and responses to comments are detailed in ***Table 4***. Complete copies of the comments submitted by individuals follows the table.

Table 4. Public Comments on Draft Evidence Report and Responses

Name (#)	Public Comment	Response
Kelly (1)	The report reads "We conclude with very low to low certainty that the addition of TTF to usual care with TMZ increases overall and progression-free survival among patients with newly diagnosed GBM. For patients with recurrent GBM, there may or may not be survival benefits associated with TTF treatment with or without second-line therapy (very low certainty)." It is our position that efficacy has been established for Optune. Outcome measures, including progression free survival (PFS) and overall survival (OS), demonstrate that adding Optune to standard of care temozolomide in newly diagnosed GBM produces superior clinical results to temozolomide alone. This position is supported by data from randomized controlled trials (RCTs) with appropriate sample sizes. The trials were designed with feedback from the U.S. Food and Drug Administration (FDA) and subsequently the FDA approved Optune, first for recurrent GBM and later for newly diagnosed GBM, on the basis of these trials. Newly Diagnosed GBM - Use of Optune with maintenance temozolomide improves both PFS and OS over maintenance temozolomide alone. The published final analysis of the EF-14 pivotal trial (695 patients, n=466 study arm, n=229 control arm) in newly diagnosed GBM shows a	This HTA evaluates the effectiveness, safety and cost-effectiveness of TTF treatment. The effectiveness, safety, and cost-effectiveness of other treatments (e.g., chemotherapy) is beyond the scope of this HTA. As such, we will refrain from contrasting the findings of this HTA to bodies of evidence related to other interventions of interest. This HTA does not evaluate the quality of studies. Instead, we evaluate the risk of bias (i.e., low, some concerns, high) for each outcome within a study, intentionally avoiding any statements about overall study quality. Details about the risk of bias methodology are available in section 2.1.4 of the report and detailed risk of bias ratings for included studies are available in Appendix Tables F-1 through F-16. We graded the strength of evidence among comparative studies using GRADE. With GRADE, the strength of evidence represents the overall certainty of the findings and can be graded as "very low," "low," "moderate," or "high." Details about the strength of evidence methodology are available in section 2.1.5 of the report. There is heterogeneity in the types of studies that evaluated the effectiveness of TTF and as such, it would be inappropriate to

Name (#)	Public Comment	Response
	statistically significant improvement in both median PFS (6.7 months vs 4 months) and median OS (20.9 months vs 16.0 months) in the study arm vs control arm. Survival times in this trial were reported from randomization, not from diagnosis, so 3.8 months should be added in both groups for an estimation of the overall outcome. This is in contrast to median PFS from diagnosis reported in chemotherapy clinical trials of 6-7 months.) - PFS is extended at six months when Optune is used with temozolomide (56% vs 37%). (Stupp 2017) - Long-term survival is improved appreciably when Optune is added to the standard of care. The percentage of patients alive at two-years was 43% in the study arm vs 31% in the control group; at three years - 26% vs 16%; and at five years 13% vs 5%. (Stupp 2017) - The author concludes: "These findings are in contrast to the more than 23 randomized trials conducted over the last decade that have evaluated novel agents or intensified treatment strategies (e.g. dose-dense temozolomide, cilengitide, nimotuzumab, bevacizumab, and rindopepimut) for treatment of patients with newly diagnosed glioblastoma and have failed to demonstrate improved survival." (Stupp 2017) Recurrent GBM - In the RCT for recurrent GBM, OS and PFS were comparable to best standard care. However, a subsequent post-hoc analysis of the modified intention-to-treat population found that when used as intended (more than 18 hours/day) Optune patients experienced a median OS of 7.7 months vs 4.5 for control arm. - Published registry data for the recurrent GBM population confirm that OS is better than best standard care, showing a median OS of 9.6 months vs 6.6 months in the control arm. One- and two-year OS rates were nearly double for Optune (1-yr: 44% vs 20%; 2-yr: 30% vs 9%). The analysis also confirms the Kanner findings that use of the device for greater than 18 hours/day increases the benefit. Median OS in this sub-population was 13.5% vs 4% in the control arm. Indeed, despite some negative comments about the quality of the studies, the HTA does conclude, in several sections, that both newly diagnosed GBM and recurrent GBM patients have better OS and PFS. Certainly, improved OS and PFS are the most important endpoints in any cancer trial. In summary, Optune is a proven option for prolonging the lives of GBM patients, and a growing body of clinical evidence supports this conclusion.	evaluate the strength of evidence for all studies combined. We stratified our strength of evidence assessments by these sources of heterogeneity: (1) indication for treatment (e.g., newly diagnosed GBM, recurrent GBM), (2) specific treatment comparison (e.g., TTF with or without second line therapy), and (3) study design (i.e., randomized trial or observational study). Within those stratifications, there is limited evidence on which to draw conclusions about the effectiveness of TTF, resulting in very low to low certainty of effect for all outcomes. Among those stratifications, there was heterogeneity of effect (i.e. benefit and no benefit). In regard to your comment about adding 3.8 months to both groups for the overall survival outcome, please note that patients enrolled in the EF-14 trial were randomized a median 3.8 months after diagnosis (range 0 to 6 months). Therefore, we did not add 3.8 months to the overall survival.

Name (#)	Public Comment	Response
Kelly (2)	We strongly agree with the report's conclusion that safety of Optune has been established but disagree with the determination that the supporting clinical trial data is of low or very low quality. Optune therapy is very safe as evidenced by the results of the RCTs and subsequent follow-up literature. The HTA authors consider the safety data to be of low quality because there is no comparison with a control group. Yet the newly diagnosed GBM trial does compare the adverse events between the group receiving Optune and temozolomide (466 patients) and temozolomide alone (229 patients). (Stupp 2017) The recurrent GBM trial also reports on adverse events by Optune (116 patients) and active control (91 patients). Additionally, we note: - The overall incidence, distribution, and severity of adverse events were not statistically different in the two arms of the RCT for newly diagnosed GBM (48% vs 44%, respectively). The numerically higher incidence of some adverse events in the Optune with temozolomide arm was a reflection of the longer duration of temozolomide treatment in this group due to delayed occurrence of progression. (When duration of treatment was factored into the adverse event incidence, these differences disappeared.) The only exception was a higher incidence of localized mild to moderate skin irritation beneath the transducer arrays which occurred in more than half of the patients using Optune. (Stupp 2017) - The most common adverse event for patients in the recurrent GBM trial was localized mild to moderate skin toxicity at the site of the transducer arrays, which was adequately managed by using published skin care guidelines. There was significantly more gastrointestinal, hematologic, and infection adverse events seen in the standard of care chemotherapy arm than the Optune arm. (Stupp 2012) - Published registry data for recurrent GBM confirm no serious adverse events (Mrugala 2014) - Optune has been used commercially since 2011, in over 7000 patients, and has follow-up data for some patients as long as over 10 years. To date no deaths related to device or malfunctions associated with serious injury have been seen with Optune.	This HTA does not evaluate the quality of studies. The strength of evidence was evaluated separately by indication for treatment and study design. As such, there is one strength of evidence rating based on 1 RCT among patients with newly diagnosed GBM (i.e., EF-14 trial) and one strength of evidence rating based on 1 RCT among patients with recurrent GBM (i.e., EF-1 trial). Each strength of evidence rating was downgraded two steps due to some concerns for risk of bias related to the safety outcomes and unknown consistency due to a single-study body of evidence. Among patients with recurrent GBM, the strength of evidence rating was downgraded an additional step due to imprecision (i.e., there were only 207 patients evaluated in the EF-11 trial for safety). These downgrades resulted in a low strength of evidence for minimal harm of TTF among patients with newly diagnosed GBM and a very low strength of evidence for minimal harm of TTF among patients with recurrent GBM. Similar strength of evidence ratings are provided for the comparative observational studies. Though strength of evidence from observational studies can be upgraded in GRADE, it was not upgraded from very low certainty in the relevant studies of TTF because of high risk of bias, unknown or some inconsistency of results, and imprecision. Details about the strength of evidence assessment methodology are available in section 2.1.5 of the report.
Kelly (3)	For both newly diagnosed GBM and recurrent GBM, the HTA cites the following limitation related to the GBM clinical trials: patients were not blinded to their treatment—"Knowledge of treatment allocation has the potential to influence other decisions about care that may be related to the outcome and to influence the outcome assessment	While we recognize that a sham-controlled trial is not feasible, knowledge of treatment still introduces the potential for bias in patient-reported outcomes. We have clarified the concerns related to lack of blinding as it pertains to the different outcomes of interest in section 4.2.2 of the report.

Name (#)	Public Comment	Response
	itself. The report suggests that the results may have been influenced by a placebo effect on either side." A sham-controlled study may be relevant when a placebo effect can artificially inflate a trial response where there is subjective analysis. However, in the EF-14 trial the primary endpoint of progression free survival was measured by independent, blinded reviewers. (Stupp 2017) - As explained by the author, "although a placebo effect may affect subjective end points like quality of life or even progression-free survival by influencing the frequency of imaging and its interpretation, in the current trial a consistent benefit was observed in progression-free survival as assessed by blinded central radiology review, as well as in the gold standard of objective outcome, overall survival." (Stupp 2017) - Further, the author states, "The magnitude of the effect size… is beyond what could be attributed to a placebo effect." - To repeat, the primary endpoint was progression free survival measured by a central radiology review based on MRIs every second month. The radiologists were blinded as to the treatment arm. There is no evidence of a placebo having the ability to stop tumor growth and therefore no reason to believe that a placebo effect led to extended PFS for Optune treated patients. The blinded panel was able to make independent conclusions without contamination. A sham-controlled study was discussed with both the FDA and the clinical investigators. The FDA did not require a placebo as a condition for the trial to be accepted for consideration of approval. The investigators decided it was "practically unfeasible (heat and easy measure of current associated with Optune) and ethically unacceptable to expose patients to a sham device." (Stupp 2017) Moreover, as Hottinger et al have noted, "requiring a placebo or sham device would also mean a paradigm shift in conducting clinical trials with survival endpoints in oncology. Sham radiation therapy (RT) would be required for RT trials, and a placebo control would only be feasible for agents that have rare and mild toxicities." We also want to note that other chemotherapy trials without placebo controls have failed to show significant PFS and OS gains in glioblastoma. In contrast, the powerful magnitude of results shown in the Optune trial overpowers any placebo effect.	
Kelly (4)	"We also concluded with very low certainty from RCT evidence that the addition of TTF to usual care treatment	As described above with respect to the survival and safety outcomes, we stratified the strength of evidence assessment for the quality of life and

Name (#)	Public Comment	Response
	with TMZ improved quality of life and functional status among patients with newly diagnosed GBM." Quality of life (QoL) was evaluated in both RCTs of Optune. The data show that patients are highly motivated to undertake treatment with Optune, and do not experience lower QoL with the device. There were high compliance rates in both studies demonstrating that the device is well tolerated and easily adopted into daily activities. A detailed analysis of Health-Related Quality of Life (HRQoL) data from the newly diagnosed GBM trial has recently been reported and confirms there is no negative impact with the addition of Optune to standard of care treatment. Also, QoL data from the recurrent GBM trial demonstrates superiority to best standard of care. Specifically, we note: - HRQOL, a predefined secondary endpoint in the EF-14 trial for newly diagnosed GBM, was evaluated using the validated European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30) and brain module (QLQ-BN-20). Questionnaires were administered at baseline and every three months for up to 12 months. The nine preselected scales and items tailored to GBM and the effect of Optune on patients included: global health status; physical, cognitive, role, social, and emotional functioning; itchy skin; pain; and weakness of legs. Mean changes from baseline and changes over time were evaluated. Deterioration-free survival and time to deterioration were assessed for each of the nine scales and items. As is common with HRQOL evaluations, there was a drop-off in the number of evaluations available over time. However, sensitivity analysis with mix-model analysis used to account for missing data, confirms the findings. Taphoorn et al found no significant difference in HRQOL between the study and control groups over time except for itchy skin, reported more often for Optune patients due to the transducer arrays placed on the scalp. The authors hypothesized that Optune would result in worse role and social functioning (due to visibility of the device) and worse physical functioning but the data showed no difference between study arms. Also, cognitive functioning, pain, and weakness in legs were comparable between groups. The authors expected study group HRQOL to improve in some emotional and social scales resulting from active participation in fight against cancer and frequent interaction with caregivers/staff but this did not occur. Indeed, global health status and emotional functioning were not significantly different between the treatment arms. Most relevant for patients, HRQOL was maintained in 8 of 9 of the predetermined scales/items	functional status outcomes by multiple factors. There was only 1 RCT (i.e., EF-14) that evaluated these outcomes among patients newly diagnosed with GBM and only 1 RCT (i.e., EF-11) that evaluated these outcomes among patients with recurrent GBM. For both treatment indications (i.e., new or recurrent GBM diagnosis), the strength of evidence was downgraded for high risk of bias, unknown consistency, and lack of precision primarily due to small sample sizes. Based on the strength of evidence assessments, we could only conclude with very low certainty that there is a benefit with TTF treatment as it relates to quality of life and functional status for patients with both new and recurrent GBM diagnoses.

Name (#)	Public Comment	Response
	over time. The authors conclude that the addition of Optune to the treatment regimen for newly diagnosed GBM does not negatively affect or improve the well-being of patients. (Taphoorn 2018) - By predesign, the newly diagnosed GBM trial also looked at the association of Optune use with patient's activities of daily living and cognition as a measure of tolerability. Time to a sustained 6-point decline in the Mini-Mental State Examination was significantly longer in the Optune plus temozolomide arm than the temozolomide arm alone (16.7 months vs 14.2 months, respectively). Time to sustained 10-point decrease in Karnofsky performance score was also significantly longer in the study arm over the control arm (5.5 months vs 3.9 months, respectively). (Stupp 2017) - The majority of patients in the newly diagnosed GBM trial were able to use the device independently or with some help from a care giver. The fact that 75% of patients were able to use the device for ≥18hr./day is a great indicator of tolerability. (Stupp 2017) Of note: The second generation Optune system, introduced after the trial, uses new digital signal generation technology that reduces the size and weight of the device by about half (1.2 kg vs. 2.7 kg). Patients report greater ease of use and improved compliance. - In the ITT population of the recurrent trial, QOL, based on QLQ C-30 and BN-20 questionnaires, was consistently better in the Optune group than the control group. There was improvement over the control group in 5 out of 6 general scales, including cognitive and emotional functioning, and 7 of 9 symptom scales, including nausea, vomiting, diarrhea, constipation and pain. (Stupp 2012) - Median compliance in the recurrent GBM trial was 86% (range 41-98%) in each treatment month, translating into a mean use of 20.6 hours per day. As the author comments, "despite the inconvenience of carrying and using the device, compliance was high and patients reported improvement in QOL, in the absence of chemotherapy related toxicities." (Stupp 2012)	
Kelly (5)	Optune "likely not cost-effective for newly diagnosed GBM (low certainty)." The HTA does not reflect the current state of the literature related to health economic evaluations of TTFields for glioblastoma. The HTA only reports the results of a single health economic model and fails to identify or analyze two fundamentally flawed assumptions in this publication. Finally, the HTA fails to report that the governments of Japan and Sweden have both completed comprehensive	We are not able to access an English copy of the HTA conducted by the government of Japan. There are some documents at Japan's Ministry of Health, Labour, and Welfare website, but they are not in English and we cannot independently verify that an HTA was conducted or that a reimbursement decision that covers TTF was made. We have not been able to independently confirm that the Swedish government covers TTF treatment. We

Name (#)	Public Comment	Response
	health economic assessments of TTFields and subsequently approved the therapy for reimbursement. As background, the concept of "cost-effectiveness" in health is most commonly measured by calculating the costs of a treatment for a defined time period and then dividing those costs by the observed efficacy benefit. The challenge for health economists is that clinical trials report on outcomes within a limited time period. Healthcare payers have to measure costs and efficacy in periods that are much longer than those reported in a trial. Government payers typically want to analyze treatments in terms of lifetime costs and benefits. Health economists therefore have to forecast or extrapolate data, and it is critical that modeling assumptions and decisions are accurately reported in publications. The EF-14 trial reported that the 5-year survival rate for the TTFields and TMZ arm was 13%, and 5% for the TMZ alone arm. Health economic analysis of the EF-14 trial must therefore determine how to model future survival for the patients still alive five years after starting treatment.	have retrieved and reviewed the Swedish HTA cited in the public comment. In this HTA an independent CEA was not conducted; rather, Swedish experts provided critique of a CEA conducted and provided by the manufacturer to the Swedish government. The manufacturer's CEA is not cited in the Swedish HTA and does not appear to be publicly accessible. It is also not clear whether the survival model used in the CEA conducted by the manufacturer is the same study cited by the manufacturer comments (Guzauskas et al.) as using a more appropriate survival model compared to the independently-conducted CEA cited in the State of Washington HTA. Assuming the CEA performed for the Swedish HTA used the Guzauskas et al. model, the incremental cost-effectiveness ratio (ICER) that was estimated in the base-case scenario was 1,782,299 Swedish Kroner (approximately $198,033 USD at the time of analysis) per QALY gained. Although this estimate is significantly less than the estimate provided by the independent CEA we cited in our HTA, it is still above a threshold that most would not consider cost-effective; thus, our overall conclusion about cost-effectiveness is not altered. We concur with the manufacturer that the choice of survival model used appears to have profound impact on any CEA; this fact is appropriately considered in our GRADE rating for the CEA outcome of "very low" certainty. Further, no CEA has been conducted in US populations, using US costs. With respect to the proposed flaws in the included Bernard-Arnoux cost effectiveness analysis, we consulted with a resident health economist for another opinion on the methodological quality of the study, who after consideration and review of the Bernaud-Arnoux et al. and Guzauskas et al. studies found our conclusion to be unchanged. In fact, using an incremental life-year gain of 1.2 years for TTF versus TMZ (as suggested by the Guzauskas study) which is about 4 times greater than that suggested by Bernard-Arnoux, the incremental cost effectiveness ratio (ICER) remains outside of the 100,000 euro willingness to pay threshold used in the Bernaud-Arnoux analysis.
Kelly (6)	Research that should be included in the report Researchers at the University of Washington and Tufts University worked with Novocure to address this issue of forecasting GBM survival. The research has been	Thank you for giving us the opportunity to review the 2018 Guzaukas study. The article was dually reviewed and excluded for wrong outcome. Modelling studies are not eligible for inclusion in this HTA, unless they are cost-effectiveness analyses

Name (#)	Public Comment	Response
	published and is attached to our response. This survival model reflected the growing body of research related to the need for advanced techniques to model cancer survival. As reported by Guzauskas et al, the estimated incremental mean lifetime survival benefit of adding TTFields to TMZ was 1.8 years without discounting. The incremental survival benefit was still substantial at 1.2 years after applying a 3% discount rate to deflate the value of the future survival benefits back to present time. The HTA does not include a reference to the Guzauskas et al publication. We ask that it be considered in any final review of health economic literature. We believe that the Guzauskas et al paper is particularly important for consideration given the two fundamental flaws contained in the economic analysis that is reported in the HTA.	that are eligible for the CQ. This article did not include any outcomes related to cost or cost-effectiveness.
Kelly (7)	Limitations of the one HEOR study reported in the HTA The Bernard-Arnoux et al. study modelled lifetime survival from the EF-14 trial using the declining exponential approximation of life expectancy (DEALE) method. Per the standards established by the International Society for Pharmacoeconomics & Outcomes Research (ISPOR), the publication should have provided a detailed explanation for why this method was selected and how it was validated. The publication does not provide any of these details, nor does it provide a visual representation of the forecasted survival curves projected by its model for a face validity assessment. The Bernard-Arnoux et al study's lack of explanation and validation for its survival model structure is particularly troubling because the DEALE method has been proven to be unreliable in projecting cancer survival. The fundamental issue is that exponential extrapolation assumes a constant hazard of death (i.e., the risk of dying is constant and all previous time points can be used to extrapolate future survival). However, that assumption is not clinically valid for glioblastoma. Glioblastoma is characterized by an initial period of high mortality, followed by increasing probabilities of surviving as time passes from diagnosis. The Guzauskas et al paper provides a detailed explanation of these points. Specifically, the Guzauskas et al study compares the outcomes of the DEALE method survival model to actual real-world reported survival trends for GBM patients alive more than five years after diagnosis. The DEALE method is shown to underestimate survival	Please see the response to comment #5 above. In addition, after consultation with a health economist, the methods employed by Bernard-Arnoux and colleagues are considered methodologically sound and adhere to best practices. The authors justified their use of the DEALE approach to estimate life-years gained. With respect to possible over estimation of hospitalization costs, those costs would have been overestimated for both arms of the model, essentially canceling each other out when calculating the incremental costs. It was noted that the Bernard-Arnoux CEA was very conservative in the bounds employed for the sensitivity analysis (only estimating +/-2 weeks on median survival) but widening these sensitivity analysis bounds would not have changed the overall conclusion that TTF is not cost effective.

Name (#)	Public Comment	Response
	substantially compared to real world data and fails to match the actual 5-year survival reported from EF-14. Additionally, the Bernard-Arnoux study fails to discuss how it estimates healthcare utilization in the different disease states. GBM patients tend to require intensive care at the time of diagnosis or shortly following a progression of the tumor. As time passes from diagnosis or progression, patients tend to stabilize. The most obvious example is surgery: patients typically get surgery at diagnosis. They are less likely to get another surgery if the disease remains stable. The Bernard-Arnoux paper does not describe how their study adjusted for or analyzed the impact of declining healthcare utilization based on the length of time a patient is alive. While not described in the paper, the authors appear to have taken a simplified approach and applied a constant rate of healthcare utilization regardless of how long patients exist in a given health state. So a patient alive and progression free 12 months after diagnosis will be assumed to require the same amount of surgery as someone recently diagnosed. That assumption introduced a significant bias in the model that resulted in costs being presented at likely the maximum levels. The overall result is that the Bernard-Arnoux study underestimates survival compared to demonstrated real world epidemiological results and likely over-states costs. The Bernard-Arnoux et al study estimated mean incremental lifetime survival of only 0.3 years (discounted) compared to the 1.2 years (discounted) estimated by Guzauskas et al. The substantial difference between the estimated survival benefits of 1.2 years (Guzauskas) and 0.3 years (Bernard-Arnoux) is evidence that the choice of survival model has profound impact on health economic estimates, and the lack of validation of the model presented by the Bernard-Arnoux et al study should be viewed as disqualifying in the context of an HTA.	
Kelly (8)	Global health economic reviews As noted above, the Washington State HTA also fails to note that TTFields was subject to formal health technology assessments in Sweden and Japan. In both locations the review was conducted by a qualified national healthcare agency. Both healthcare agencies reviewed economic models based on the survival model presented in Guzauskas et al. Both nations ultimately approved Optune for reimbursement after considering his health economic data. We believe that Washington State should feel confident that qualified payers in the United States and around the	We are not able to access an English copy of the HTA conducted by the government of Japan. There are some documents at Japan's Ministry of Health, Labour, and Welfare website, but they are not in English and we cannot independently verify that an HTA was conducted or that a reimbursement decision that covers TTF was made. We have not been able to independently confirm that the Swedish government covers TTF treatment. We have retrieved and dually reviewed the Swedish HTA cited in the manufacturer's comments. As an HTA, it is ineligible for inclusion in this HTA but is

Name (#)	Public Comment	Response
	world have already conducted thorough clinical and economic evaluations of TTFields. We ask that you consider the new literature regarding TTFields, foreign reimbursement approvals based on economic analysis, and what we view as disqualifying limitations of the one health economic study in the current HTA.	briefly described in section 4.3 (Other Related HTAs) of the report.
Taylor (1)	Request for Consideration of Coverage As I am sure you are aware, glioblastoma multiforme is an orphan disease with extremely limited treatment options. Optune is the first FDA-approved therapy in more than a decade to demonstrate statistically significant extension of survival in newly diagnosed glioblastoma patients. The published 5-year survival builds upon the available literature supporting both the safety and efficacy of Optune in appropriate patients. I strongly urge you to consider this information and issue a positive coverage policy for this Medicaid and PEBB patients with glioblastoma multiforme brain tumors.	We have shared your comment with the State of Washington; the independent Health Technology Clinical Committee is tasked with determining coverage for tumor treating fields.

Abbreviations: CEA = cost effectiveness analysis; CQ = cost question; DEALE = declining exponential approximation of life expectancy; EORTC = European Organization for Research and Treatment of Cancer; FDA = United States Food and Drug Administration; GBM = glioblastoma multiforme; HEOR = Health Economics Outcomes Research; HRQOL = Health-Related Quality of Life; HTA = health technology assessment; ICER = incremental cost effectiveness ratio; ITT = intent to treat; ISPOR = International Society for Pharmacoeconomics & Outcomes Research; OS = overall survival; PEBB = Public Employees Benefits Board; PFS = progression free survival; QLQ = Quality of Life Questionnaire; QOL = quality of life; RCT = randomized controlled trial; RT = radiation therapy; TMZ = temozolomide; TTF = tumor treating fields; US = United States; USD = United States Dollars.

195 Commerce Way
Portsmouth, NH 03801

603.436.2809
novocure.com

October 1, 2018

By Electronic Submission to shtap@hca.wa.gov

Health Technology Assessment Program (HTA)
Washington State Health Care Authority
PO Box 42712
Olympia, WA 98504-2712

RE: Novocure Comments to Tumor Treating Fields (Optune®) Draft Evidence Report

To whom it may concern:

Novocure appreciates the opportunity to submit comments regarding the draft evidence report related to the clinical data supporting the efficacy and safety of Optune in both newly diagnosed as well as recurrent glioblastoma (GBM). As background, our estimate is that GBM will affect approximately **sixty-three** Washington State residents covered under this HTA each year.

In addition to the comments submitted below for consideration, Novocure respectfully requests that the HTAA public meeting scheduled for November 16, 2018 be rescheduled due to the fact that it conflicts with the Society for Neuro-Oncology annual meeting. Novocure expects that most brain-tumor experts in Washington State will be in Louisiana for this annual conference and would be unable to participate in the public meeting.

Before commenting on specific aspects of the RTI International Draft Evidence Report (HTA), we would like to start by highlighting three simple and essential facts about Optune:

1. Optune was FDA approved through the premarket approval process based on the largest successful randomized, controlled clinical trial ever conducted in newly diagnosed GBM.

2. The results of this 695 patient trial are published in the *Journal of the American Medical Association*.

3. The National Comprehensive Cancer Network (NCCN) has issued a category 1 recommendation for the use of Optune in newly diagnosed GBM in combination with temozolomide and a category 2B recommendation for recurrent GBM as monotherapy.

In 2016, the U.S. Federal Government launched a “moon shot” to cure cancer, with an emphasis on innovation to speed therapeutics and breakthroughs to patients. Optune is just such an innovative treatment and one that is FDA-approved to treat a disease with otherwise dire consequences. It is proven to extend life in newly diagnosed GBM and to be as effective as chemotherapy in recurrent GBM with decreased toxic side effects. Optune has wide acceptance among neuro-oncology and radiation oncology clinicians; over 1000 providers have been trained to administer it. Further, Optune is included in the standard of care treatment guidelines of the National Comprehensive Cancer Network (NCCN), which granted it a category 1 recommendation for newly diagnosed GBM and a category 2B recommendation for recurrent GBM. Almost every commercial insurance company in the United States now cover Optune through published coverage policy including Aetna, Humana, CIGNA, Anthem Blue

195 Commerce Way
Portsmouth, NH 03801

603.436.2809
novocure.com

Cross and Blue Shield (BCBS), Premera Blue Cross, Regence Blue Cross Blue Shield, Kaiser Permanente and many others. Moreover, Medicare is approving treatment on a case-by-case basis on appeal and is currently reviewing our request to reconsider their local coverage decision. Finally, multiple state Medicaid programs have reviewed the clinical evidence supporting the use of Optune in GBM and have determined that Optune is a covered benefit under their programs.

We believe that the current body of evidence supports the use of Optune in treating GBM, a devastating disease, which had not seen any breakthrough treatments in more than a decade prior to the FDA approval of Optune. In light of the published clinical trial data and considerable support from clinicians and insurers, we recommend that RTI International reevaluate its position on Optune. It is imperative that patients have access to this technology with proven benefits, just like any other resident of Washington State who has commercial or other government insurance.

Detailed Comments

We would like to comment on the following aspects of the HTA:

RTI International Statement 1: The report reads "We conclude with very low to low certainty that the addition of TTF to usual care with TMZ increases overall and progression-free survival among patients with newly diagnosed GBM. For patients with recurrent GBM, there may or may not be survival benefits associated with TTF treatment with or without second-line therapy (very low certainty)."

Novocure Comment 1a: It is our position that efficacy has been established for Optune. Outcome measures, including progression free survival (PFS) and overall survival (OS), demonstrate that adding Optune to standard of care temozolomide in newly diagnosed GBM produces superior clinical results to temozolomide alone. This position is supported by data from randomized controlled trials (RCTs) with appropriate sample sizes. The trials were designed with feedback from the U.S. Food and Drug Administration (FDA) and subsequently the FDA approved Optune, first for recurrent GBM and later for newly diagnosed GBM, on the basis of these trials.

Newly Diagnosed GBM

- Use of Optune with maintenance temozolomide improves both PFS and OS over maintenance temozolomide alone. The published final analysis of the EF-14 pivotal trial (695 patients, n=466 study arm, n=229 control arm) in newly diagnosed GBM shows a statistically significant improvement in both median PFS (6.7 months vs 4 months) and median OS (20.9 months vs 16.0 months) in the study arm vs control arm. Survival times in this trial were reported from randomization, not from diagnosis, so 3.8 months should be added in both groups for an estimation of the overall outcome. This is in contrast to median PFS from diagnosis reported in chemotherapy clinical trials of 6-7 months.)[1]

- PFS is extended at six months when Optune is used with temozolomide (56% vs 37%). (Stupp 2017)

[1] Stupp R, Taillibert S , Kanner A, et al. Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma A Randomized Clinical Trial. JAMA. 2017;318(23):2306-2316. doi:10.1001/jama.2017.18718

195 Commerce Way
Portsmouth, NH 03801

603.436.2809
novocure.com

- Long-term survival is improved appreciably when Optune is added to the standard of care. The percentage of patients alive at two-years was 43% in the study arm vs 31% in the control group; at three years - 26% vs 16%; and at five years 13% vs 5%. (Stupp 2017)

- The author concludes: "These findings are in contrast to the more than 23 randomized trials conducted over the last decade that have evaluated novel agents or intensified treatment strategies (e.g. dose-dense temozolomide, cilengitide, nimotuzumab, bevacizumab, and rindopepimut) for treatment of patients with newly diagnosed glioblastoma and have failed to demonstrate improved survival." (Stupp 2017)

Recurrent GBM

- In the RCT for recurrent GBM, OS and PFS were comparable to best standard care. However, a subsequent post-hoc analysis of the modified intention-to-treat population found that when used as intended (more than 18 hours/day) Optune patients experienced a median OS of 7.7 months vs 4.5 for control arm. [2]

- Published registry data for the recurrent GBM population confirm that OS is better than best standard care, showing a median OS of 9.6 months vs 6.6 months in the control arm. One- and two-year OS rates were nearly double for Optune (1-yr: 44% vs 20%; 2-yr: 30% vs 9%). The analysis also confirms the Kanner findings that use of the device for greater than18 hours/day increases the benefit. Median OS in this sub-population was 13.5% vs 4% in the control arm. [3]

Indeed, despite some negative comments about the quality of the studies, the HTA does conclude, in several sections, that both newly diagnosed GBM and recurrent GBM patients have better OS and PFS. Certainly, improved OS and PFS are the most important endpoints in any cancer trial. In summary, Optune is a proven option for prolonging the lives of GBM patients, and a growing body of clinical evidence supports this conclusion.

Novocure Comment 1b: We strongly agree with the report's conclusion that safety of Optune has been established, but disagree with the determination that the supporting clinical trial data is of low or very low quality. Optune therapy is very safe as evidenced by the results of the RCTs and subsequent follow-up literature.

The HTA authors consider the safety data to be of low quality because there is no comparison with a control group. Yet the newly diagnosed GBM trial does compare the adverse events between the group receiving Optune and temozolomide (466 patients) and temozolomide alone (229 patients). (Stupp 2017) The recurrent GBM trial also reports on adverse events by Optune (116 patients) and

[2] Kanner AA, Wong ET, Villano JL, Ram Z; on behalf of EF-11 Investigators. Post hoc analysis of intention-to-treat population in phase 3 comparison of NovoTTF-100A™ System versus best physician's choice chemotherapy. Semin Oncol. 2014;41(5)(suppl 6):S25-S34.

[3] Mrugala MM, Engelhard HH, Dinh Tran D, et al. Clinical practice experience with NovoTTF-100A™ System for glioblastoma: the Patient Registry Dataset (PRiDe). Semin Oncol. 2014;41(5)(suppl 6):S4-S13.

195 Commerce Way
Portsmouth, NH 03801

603.436.2809
novocure.com

active control (91 patients).[4] Additionally, we note:

- The overall incidence, distribution, and severity of adverse events were not statistically different in the two arms of the RCT for newly diagnosed GBM (48% vs 44%, respectively). The numerically higher incidence of some adverse events in the Optune with temozolomide arm was a reflection of the longer duration of temozolomide treatment in this group due to delayed occurrence of progression. (When duration of treatment was factored into the adverse event incidence, these differences disappeared.) The only exception was a higher incidence of localized mild to moderate skin irritation beneath the transducer arrays which occurred in more than half of the patients using Optune. (Stupp 2017)

- The most common adverse event for patients in the recurrent GBM trial was localized mild to moderate skin toxicity at the site of the transducer arrays, which was adequately managed by using published skin care guidelines. There was significantly more gastrointestinal, hematologic, and infection adverse events seen in the standard of care chemotherapy arm than the Optune arm. (Stupp 2012)

- Published registry data for recurrent GBM confirm no serious adverse events (Mrugala 2014)

- Optune has been used commercially since 2011, in over 7000 patients, and has follow-up data for some patients as long as over 10 years. To date no deaths related to device or malfunctions associated with serious injury have been seen with Optune.[5]

RTI International Statement 2: For both newly diagnosed GBM and recurrent GBM, the HTA cites the following limitation related to the GBM clinical trials: patients were not blinded to their treatment—"Knowledge of treatment allocation has the potential to influence other decisions about care that may be related to the outcome and to influence the outcome assessment itself. The report suggests that the results may have been influenced by a placebo effect on either side."

Novocure Comment 2: A sham-controlled study may be relevant when a placebo effect can artificially inflate a trial response where there is subjective analysis. However, in the EF-14 trial the primary endpoint of progression free survival was measured by independent, blinded reviewers. (Stupp 2017)

- As explained by the author, "although a placebo effect may affect subjective end points like quality of life or even progression-free survival by influencing the frequency of imaging and its interpretation, in the current trial a consistent benefit was observed in progression-free survival as assessed by blinded central radiology review, as well as in the gold standard of objective outcome, overall survival." (Stupp 2017)

[4] Stupp R, Wong ET, Kanner AK, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomised phase III trial of a novel treatment modality. *Eur J Cancer*. 2012;48;14:2192-2202.

[5] U.S. Food and Drug Administration (2018, October 1). MAUDE – Manufacturer and User Facility Device Experience. Retrieved from https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM

195 Commerce Way
Portsmouth, NH 03801

603.436.2809
novocure.com

- Further, the author states, "The magnitude of the effect size… is beyond what could be attributed to a placebo effect." [6]

- To repeat, the primary endpoint was progression free survival measured by a central radiology review based on MRIs every second month. The radiologists were blinded as to the treatment arm. There is no evidence of a placebo having the ability to stop tumor growth and therefore no reason to believe that a placebo effect led to extended PFS for Optune treated patients. The blinded panel was able to make independent conclusions without contamination.

A sham-controlled study was discussed with both the FDA and the clinical investigators. The FDA did not require a placebo as a condition for the trial to be accepted for consideration of approval. The investigators decided it was "practically unfeasible (heat and easy measure of current associated with Optune) and ethically unacceptable to expose patients to a sham device." (Stupp 2017) Moreover, as Hottinger et al have noted, "requiring a placebo or sham device would also mean a paradigm shift in conducting clinical trials with survival endpoints in oncology. Sham radiation therapy (RT) would be required for RT trials, and a placebo control would only be feasible for agents that have rare and mild toxicities."[7] We also want to note that other chemotherapy trials without placebo controls have failed to show significant PFS and OS gains in glioblastoma.[8] In contrast, the powerful magnitude of results shown in the Optune trial overpowers any placebo effect.

RCI International Statement 3: "We also concluded with very low certainty from RCT evidence that the addition of TTF to usual care treatment with TMZ improved quality of life and functional status among patients with newly diagnosed GBM."

Novocure Comment 3: Quality of life (QoL) was evaluated in both RCTs of Optune. The data show that patients are highly motivated to undertake treatment with Optune, and do not experience lower QoL with the device. There were high compliance rates in both studies demonstrating that the device is well tolerated and easily adopted into daily activities. A detailed analysis of Health-Related Quality of Life (HRQoL) data from the newly diagnosed GBM trial has recently been reported and confirms there is no negative impact with the addition of Optune to standard of care treatment. Also, QoL data from the recurrent GBM trial demonstrates superiority to best standard of care. Specifically, we note:

- HRQOL, a predefined secondary endpoint in the EF-14 trial for newly diagnosed GBM, was evaluated using the validated European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30) and brain module (QLQ-BN-20). Questionnaires were administered at baseline and every three months for up to 12 months. The nine preselected scales and items tailored to GBM and the effect of Optune on patients

[6] Stupp R, Wong ET, Kanner AK, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomised phase III trial of a novel treatment modality. *Eur J Cancer*. 2012;48;14:2192-2202.

[7] Hottinger AF, Pacheco P, Stupp R. Tumor treating fields: a novel treatment modality and its use in brain tumors. Neuro Oncol. 2016 Oct;18(10):1338-49.

[8] Stupp R, Taillibert S, Kanner AA, et al. Maintenance therapy with tumor-treating fields plus temozolomide vs temozolomide alone for glioblastoma: a randomized clinical trial. *JAMA. 2015;314(23):2535-2543.*

195 Commerce Way
Portsmouth, NH 03801

603.436.2809
novocure.com

included: global health status; physical, cognitive, role, social, and emotional functioning; itchy skin; pain; and weakness of legs. Mean changes from baseline and changes over time were evaluated. Deterioration-free survival and time to deterioration were assessed for each of the nine scales and items. As is common with HRQOL evaluations, there was a drop-off in the number of evaluations available over time. However, sensitivity analysis with mix-model analysis used to account for missing data, confirms the findings.

Taphoorn et al found no significant difference in HRQOL between the study and control groups over time except for itchy skin, reported more often for Optune patients due to the transducer arrays placed on the scalp. The authors hypothesized that Optune would result in worse role and social functioning (due to visibility of the device) and worse physical functioning but the data showed no difference between study arms. Also, cognitive functioning, pain, and weakness in legs were comparable between groups. The authors expected study group HRQOL to improve in some emotional and social scales resulting from active participation in fight against cancer and frequent interaction with caregivers/staff but this did not occur. Indeed, global health status and emotional functioning were not significantly different between the treatment arms. Most relevant for patients, HRQOL was maintained in 8 of 9 of the predetermined scales/items over time. [9]

The authors conclude that the addition of Optune to the treatment regimen for newly diagnosed GBM does not negatively affect or improve the well-being of patients. (Taphoorn 2018)

- By predesign, the newly diagnosed GBM trial also looked at the association of Optune use with patient's activities of daily living and cognition as a measure of tolerability. Time to a sustained 6-point decline in the Mini-Mental State Examination was significantly longer in the Optune plus temozolomide arm than the temozolomide arm alone (16.7 months vs 14.2 months, respectively). Time to sustained 10-point decrease in Karnofsky performance score was also significantly longer in the study arm over the control arm (5.5 months vs 3.9 months, respectively). (Stupp 2017)

- The majority of patients in the newly diagnosed GBM trial were able to use the device independently or with some help from a care giver. The fact that 75% of patients were able to use the device for ≥18hr./day is a great indicator of tolerability. (Stupp 2017) Of note: The second generation Optune system, introduced after the trial, uses new digital signal generation technology that reduces the size and weight of the device by about half (1.2 kg vs. 2.7 kg). Patients report greater ease of use and improved compliance. [10]

- In the ITT population of the recurrent trial, QOL, based on QLQ C-30 and BN-20

[9] Taphoorn MJB, Dirven L, Kanner AA, Lavy-Shahaf G, Weinberg U, Taillibert S, Toms SA, Honnorat J, Chen TC, Sroubek J, David C, Idbaih A, Easaw JC, Kim CY, Bruna J, Hottinger AF, Kew Y, Roth P, Desai R, Villano JL, Kirson ED, Ram Z, Stupp R. Influence of Treatment With Tumor-Treating Fields on Health-Related Quality of Life of Patients With Newly Diagnosed Glioblastoma: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Oncol. 2018 Apr 1;4(4):495-504. doi: 10.1001/jamaoncol.2017.5082.*

[10] Kinzel, A., Ambrogi, M., Varshaver, M., Benson, L., & Kirson, E. (2017). P09.23 Tumor Treating Fields delivery using second generation Optune® system for glioblastoma treatment: patient experience and compliance. *Neuro-Oncology*, *19*(Suppl 3), iii74–iii75. http://doi.org/10.1093/neuonc/nox036.279

195 Commerce Way
Portsmouth, NH 03801

603.436.2809
novocure.com

questionnaires, was consistently better in the Optune group than the control group. There was improvement over the control group in 5 out of 6 general scales, including cognitive and emotional functioning, and 7 of 9 symptom scales, including nausea, vomiting, diarrhea, constipation and pain. (Stupp 2012)

- Median compliance in the recurrent GBM trial was 86% (range 41-98%) in each treatment month, translating into a mean use of 20.6 hours per day. As the author comments, "despite the inconvenience of carrying and using the device, compliance was high and patients reported improvement in QOL, in the absence of chemotherapy related toxicities." (Stupp 2012)

RCI International Statement 4: Optune "likely not cost-effective for newly diagnosed GBM (low certainty)."

Novocure Comment 4: The HTA does not reflect the current state of the literature related to health economic evaluations of TTFields for glioblastoma. The HTA only reports the results of a single health economic model, and fails to identify or analyze two fundamentally flawed assumptions in this publication. Finally, the HTA fails to report that the governments of Japan and Sweden have both completed comprehensive health economic assessments of TTFields and subsequently approved the therapy for reimbursement.[11,12]

As background, the concept of "cost-effectiveness" in health is most commonly measured by calculating the costs of a treatment for a defined time period and then dividing those costs by the observed efficacy benefit. The challenge for health economists is that clinical trials report on outcomes within a limited time period. Healthcare payers have to measure costs and efficacy in periods that are much longer than those reported in a trial. Government payers typically want to analyze treatments in terms of lifetime costs and benefits.[13] Health economists therefore have to forecast or extrapolate data, and it is critical that modeling assumptions and decisions are accurately reported in publications.[14]

The EF-14 trial reported that the 5-year survival rate for the TTFields and TMZ arm was 13%, and 5% for the TMZ alone arm. Health economic analysis of the EF-14 trial must therefore determine how to model future survival for the patients still alive five years after starting treatment.

Research that should be included in the report

[11] Swedish Association of Local Authorities and Regions. 2017. Available at: http://www.janusinfo.se/Documents/Nationellt_inforande_av_nya_lakemedel/Motesprotokoll/Protokoll-NT-radet-180207.pdf Accessed 5/21/2018.

[12] Japan Ministry of Health Labour and Welfare. MHLW Official Gazette. 2017;154(258).

[13] Briggs AH, Weinstein MC, Fenwick EA, et al. Model parameter estimation and uncertainty: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--6. Value Health. 2012;15: 835-842.

[14] Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value Health. 2013;16: 231-250.

195 Commerce Way
Portsmouth, NH 03801

603.436.2809
novocure.com

Researchers at the University of Washington and Tufts University worked with Novocure to address this issue of forecasting GBM survival. The research has been published and is attached to our response.[15] This survival model reflected the growing body of research related to the need for advanced techniques to model cancer survival.[16]

As reported by Guzauskas et al, the estimated incremental mean lifetime survival benefit of adding TTFields to TMZ was 1.8 years without discounting. The incremental survival benefit was still substantial at 1.2 years after applying a 3% discount rate to deflate the value of the future survival benefits back to present time.

The HTA does not include a reference to the Guzauskas et al publication. We ask that it be considered in any final review of health economic literature. We believe that the Guzauskas et al paper is particularly important for consideration given the two fundamental flaws contained in the economic analysis that is reported in the HTA.

Limitations of the one HEOR study reported in the HTA

The Bernard-Arnoux et al. study modelled lifetime survival from the EF-14 trial using the declining exponential approximation of life expectancy (DEALE) method.[17] Per the standards established by the International Society for Pharmacoeconomics & Outcomes Research (ISPOR), the publication should have provided a detailed explanation for why this method was selected and how it was validated. The publication does not provide any of these details, nor does it provide a visual representation of the forecasted survival curves projected by its model for a face validity assessment.[18]

The Bernard-Arnoux et al study's lack of explanation and validation for its survival model structure is particularly troubling because the DEALE method has been proven to be unreliable in projecting cancer survival.[19,20] The fundamental issue is that exponential extrapolation assumes a constant hazard of death (i.e., the risk of dying is constant and all previous time points can be used to extrapolate future survival). However, that assumption is not clinically valid for glioblastoma. Glioblastoma is characterized by an initial period of high mortality, followed by increasing probabilities of surviving as time passes

[15] Guzauskas GF, Salzberg M, Wang BCM. Estimated lifetime survival benefit of tumor treating fields and temozolomide for newly diagnosed glioblastoma patients. CNS Oncology. 2018; Aug 20.

[16] Huang M, Latimer, N, Zhang, Y et al. Estimating the Long-Term Outcomes Associated With Immuno-Oncology Therapies: Challenges and Approaches for Overall Survival Extrapolations. Value & Outcomes Spotlight. 2018; January/February (28-30).

[17] Bernard-Arnoux F, Lamure M, Ducray F, Aulagner G, Honnorat J, Armoiry X. The cost–effectiveness of tumor-treating fields therapy in patients with newly diagnosed glioblastoma. Neuro. Oncol. 18(8), 1129–1136 (2016).

[18] Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value Health. 2013;16: 231-250.

[19] Holland RR, Ellis CA, Geller BM, Plante DA, Secker-Walker RH. Life expectancy estimation with breast cancer: bias of the declining exponential function and an alternative to its use. Med. Decis. Making 19(4), 385–393 (1999).

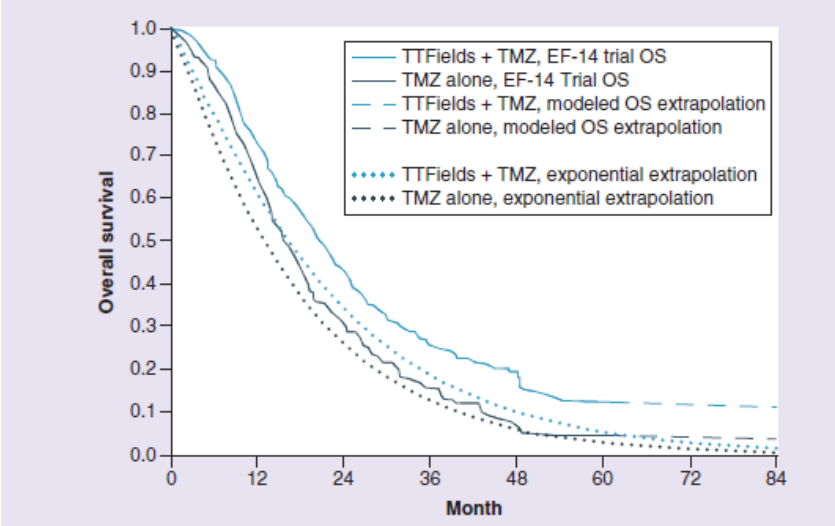
[20] Benbassat J, Zajicek G, Van Oortmarssen GJ, Ben-Dov I, Eckman MH. Inaccuracies in estimates of life expectancies of patients with bronchial cancer in clinical decision making. Med. Decis. Making 13(3), 237–244 (1993).

195 Commerce Way
Portsmouth, NH 03801

603.436.2809
novocure.com

from diagnosis.[21,22]

The Guzauskas et al paper provides a detailed explanation of these points. Specifically, the Guzauskas et al study compares the outcomes of the DEALE method survival model to actual real-world reported survival trends for GBM patients alive more than five years after diagnosis. The DEALE method is shown to underestimate survival substantially compared to real world data, and fails to match the actual 5-year survival reported from EF-14:



Additionally, the Bernard-Arnoux study fails to discuss how it estimates healthcare utilization in the different disease states. GBM patients tend to require intensive care at the time of diagnosis or shortly following a progression of the tumor. As time passes from diagnosis or progression, patients tend to stabilize. The most obvious example is surgery: patients typically get surgery at diagnosis. They are less likely to get another surgery if the disease remains stable. The Bernard-Arnoux paper does not describe how their study adjusted for or analyzed the impact of declining healthcare utilization based on the length of time a patient is alive. While not described in the paper, the authors appear to have taken a simplified approach and applied a constant rate of healthcare utilization regardless of how long patients exist in a given health state. So a patient alive and progression free 12 months after diagnosis will be assumed to require the same amount of surgery as someone recently diagnosed. That assumption introduced a significant bias in the model that resulted in costs being presented at likely the maximum levels.

The overall result is that the Bernard-Arnoux study underestimates survival compared to demonstrated real world epidemiological results and likely over-states costs. The Bernard-Arnoux et al study

[21] Polley MY, Lamborn KR, Chang SM, Butowski N, Clarke JL, Prados M. Conditional probability of survival in patients with newly diagnosed glioblastoma. J. Clin. Oncol. 29(31), 4175–4180 (2011).

[22] Porter KR, McCarthy BJ, Berbaum ML, Davis FG. Conditional survival of all primary brain tumor patients by age, behavior and histology. Neuroepidemiology 36(4), 230–239 (2011).

195 Commerce Way
Portsmouth, NH 03801

603.436.2809
novocure.com

estimated mean incremental lifetime survival of only 0.3 years (discounted) compared to the 1.2 years (discounted) estimated by Guzauskas et al. The substantial difference between the estimated survival benefits of 1.2 years (Guzauskas) and 0.3 years (Bernard-Arnoux) is evidence that the choice of survival model has profound impact on health economic estimates, and the lack of validation of the model presented by the Bernard-Arnoux et al study should be viewed as disqualifying in the context of an HTA.

Global health economic reviews

As noted above, the Washington State HTA also fails to note that TTFields was subject to formal health technology assessments in Sweden and Japan. In both locations the review was conducted by a qualified national healthcare agency. Both healthcare agencies reviewed economic models based on the survival model presented in Guzauskas et al. Both nations ultimately approved Optune for reimbursement after considering his health economic data.

We believe that Washington State should feel confident that qualified payers in the United States and around the world have already conducted thorough clinical and economic evaluations of TTFields. We ask that you consider the new literature regarding TTFields, foreign reimbursement approvals based on economic analysis, and what we view as disqualifying limitations of the one health economic study in the current HTA.

Conclusion

We appreciate the opportunity to comment on the clinical value of Optune therapy in treating both newly diagnosed and recurrent GBM. We strongly disagree with the way in which data from large, well designed randomized controlled trials was presented in the HTA. The results of these trials have been published in high impact-factor journals, such as the Journal of the American Medical Association, and the results have led to Optune being included in the NCCN guidelines.

We note that the authors of the HTA acknowledge that the randomized controlled trials for Optune were "fairly well designed with adequate randomization, intention-to-treat analysis, and blinding of the outcomes assessors." The main criticism appears to be the lack of sham control. These criticisms have been addressed in this document and should not detract from a balanced review of the literature.

We encourage Washington State to join the broad community of commercial, U.S. governmental and foreign healthcare payers to cover the therapy. We ask that you focus on the core facts and engage in reading the clinical trial publications and clinical guidelines directly. Optune was tested in the largest successful randomized controlled trial in newly glioblastoma ever conducted, the results of the trial are published in a top-tier journal (*JAMA*) and the therapy has been adopted in the NCCN Guidelines as a treatment for newly diagnosed (category 1) and recurrent glioblastoma (category 2b).

Finally, we ask the Washington State Healthcare Authority reschedule the public comment meeting for this HTA. The current hearing is scheduled for November 16, 2018, which conflicts with the Annual Meeting of the Society for Neuro-Oncology (SNO) (Nov 15-18). We believe that most GBM experts and most of the GBM advocacy community will be attending the SNO meeting and not able to provide feedback on this date.

195 Commerce Way
Portsmouth, NH 03801

603.436.2809
novocure.com

Thank you for your consideration of these comments. We look forward to continuing to work with you on this important issue. If you have any questions, please contact me at jkelly@novocure.com or (603) 501-4299.

Sincerely,

[redacted]

Justin M. Kelly, RN, BSN
Regional Vice President, Health Policy
Novocure

patientforward

UW Medicine
NEUROSCIENCES INSTITUTE
ALVORD BRAIN TUMOR CENTER

Washington Health Care Authority
Health Technology Clinical Committee (HTCC)
626 8th Ave SE
Olympia, WA 98501

E-Mail: shtap@hca.wa.gov

RE: Tumor treating fields (Optune)

Dear Medical Policy Group:

Thank you for the opportunity to offer updated information on Optune™, an FDA-approved treatment option for patients with newly diagnosed and recurrent glioblastoma multiforme (GBM). My name is Dr. Lynne Taylor, and I am co-director of the Alvord Brain Tumor Center at UW Medical Center, the UW Alexander M. Spence Endowed Chair in Neuro-oncology, and a UW professor of Neurology and Oncology. I am triple board certified in Neurology, Neuro-oncoloy and Pallative Care.

My clinical focus is in the care of patients with primary brain tumors, metastatic brain tumors and spinal tumors, as well as neurologic complications of cancer. I would like to respectfully submit the following informations for positive coverage policy consideration by the Washington Health Care Authority.

Therapy Overview:
Optune is a prescription only device that is intended for continuous use throughout the day by the patient. Optune delivers alternating electrical fields, called tumor treatment fields ("TTFields") within the human body. TTFields are applied to the patient by electrically insulated surface transducer arrays. TTFields disrupt the rapid cell divison exhibited by cancer cells.

Summary of Clinical Studies:
The final analysis of the EF-14 clinical trial was published in the Journal of the American Medical Association in December 2017. This publication includes the unprecedented five year survival extension seen in patients using Optune in combination with temozolomide in newly diagnosed glioblastoma. Additionally, a publication examining the quality of life of patients in the EF-14 clinical trial was published in February 2018. The reference citations are listed below.

Stupp R, Taillibert S, Kanner A, et al. Effect of Tumor-Treating Fields Plus Maintenace Temozolomide vs Maintenance Temozolomide Alone on Surivial in Patients With Glioblastoma A Randomized Clinical Trial. *JAMA*. 2017;318(23):2306-2316. doi:10.1001/jama.2017.18718

Taphroon MJB, Dirven L, Kanner AA, et al. Influence of Treatment With Tumor-Treating Fields on Health-Related Quality of Life of Patients With Newly Diagnosed Glioblastoma – A Secondary Analysis of a Randomized Clinical Trial. JAMA Oncol. Published online February 01. 2018. doi:10.1001/jamaoncol.2017.5082

National Comprehensive Cancer Network Guidelines (NCCN):
Optune is also included in the National Comprehensive Cancer Network guidelines with a uniform Category 1 consensus recommendation for newly diagnosed GBM in combination with temozolomide and a consensus Category 2B recommendation for recurrent glioblastoma.

Request for Consideration of Coverage:
As I am sure you are aware, glioblastoma multiforme is an orphan disease with extremely limited treatment options. Optune is the first FDA-approved therapy in more than a decade to demonstrate statistically significant extension of survival in newly diagnosed glioblastoma patients. The published 5-year survival builds upon the available literature supporting both the safety and efficacy of Optune in appropriate patients.

I strongly urge you to consider this information and issue a positive coverage policy for those Medicaid and PEBB patients with glioblastoma multiforme brain tumors.

Thank you for your consideration.

Kind regards,

[redacted]
Lynne P. Taylor, MD

Attending Physician, University of Washington Medical Center, Seattle Cancer Care Alliance
Clinical Professor, Department of Neurology
Neuro-Oncologist, Co-Director Alvord Brain Tumor Center
1959 NE Pacific St, Pacific Tower, 7th Flr, EE728
Box 356182
Seattle, WA 98195-6182
Phone: 206-598-2282
[redacted]
ltaylor@uw.edu