



Topic Brief: Radiation Therapy for Grade 4 Adult Gliomas

Date: 7/19/2022

Nomination Number: 0996

Purpose: This document summarizes the information addressing a nomination submitted on May 31, 2022, through the Effective Health Care Website. This information was used to inform the Evidence-based Practice Center (EPC) Program decisions about whether to produce an evidence report on the topic, and if so, what type of evidence report would be most suitable.

Issue: The nominators for this topic are requesting a new systematic review to be used to update existing 2016 guidelines on radiation therapy for glioblastoma.

Findings: The scope of this topic met all EHC Program selection criteria and was considered for a systematic review. However, it was not selected.

Background

Gliomas are the most common form of central nervous system neoplasm originating from glial cells, with six cases per 100,000 people per year in the United States.¹ The cost to Medicare for the treatment of glioblastoma, a type of glioma, measured from 2007 to 2013, was \$95,377 per patient on average.²

Gliomas grow diffusely in the brain, affecting surrounding tissue. Grading is based on cell morphology, mitotic activities, and molecular markers.¹ The most common symptoms are headaches, nausea, vomiting, seizures, and, in advanced cases, weakness or altered mental status.³ Initial treatment may include surgery, radiotherapy, and/or chemotherapy. There is no standard of care for recurrent or progressive glioblastoma.⁴

The nominating organization, ASTRO, is requesting a new systematic review to update their 2016 guideline on radiation treatment for gliomas. The search for the 2016 guideline ended in February 2014. The guideline included 157 citations. In ASCO's endorsement of the ASTRO guideline¹, they updated the search to June 2016, and identified four additional studies that did not change conclusions. One of these studies was identified in our extended targeted search for this assessment⁸.

Scope

¹ Radiation Therapy for Glioblastoma: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Society for Radiation Oncology Guideline. Erik P. Sulman, Nofisat Ismaila, Terri S. Armstrong, Christina Tsien, Tracy T. Batchelor, Tim Cloughesy, Evanthia Galanis, Mark Gilbert, Vinai Gondi, Mary Lovely, Minesh Mehta, Matthew P. Mumber, Andrew Sloan, and Susan M. Chang. *Journal of Clinical Oncology* 2017 35:3, 361-369

1. What are the effectiveness and harms of radiation therapy for people after biopsy/resection of grade 4 adult-type diffuse gliomas?
 - a. Which patient characteristics (e.g., age, sex, socioeconomic status, race/ethnicity, histology of primary tumor) are associated with effectiveness?
 - b. Do additional therapies (i.e., systemic therapy or adjunct tumor treating fields) affect outcomes?
2. What are the effectiveness and harms of radiation dose escalation in patients with grade 4 adult-type diffuse gliomas receiving radiation therapy after biopsy or resection?
 - a. Which patient characteristics (e.g., age, sex, socioeconomic status, histology of the primary tumor) are associated with effectiveness?
 - b. How do target volumes and techniques affect outcomes?
3. Among patients with grade 4 adult-type diffuse gliomas receiving radiation therapy after biopsy or resection, what are the effectiveness and harms of employing smaller clinical target volumes?
 - a. Which patient characteristics (e.g., age, sex, histology of the primary tumor) are associated with effectiveness?
 - b. How do different techniques affect outcomes?
4. What are the effectiveness and harms of re-irradiation in patients with grade 4 adult-type diffuse glioma whose disease recurs following completion of standard first-line therapy?
 - a. Which patient characteristics (e.g., age, sex, socioeconomic status, race/ethnicity, histology of primary tumor) are associated with effectiveness?
 - b. How do target volumes and techniques affect outcomes?

Table 1. Questions and PICO (population, intervention, comparator, outcome)

Questions	1. Radiation therapy for gliomas	2. Radiation dose escalation
Population	<p>Patients with newly diagnosed grade 4 adult-type diffuse gliomas</p> <p><u>Patient and tumor characteristics:</u> e.g., age, sex, socioeconomic status, histology of the primary tumor (e.g., IDH-wildtype vs. IDH-mutant), Karnofsky Performance Status, mental status (e.g., MMSE score), MGMT promoter methylation status, extent of resection, tumor location</p>	<p>Patients with grade 4 adult-type diffuse gliomas receiving external beam radiation therapy after biopsy/resection</p> <p><u>Patient characteristics:</u> e.g., age, sex, histology of the primary tumor (e.g., IDH-wildtype vs IDH-mutant), Karnofsky Performance Status, MGMT promoter methylation status</p>
Interventions	<p>Radiation therapy</p> <p>Adjunct therapy subgroups:</p> <ul style="list-style-type: none"> • Systemic therapy (e.g., temozolomide, bevacizumab, lomustine) • Adjuvant Tumor Treating Fields 	<p>External beam radiation therapy dose-fractionation schedules with higher biological equivalent dose. Techniques for dose escalation include conventionally fractionated external beam radiotherapy boost, hyperfractionation, stereotactic radiosurgery, and brachytherapy</p> <p><u>Subgroups (ie, means of dose escalation):</u></p> <ul style="list-style-type: none"> • Conventionally fractionated external beam radiotherapy boost • Hyperfractionation • Stereotactic radiosurgery (single fraction or fractionated) • Brachytherapy • Particle therapy • Hypofractionation

		<ul style="list-style-type: none"> Target volumes (e.g., two-phase, one-phase)
Comparators	No radiation therapy Chemotherapy Other palliative treatment	External beam radiation therapy dose-fractionation schedules with lower biological equivalent dose (e.g., conventionally fractionated schedules with a lower total dose, hypofractionated regimens with lower biological equivalent dose) Chemotherapy alone (e.g., in the elderly) Best supportive care alone
Outcomes	Survival, progression-free survival, quality of life, harms	Survival, progression-free survival, quality of life, harms

Abbreviations: MMSE=mini mental state evaluation.

Questions	3. Clinical target volumes	4. Re-irradiation
Population	Patients with grade 4 adult-type diffuse gliomas receiving external beam radiation therapy after biopsy/resection Patient characteristics: e.g., age, sex, histology of the primary tumor (e.g., IDH-wildtype vs IDH-mutant), Karnofsky Performance Status, MGMT promoter methylation status	Patients with grade 4 adult-type diffuse gliomas whose disease recurs following completion of standard first-line therapy Patient characteristics: (e.g., age, sex, histology of the primary tumor, performance status, MGMT promoter methylation status, tumor size, tumor location)
Interventions	External beam radiation therapy plans employing clinical target volume expansions smaller than those used in RTOG protocols (e.g., RTOG 0825) <u>Subgroups (i.e., techniques):</u> <ul style="list-style-type: none"> 3d conformal radiotherapy Intensity modulated radiation therapy Particle therapy One-phase vs two phase (i.e., boost) plans 	Re-irradiation (with or without systemic therapy, e.g., bevacizumab) <u>Subgroups (techniques):</u> <ul style="list-style-type: none"> Stereotactic radiosurgery (single fraction or fractionated) Hypofractionation Hyperfractionation Conventional fractionation Brachytherapy Particle therapy
Comparators	External beam radiation therapy plans employing clinical target volume expansions used in RTOG protocols	No re-irradiation therapy Other treatment for palliative treatment (e.g., chemotherapy, surgery)
Outcomes	Survival, progression-free survival, quality of life, harms	Survival, progression-free survival, quality of life, harms

Abbreviations: RTOG=Radiation Therapy Oncology Group.

Assessment Methods

See Appendix A.

Summary of Literature Findings

We did not find any systematic reviews addressing any portions of the nomination and found very limited primary studies. The one primary study we found was a retrospective study that addressed Key Question (KQ) 4, comparing gamma knife surgery + bevacizumab + irinotecan with bevacizumab + irinotecan without gamma knife surgery as second-line treatment following chemoradiotherapy with temozolomide.⁵

Since the 2016 ASTRO guideline search ended in February 2014, the current search, which began in July 2017, did not include potential studies in this gap that would be relevant to a guideline update. Consequently, we conducted an additional search, spanning from February 2014 (the end of the search used in the 2016 ASTRO guideline) to July 2017 (the beginning of the current search). From that search, we found three studies addressing KQ 2,⁶⁻⁸ three studies addressing KQ 4,⁹⁻¹¹ and no studies addressing KQs 1 and 3.

Table 2. Literature identified for each Key Question

Question	Systematic reviews (7/2019-7/2022)	Primary studies (7/2017-7/2022)	Primary studies (2/2014 [end of 2016 guideline search]-7/2017 [beginning of current search])
Question 1: Radiation therapy for gliomas	Total: 0	Total: 0	Total: 0
Question 2: Radiation dose escalation	Total: 0	Total: 0	Total: 3 <ul style="list-style-type: none"> • RCT: 1⁸ • Retrospective: 2^{6,7}

Abbreviations: RCT=randomized controlled trial.

Question	Systematic reviews (7/2017-7/2022)	Primary studies (7/2019-7/2022)	Primary studies (2/2014 [end of 2016 guideline search]-7/2017 [beginning of current search])
Question 3: Clinical target volumes	Total: 0	Total: 0	Total: 0
Question 4: Re-irradiation	Total: 0	Total: 1 <ul style="list-style-type: none"> • Retrospective: 1⁵ 	Total: 3 <ul style="list-style-type: none"> • Non-randomized controlled: 2^{9,10} • Retrospective: 1¹¹

See Appendix B for detailed assessments of all EPC selection criteria.

Summary of Selection Criteria Assessment

A new systematic review would serve to update guidelines published in 2016. The nominators expect that new relevant studies have been published since that time that could contribute to changes in practices. We found only one study supporting the nomination.

We shared the search yield with the nominator. They agreed that a five year search would not yield many studies. They indicated that this was likely for more rare tumors like primary central

nervous system malignancies. We then conducted an additional search covering the gap between the end of the search conducted for the guideline and the beginning of our original search. We found three studies each for KQs 2 and 4, and no studies for KQs 1 and 3.

Please see Appendix B for detailed assessments of individual EPC Program selection criteria.

References

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4. Fernandes C CA, Osório L. Current Standards of Care in Glioblastoma Therapy. 2017. doi: <https://www.ncbi.nlm.nih.gov/books/NBK469987/>.
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Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

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Appendix A: Methods

We assessed nomination for priority for a systematic review or other AHRQ Effective Health Care report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix B for detailed description of the criteria.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Absence of Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years July 20, 2019 - July 20, 2022, on the questions of the nomination from these sources:

- AHRQ: Evidence reports and technology assessments
 - AHRQ Evidence Reports <https://www.ahrq.gov/research/findings/evidence-based-reports/index.html>
 - EHC Program <https://effectivehealthcare.ahrq.gov/>
 - US Preventive Services Task Force <https://www.uspreventiveservicestaskforce.org/>
 - AHRQ Technology Assessment Program <https://www.ahrq.gov/research/findings/ta/index.html>
- US Department of Veterans Affairs Products publications
 - Evidence Synthesis Program <https://www.hsrd.research.va.gov/publications/esp/>
 - VA/Department of Defense Evidence-Based Clinical Practice Guideline Program <https://www.healthquality.va.gov/>
- Cochrane Systematic Reviews <https://www.cochranelibrary.com/>
- PROSPERO Database (international prospective register of systematic reviews and protocols) <http://www.crd.york.ac.uk/prospero/>
- PubMed <https://www.ncbi.nlm.nih.gov/pubmed/>
- Joanna Briggs Institute <http://joannabriggs.org/>
- Epistemonikos <https://www.epistemonikos.org/>

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

We conducted a limited literature search in PubMed and PsycInfo for the last five years July 2019-July 2022. Since the 2016 ASTRO guideline search ended in February 2014, the current search, which began in July 2017, did not include potential studies in this gap that would be relevant to a guideline update. Consequently, we conducted an additional search, spanning from February 2014 (the end of the search used in the 2016 ASTRO guideline) to July 2017 (the beginning of the current search).

We reviewed all studies identified titles and abstracts for inclusion. We classified identified studies by question and study design to estimate the size and scope of a potential evidence review.

Search strategy

Ovid MEDLINE ALL 1946 to July 19, 2022

Date searched: July 20, 2022

- 1 (diffuse or diffusely or multiforme).ti,ab,kf. and (Astrocytoma/ or Glioblastoma/ or exp Glioma/) (13576)
- 2 ((diffuse or diffusely or multiforme) adj5 (ATRX or astrocyt* or GBM or rGBM or GSM or gliosarcom* or glioblastom\$3 or gliom\$3 or HGG or oligoastrocyt* or oligodendrogli* or IDH\$3 or isocitrate-dehydrogenase or TP53* or wildtype or "wild type")).ti,ab,kf. (16465)
- 3 or/1-2 (17526)
- 4 exp Radiotherapy/ or (re or rt).fs. (493944)
- 5 (brachytherap* or chemoradi* or chemo-radi* or fraction* or HART or hyperfraction* or hyper-fraction* or hypofraction* or hypo-fraction* or neutron or "one phase" or particle or proton or radia* or radio* or irradiat* or reirradiat* or reradiat* or ReRT or "two phase" or ultrafraction* or ultra-fraction*).ti,ab,kf. (2612025)
- 6 or/4-5 (2744306)
- 7 and/3,6 (5945)
- 8 7 not ((Animals/ not Humans/) or (animal* or append* or breast or canine or case or cat\$1 or child* or colorectal* or dog\$1 or endometr* or feline or hepatic* or leukemi* or leukaem* or liver or "low-grade" or lung or melanom* or mice or mouse or murine or non-neuroendocrine or ovarian or pediater* or paediatr* or prostat* or rat\$3 or renal or rectal* or rodent\$3 or uterine).ti. or (editorial or comment).pt.) (4657)
- 9 limit 8 to english language (4487)
- 10 (Meta-analysis or "systematic review").pt. or (meta-analy* or metaanaly* or ((evidence or scoping or systematic or umbrella) adj4 (review or synthesis))).ti,kf. (369261)
- 11 and/9-10 (68)
- 12 limit 11 to yr="2019 -Current" (32)
- 13 ("controlled clinical trial" or "randomized controlled trial").pt. or (control* or random* or placebo or trial).ti. (1313687)
- 14 and/9,13 (263)
- 15 limit 14 to yr="2017 -Current" (34)
- 16 exp Cohort Studies/ or exp Epidemiologic Studies/ or Observational Studies as Topic/ or "Observational Study".pt. (3031266)
- 17 (before-after or case-control or cohort\$1 or follow-up* or "interrupted time" or longitudinal\$2 or observational or pre-post or prospective\$2 or retrospective\$2).ti,ab,kf. (3231301)
- 18 or/16-17 (4418095)
- 19 and/9,18 (1408)
- 20 limit 19 to yr="2017 -Current" (435)
- 21 (high-grade or (grade adj3 ("4" or four or "IV"))).ti,ab,kf. (120331)
- 22 and/20-21 (74)

EBM Reviews - Cochrane Central Register of Controlled Trials June 2022

Date searched: July 20, 2022

- 1 (diffuse or diffusely or multiforme).ti,ab. and (Astrocytoma/ or Glioblastoma/ or Glioma/ or Ependymoma/ or Glioma, Subependymal/ or Ganglioglioma/ or Gliosarcoma/ or Medulloblastoma/ or Oligodendroglioma/ or Optic Nerve Glioma/) (277)
- 2 ((diffuse or diffusely or multiforme) adj5 (ATRX or astrocyt* or GBM or rGBM or GSM or gliosarcom* or glioblastom\$3 or gliom\$3 or HGG or oligoastrocyt* or oligodendrogli* or IDH\$3 or isocitrate-dehydrogenase or TP53* or wildtype or "wild type")).ti,ab. (722)
- 3 or/1-2 (730)

4 Radiotherapy/ or Brachytherapy/ or Chemoradiotherapy/ or Chemoradiotherapy, Adjuvant/ or Cranial Irradiation/ or Craniospinal Irradiation/ or Heavy Ion Radiotherapy/ or Proton Therapy/ or Hemibody Irradiation/ or Lymphatic Irradiation/ or Radioimmunotherapy/ or Radiosurgery/ or Radiotherapy Dosage/ or Dose Fractionation, Radiation/ or Radiotherapy, Adjuvant/ or Radiotherapy, Computer-Assisted/ or Radiotherapy, Conformal/ or Radiotherapy, High-Energy/ or Neutron Capture Therapy/ or Radioisotope Teletherapy/ or Radiotherapy, Image-Guided/ or Re-Irradiation/ (6426)

5 (brachytherap* or chemoradi* or chemo-radi* or fraction* or HART or hyperfraction* or hyper-fraction* or hypofraction* or hypo-fraction* or neutron or "one phase" or particle or proton or radia* or radio* or irradiat* or reirradiat* or reradiat* or ReRT or "two phase" or ultrafraction* or ultra-fraction*).ti,ab. (148662)

6 or/4-5 (149057)

7and/3,6 (492)

8 7 not ((Animals/ not Humans/) or (animal* or append* or breast or canine or case or cat\$1 or child* or colorectal* or dog\$1 or endometr* or feline or hepatic* or leukemi* or leukaem* or liver or "low-grade" or lung or melanom* or mice or mouse or murine or non-neuroendocrine or ovarian or pediater* or paediatr* or prostat* or rat\$3 or renal or rectal* or rodent\$3 or uterine).ti. or (editorial or comment).pt.) (418)

9 limit 8 to yr="2017 -Current" (99)

EPISTEMONIKOS

Date searched: July 20, 2022

(title:((title:((diffuse OR diffusely OR multiforme) AND (ATRX OR Astrocytoma OR Ependymoma OR Ganglioglioma OR GBM OR rGBM OR GSM OR gliosarcoma OR glioblastoma OR glioma OR oligoastrocytoma OR oligodendroglioma OR IDH1 OR IDH2 OR isocitrate-dehydrogenase OR TP53 OR wildtype OR "wild type"))) OR abstract:((diffuse OR diffusely OR multiforme) AND (ATRX OR Astrocytoma OR Ependymoma OR Ganglioglioma OR GBM OR rGBM OR GSM OR gliosarcoma OR glioblastoma OR glioma OR oligoastrocytoma OR oligodendroglioma OR IDH1 OR IDH2 OR isocitrate-dehydrogenase OR TP53 OR wildtype OR "wild type"))) AND (title:((diffuse OR diffusely OR multiforme) AND (chemoradi* OR chemo-radi* OR fraction* OR HART OR hyperfraction* OR hyper-fraction* OR hypofraction* OR hypo-fraction* OR neutron OR "one phase" OR particle OR proton OR radia* OR radio* OR irradiat* OR reirradiat* OR reradiat* OR ReRT OR "two phase" OR ultrafraction* OR ultra-fraction*)) OR abstract:((diffuse OR diffusely OR multiforme) AND (chemoradi* OR chemo-radi* OR fraction* OR HART OR hyperfraction* OR hyper-fraction* OR hypofraction* OR hypo-fraction* OR neutron OR "one phase" OR particle OR proton OR radia* OR radio* OR irradiat* OR reirradiat* OR reradiat* OR ReRT OR "two phase" OR ultrafraction* OR ultra-fraction*))) NOT title:(animal OR append* OR breast OR canine OR case OR cat OR cats OR child* OR colorectal* OR dog OR dogs OR endometr* OR feline OR hepatic* OR leukemi* OR leukaem* OR liver OR "low-grade" OR lung OR melanom* OR mice OR mouse OR murine OR non-neuroendocrine OR ovarian OR pediater* OR paediatr* OR prostat* OR rat OR rats OR rattus OR renal OR rectal* OR rodentia OR uterine)) OR abstract:((title:((diffuse OR diffusely OR multiforme) AND (ATRX OR Astrocytoma OR Ependymoma OR Ganglioglioma OR GBM OR rGBM OR GSM OR gliosarcoma OR glioblastoma OR glioma OR oligoastrocytoma OR oligodendroglioma OR IDH1 OR IDH2 OR isocitrate-dehydrogenase OR TP53 OR wildtype OR "wild type"))) OR abstract:((diffuse OR diffusely OR multiforme) AND (ATRX OR Astrocytoma OR Ependymoma OR Ganglioglioma OR GBM OR rGBM OR GSM OR gliosarcoma OR glioblastoma OR glioma OR oligoastrocytoma OR oligodendroglioma OR IDH1 OR IDH2 OR isocitrate-dehydrogenase OR TP53 OR wildtype OR "wild type"))) AND (title:((diffuse OR diffusely OR multiforme) AND

(chemoradi* OR chemo-radi* OR fraction* OR HART OR hyperfraction* OR hyper-fraction* OR hypofraction* OR hypo-fraction* OR neutron OR "one phase" OR particle OR proton OR radia* OR radio* OR irradiat* OR reirradiat* OR reradiat* OR ReRT OR "two phase" OR ultrafraction* OR ultra-fraction*) OR abstract:((diffuse OR diffusely OR multiforme) AND (chemoradi* OR chemo-radi* OR fraction* OR HART OR hyperfraction* OR hyper-fraction* OR hypofraction* OR hypo-fraction* OR neutron OR "one phase" OR particle OR proton OR radia* OR radio* OR irradiat* OR reirradiat* OR reradiat* OR ReRT OR "two phase" OR ultrafraction* OR ultra-fraction*)) NOT title:(animal OR append* OR breast OR canine OR case OR cat OR cats OR child* OR colorectal* OR dog OR dogs OR endometr* OR feline OR hepatic* OR leukemi* OR leukaem* OR liver OR "low-grade" OR lung OR melanom* OR mice OR mouse OR murine OR non-neuroendocrine OR ovarian OR pediater* OR paediatr* OR prostat* OR rat OR rats OR rattus OR renal OR rectal* OR rodentia OR uterine))) (29)

PROSPERO

Date searched: July 20, 2022

(diffuse OR diffusely OR multiforme) AND (ATRX OR Astrocytoma OR Ependymoma or Ganglioglioma or GBM OR rGBM OR GSM OR gliosarcoma OR glioblastoma OR glioma OR oligoastrocytoma OR oligodendroglioma OR IDH1 OR IDH2 OR isocitrate-dehydrogenase OR TP53 OR wildtype OR "wild type") AND (chemoradi* OR chemo-radi* OR fraction* OR HART OR hyperfraction* OR hyper-fraction* OR hypofraction* OR hypo-fraction* OR neutron OR "one phase" OR particle OR proton OR radia* OR radio* OR irradiat* OR reirradiat* OR reradiat* OR ReRT OR "two phase" OR ultrafraction* OR ultra-fraction*) AND (Systematic Review OR Meta-Analysis OR IPD OR PMA OR Network meta-analysis OR Review of reviews):RT WHERE CD FROM 20/07/2019 TO 20/07/2022 (36)

[Clinical Trials.gov](https://clinicaltrials.gov)

Value

We assessed the nomination for value. We considered whether or not the clinical, consumer, or policymaking context had the potential to respond with evidence-based change, if a partner organization would use this evidence review to influence practice, and if the topic supports a priority area of AHRQ or the Department of Health and Human Services.

Appendix B. Selection Criteria Assessment

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the United States?	Yes.
1b. Is the nomination a request for an evidence report?	Yes.
1c. Is the focus on effectiveness or comparative effectiveness?	Yes.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Gliomas are the most common form of central nervous system neoplasm originating from glial cells, with six cases per 100,000 people per year in the United States. ¹
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the United States population or for a vulnerable population	Yes. Gliomas are the most common form of central nervous system neoplasm originating from glial cells, with six cases per 100,000 people per year in the United States. ¹ The cost to Medicare for treatment of glioblastoma, a type of glioma, measured from 2007 to 2013, was an average of \$95,377 per patient. ²
2c. Incorporates issues around both clinical benefits and potential clinical harms	Yes.
2d. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes. The cost to Medicare for treatment of glioblastoma, a type of glioma, measured from 2007 to 2013, was an average of \$95,377 per patient. ²
3. Desirability of a New Evidence Review/Absence of Duplication	
3. A recent high-quality systematic review or other evidence review is not available on this topic	Yes. We did not find any systematic reviews addressing the scope of the nomination.
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Yes. Initial treatment may include surgery, radiotherapy, and/or chemotherapy. There is no standard of care for recurrent or progressive glioblastoma. ⁴
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Yes. There is practice variation in the treatment of glioblastoma. ¹²
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	We found one study (for KQ 4) addressing the KQs in a review of the entire search yield. From an additional search of the gap between the end of the search conducted for the guideline and the beginning of our original search, we found three studies for KQ 2 and three studies for KQ 4.

	The estimated size of a new systematic review would be limited.
6. Value	
6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change and supports a priority of AHRQ or Department of Health and Human Services	Yes. A new systematic review would serve to update guidelines published in 2016. The nominators expect that new relevant studies have been published since that time that could contribute to changes in practices.
6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)	Yes. ASTRO would use a new systematic review to develop a new guideline.

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; ASTRO=American Society of Radiation Oncology; KQ=key question.