Topic Brief: Non-functioning Pituitary Adenoma

Date: 1/27/2023
Nomination Number: 995

Purpose: This document summarizes the information addressing a nomination submitted on May 31, 2022 (https://effectivehealthcare.ahrq.gov/get-involved/nominated-topics/nonfunctional-pituitary-adenomas) 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 nominator is concerned with the optimal assessment and management of non-functioning pituitary adenomas in adults, given their prevalence and number that are found incidentally. They note the uncertainty around management leading to variation in care and potential for unnecessary harm from treatment. They have a 2016 American Academy of Neurological Surgeons (AANS) and Congress of Neurological Surgeons (CNS) joint guideline that is now out of date given more recent studies and new interventions and approaches to treatment. They request a systematic review to inform new guidance.

Program Decision: Though the nomination met selection criteria it was not selected for further development as a systematic review.

Key Findings

- We found multiple systematic reviews that addressed part of the nomination, with a diversity of methodological rigor, inclusion criteria, and search dates.
- While a new systematic review is feasible, considering the large evidence base already identified in the review informing the 2016 AANS/CNS guideline, AHRQ should consider limiting the scope of a new review to higher-priority areas or commission multiple systematic reviews to ensure that a new review is feasible to complete under the contractual timeframe.

Background

Pituitary adenomas comprise approximately 10-20% of intracranial tumors. Non-functioning pituitary adenomas (NFPAs) are benign tumors not associated with clinical evidence of hormonal hypersecretion. They represent a sizeable proportion (between 22% to 54%) of all pituitary adenomas. Patients with NFPAs may present with headaches, visual disorders, hormone deficiency, and/or cranial nerve dysfunction caused by tumors large enough to damage surrounding structures. Some cases may be identified incidentally through imaging performed for other purposes[1, 2].

Treatment includes active surveillance/observation, surgery, radiation, and pharmacologic treatment. Complications of surgery include cerebrospinal fluid (CSF) leakage, fistula, meningitis, vascular injury, or new visual field defect. Another complication, Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH) may occur within the first 3–7 days postoperatively. In rare cases, it may result in severe, life-threatening, acute hyponatremia[3].

NFPAs may progress after surgical treatment, with regrowth rates of 15–66% in NFPA patients treated with surgery alone and 2–28% in those treated with surgery and radiotherapy. Surveillance after treatment may vary and may include imaging, visual assessments, and hormone assessments. Management of recurrence includes surgery, radiation, and medication[3].

The nominator is a clinical organization representing neurological surgeons. They plan to update their clinical practice guidance using an AHRQ review. Nomination questions were updated after discussion with nominator representatives and input from content experts. The scope of the nomination is broad, ranging from initial assessment, treatment modalities, surgical techniques, intraoperative adjunct modalities, post-surgical surveillance, and post-surgical treatment.

Previous review for their 2016 guideline was large[4-11] and included 281 studies (122 articles on preoperative imaging; 6 on pretreatment visual assessment; 28 for treatment; 56 on surgical techniques and intraoperative adjunct; 46 on residual/recurrent disease management; and 23 on surveillance). The scope of the nomination includes new questions around other adjunct intraoperative technologies, postoperative fluid restrictions, strategies to decreased hospital length of stay and readmission, and post-operative hormone replacement.

Scope

Initial assessment of adults with suspected NFPAs

1. What is the comparative effectiveness and harms of initial assessments of people with suspected nonfunctional pituitary adenomas (NFPAs):
    a. Imaging modalities in initial assessment of NFPA?
    b. Technology for assessing visual function in NFPA patients?
2. What is the effectiveness and harms of preoperative hormone replacement in people with NFPA?

	1a: Imaging	1b: Visual assessment	2: Hormone replacement
Population	Adults ≥ 18 yrs with suspected NFPA	Adults ≥ 18 yrs with suspected pituitary mass	Adults ≥ 18 yrs with non-functioning pituitary adenoma
Intervention	Imaging modalities: Computed Tomography (CT), Single-Photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET) Consider: scanner type (1.5T vs 3T), MR sequences,	Visual assessment using: Ophthalmologic examination, automated static perimetry, optical coherence tomography, etc.	Preoperative hormone replacement
Comparator	High resolution MRI	Other visual assessment technologies	No hormone replacement

Outcomes	Size/relative location/orientation of NFPA, firmness of the tumor mass, cavernous sinus wall invasion, vascularity and hemorrhage. Harms	Acuity, visual fields, quantitation of afferent pupillary defect, visual evoked potentials Harms	Tumor recurrence/regrowth, pituitary status/adrenal function, visual status (e.g., visual field, visual acuity) Harms

Primary management of NFPAs

3. What is the comparative effectiveness and harms of surgical vs. non-surgical treatment for initial management of adults with NFPAs?
    a. For symptomatic NFPA
    b. For asymptomatic NFPA

	3: Surgery vs. other treatment
Population	a. Adults ≥ 18 yrs with symptomatic NFPA (e.g., neurologic symptoms such as visual symptoms or headache) b. Adults ≥ 18 yrs with asymptomatic NFPAs
Intervention	Surgery
Comparator	• Observation/serial imaging including timing of serial imaging and whether to use contrast on serial imaging • radiation • medical therapies • combination non-surgical therapies
Outcome	Tumor volume, hypopituitarism, resolution of symptoms (vision deficits, headaches, etc. Harms of treatment

Surgical techniques and technologies

4. What is the comparative effectiveness and harms of endoscopic vs. microscopic transsphenoidal NFPA surgery?
5. What is the effectiveness and harms of medial cavernous sinus wall resection during NFPA surgery?

	4: Endoscopic vs. microscopic transsphenoidal surgery	**5: Medial cavernous sinus wall resection**
Population	Adults ≥ 18 yrs with NFPAs	Adults ≥ 18 yrs with NFPAs
Intervention	Endoscopic transsphenoidal NFPA surgery	Medial cavernous sinus wall resection during surgery
Comparator	Microscopic transsphenoidal NFPA surgery	No medial cavernous sinus wall resection during surgery
Outcomes	Extent of resection, postoperative sinonasal quality of life, resolution of symptoms Harms of surgery	Extent of resection, postoperative sinonasal quality of life, tumor recurrence/regrowth, pituitary status/adrenal function, visual status (e.g., visual field, visual acuity) Harms of surgery

Intraoperative adjuncts for NFPA surgery

6. What are the effectiveness and harms of intraoperative adjuncts for NFPA surgery?
    a. Prophylactic antibiotics during NFPA surgery?
    b. Stress dose steroids during NFPA surgery?
    c. Lumbar CSF diversion?
        i. During NFPA surgery?
        ii. After NFPA surgery?
    d. MRI during NFPA surgery?
    e. Intraoperative fluoroscopy?
    f. Intraoperative use of agents for tumor fluorescence visualization?

	6a: Antibiotics	**6b: Steroids**	**6c: Lumbar CSF diversion**	**6d: MRI**	**6e: Fluoroscopy**	**6f: Tumor fluorescence**
Population	Adults≥ 18 yrs with symptomatic NFPAs	Adults≥ 18 yrs with symptomatic NFPAs	Adults≥ 18 yrs with symptomatic NFPAs	Adults≥ 18 yrs with symptomatic NFPAs	Adults≥ 18 yrs with symptomatic NFPAs	Adults≥ 18 yrs with symptomatic NFPAs
Intervention	Prophylactic antibiotics during NFPA surgery	Stress dose steroids during NFPA surgery	1. Lumbar cerebrospinal fluid (CSF) diversion during NFPA surgery 2. Lumbar CSF diversion after NFPA surgery	MRI during NFPA surgery	Intraoperative fluoroscopy	Intraoperative use of agents for tumor fluorescence visualization
Comparator	No prophylactic antibiotics	No stress dose steroids during NFPA surgery	1. No lumbar CSF diversion surgery 2. No lumbar CSF diversion after surgery	Other imaging, no imaging	No intraoperative fluoroscopy	No intraoperative use of agents for tumor fluorescence visualization
Outcomes	Postoperative infection, any harms (drug resistance)	Postoperative alertness, postop ICU care, postop hypotension, Length of stay Harms	Postoperative CSF leak, Tumor descent, vision, headaches Harms	Partial/complete resection, tumor volume, hypopituitarism, vision, headaches, tumor recurrence/regro	Partial/complete resection, duration of surgery, tumor volume, hypopituitarism, tumor recurrence/regr	Partial/complete resection, tumor volume, hypopituitarism, vision, headaches, tumor recurrence/regr

				wth, pituitary status, visual status (e.g., visual field, visual acuity) Harms	owth, pituitary status/visual status (e.g., visual field, visual acuity) Harms	owth, pituitary status, visual status (e.g., visual field, visual acuity), Harms

Immediate postoperative care

7. What is the effectiveness and harms of fluid restriction to reduce syndrome of inappropriate antidiuretic hormone secretion (SIADH) in people treated with surgery for NFPA?
8. What is the comparative effectiveness and harms of immediate postoperative care strategies aimed at decreasing length of stay and 30-day readmission after surgery for NFPA?
9. What is the effectiveness and harms of maintenance steroids after NFPA surgery?

	7: Fluid restriction	**8: Care strategies**	**9: Steroids**
Population	Adults ≥ 18 yrs after surgery for NFPAs	Adults ≥ 18 yrs after surgery for NFPAs	Adults ≥ 18 yrs after surgery for NFPAs
Intervention	Fluid restriction (a salt-rich diet, and oral sodium supplementation)	Postoperative care strategies intended to decrease length of stay and hospital readmission (e.g. case management, discharge planning, medication management, telehealth, etc.)	Maintenance steroids (including hydrocortisone, prednisone, or dexamethasone) for a variable duration of time
Comparator	No fluid restriction	Other postoperative care strategies No strategy	No maintenance steroids (hydrocortisone, prednisone, or dexamethasone) after NFPA surgery
Outcomes	SIADH, Tumor volume, hypopituitarism, vision, headaches, etc. Tumor recurrence/regrowth, pituitary status/adrenal function, visual status (e.g., visual field, visual acuity), harms	Length of hospital stay, 30-day hospital readmission, Quality of life, harms	Postoperative level of alertness, pituitary status/adrenal function, visual status (e.g., visual field, visual acuity), harms

Management of residual or recurrent NFPA

10. What is the effectiveness and harms of management strategies for residual or recurrent NFPA:

    a. Radiation therapy?
    b. Radiosurgery?
    c. Medical therapy such as temozolomide?
    d. Repeat surgery?
    e. Observation?

	10: Residual or recurrent RFPA
Population	Adults ≥ 18 yrs with recurrent or residual NFPA
Intervention	a. Radiation therapy b. Radiosurgery c. Medical therapy

	d. Repeat surgery e. Observation
Comparator	a-e: Other intervention category
Outcomes	Tumor volume, hypopituitarism, vision, headaches, etc. Tumor recurrence/regrowth, pituitary status/adrenal function, visual status (e.g., visual field, visual acuity), harms

Post-treatment

11. What is the comparative effectiveness and harms of post-NFPA surgery surveillance on outcomes?

a. Timing, duration, and schedule/interval/frequency of imaging?
b. Timing of initial visual evaluation?
c. Timing of endocrine evaluation?

	11a: Imaging	**11b: Visual assessment**	**11c: Endocrine assessment**
Population	Adults ≥ 18 yrs after surgery for NFPAs	Adults ≥ 18 yrs after surgery for NFPAs	Adults ≥ 18 yrs after surgery for NFPAs
Intervention	Surveillance imaging with MRI (initiation, duration, schedule/interval/frequency)	Timing of initial visual evaluation Post NFPA surgery	Timing of initial endocrine evaluation Post NFPA surgery
Comparator	Other surveillance imaging (initiation, duration, schedule/interval/frequency)	Other time of visual evaluation post NFPA surgery	Other timepoint for endocrine evaluation post NFPA surgery
Outcomes	Tumor recurrence/regrowth, pituitary status/adrenal function, visual status (e.g., visual field, visual acuity) Harms	Visual status (e.g., visual field, visual acuity), Tumor recurrence/regrowth, pituitary status/adrenal function Harms	Pituitary status/adrenal function, Tumor recurrence/regrowth, visual status (e.g., visual field, visual acuity) Harms

12. What is the effectiveness of optional hormone supplementation in people after NFPA surgery, such as GH, DHEA, or testosterone on quality of life?

	12: Hormone supplementation
Population	Adults ≥ 18 yrs after surgery for NFPAs
Intervention	Hormone supplementation (GH, DHEA, or testosterone)
Comparator	No hormone supplementation
Outcome	Quality of life

Assessment Methods

See Appendix A.

Summary of Literature Findings

We identified completed and in-progress systematic reviews addressing parts of questions 1-4, 6, 7, and 10-12. Not all interventions were addressed and the diversity of methodological rigor and search dates would pose challenging for a group to consolidate into a single guideline.

- Question 1 (preoperative imaging and visual assessment). We identified one systematic review on preoperative MRI[12]. Other imaging modalities were not included.
- Question 2 (preoperative hormone replacement). We identified one in-progress review[13]. It will focus on dopamine receptor agonist or somatostatin receptor analogs. The review is expected to be completed in October 2023.
- Question 3 (surgery vs. non surgery). We identified one in-progress review[14]. The review will focus on radiotherapy compared to surgery, and on individuals with pituitary adenoma. It is not clear if they will analyze studies of people with nonfunctioning pituitary adenomas separately. We note that one of the authors was lead the author for several publications related to the 2016 AANS/CNS guideline[10].
- Question 4 (Endoscopic vs. microscopic transsphenoidal surgery). We identified one in-progress review[15] and three completed systematic reviews[3, 16-18]. It is not clear whether the in-progress review will analyze studies of people with nonfunctioning pituitary adenomas separately.
- Question 6 (intraoperative adjunct modalities). We identified four completed systematic reviews[19-22]. Two completed reviews[19, 22]focused on intraoperative MRI. One systematic review focused on lumbar CSF diversion[20], though it did not focus solely on people with nonfunctional pituitary adenoma. One review focused on fluorescent agents, and provided analysis separately for people with nonfunctional pituitary adenoma[21].
- Question 7 (postoperative fluid restriction). We identified one in-progress review[23] and two systematic reviews[24, 25]. Both systematic reviews did not provide conclusions for individuals with nonfunctional pituitary adenomas separately.
- Question 10 (management of residual/recurrent NFPA). We identified one completed review[26] focused on radiotherapy.
- Question 11 (surveillance). We identified one in-progress systematic review[27]. Authors are members of the Cochrane Collaboration. The scope will include both functional and non-functional pituitary adenomas. The review is complete and is pending publication.
- Question 12 (post-operative hormone replacement). The same in-progress systematic review for question 2[13] applies to this question.

We identified 20 primary studies published in the last 5 years relevant to the topic, with anywhere from 0-6 studies per key question. The question with the most studies focused on endoscopic vs. microscopic transsphenoidal surgery

Key question	Systematic reviews (August 2019-August 2022)	Study publications (August 2017-August 2022)
1. (a) Initial imaging assessment	Total-1 • Pubmed-1[12]	Total-2[28, 29]
1. (b) Initial visual assessment	Total-0	Total-2[30 31]
2. Preoperative hormone replacement	Total-1 • PROSPERO-1[13]	Total-3[32 33 34]
3. Surgery vs. non-surgery	Total-1 • PROSPERO-1[14]	Total-1[35]
4. Endoscopic vs. microscopic transsphenoidal surgery	Total-5 • Pubmed-3[16, 17, 36,37] • PROSPERO-1[15]	Total-6[38-40 41, 42 43]

5. Medial cavernous sinus wall resection during surgery	Total 0	Total-1[44]
6. Intraoperative adjuncts	Total-4 • Lumbar CSF diversion- ○ Pubmed-1[20] • MRI ○ Pubmed-1[19] ○ PROSPERO-1[45] • Fluorescence ○ Pubmed -1[21]	Total-5 • Fluorescence-3[46-48] • Lumbar CSF drainage-1[49] • Intraoperative MRI-1[50]
7. Post-operative fluid restriction	Total-3 • PROSPERO-1[23] • Pubmed-2[24, 25]	Total-1[51]
8. Postoperative care strategies aimed at decreasing length of stay and 30 day readmission	Total 0	Total-1[52]
9. Post-operative maintenance steroids	Total 0	Total-0
10. Management of residual or recurrent NFPA	Total-1 • Pubmed-1[26]	Total-4[53-55 56]
11. Post-operative surveillance	Total-1 • PROSPERO-1[27](publication forthcoming)	Total-4[29, 57-59]
12. Post-operative hormone supplementation	Total-1 • PROSPERO-1[13]	Total-0

KQ=key question; NFPA=non-functioning pituitary adenoma

Table 2. AANS/CNS 2016 Guideline Recommendations for draft key question

Key question	Recommendation from 2016 Guideline
1. (a) Initial imaging assessment	High-resolution MRI (Level II) is recommended as the standard but may be supplemented with CT (Level III).[10] While promising results are available pertaining to MR spectroscopy, MR perfusion, PET, and SPECT for preoperative assessment of NFPA histology and characteristics, there is insufficient evidence to make a formal recommendation for their use.[10]
1. (b) Initial visual assessment	Pretreatment evaluation of NFPA patients by an ophthalmologist is recommended. Ophthalmologic evaluation identifies patients with asymptomatic visual deficits due to the ophthalmologist's ability to quantitate psychophysical (acuity and visual fields), functional (quantitation of afferent pupillary defect and visual evoked potentials [VEP]), and anatomical (disc appearance and ocular coherence tomography [OCT]) assessment. Ophthalmologic evaluation may also provide prognostic factors for recovery and, when paired with postoperative evaluation, documents postoperative change. (Level III)[6] Automated static perimetry is recommended for early detection of visual field deficits, many of which the patient will be unaware of, in patients with nonfunctioning pituitary adenomas. Automated static perimetry, even with a standard III size test object, will often pick up subtle bitemporal visual field defects, less commonly homonymous defects, and, infrequently, arcuate defects characteristic of optic nerve pathology. (Level III)[6] Visual evoked potentials may be used to assess the optic nerves in nonfunctioning pituitary adenoma patients in a manner that may correlate with visual field deficits,

	but false positives and negatives may limit this testing to cases in which psychophysical areas, such as acuity and visual fields, cannot be assessed. (Level III) [6]
2. Preoperative hormone replacement	Routine endocrine evaluation of all anterior pituitary axes to assess for hypopituitarism is recommended because, beyond revealing a significant rate of deficits beyond the level of clinical suspicion for all pituitary axes, the cutoff values to initiate thyroid and adrenal replacement might be different in a patient with panhypopituitarism versus isolated deficiencies. (Level III) [9] Routine prolactin testing is recommended in all patients with suspected NFPA to rule out hypersecretion that might not be clinically suspected. (Level III) [9] Routine insulin-like growth factor 1 (IGF-1) evaluation is recommended in all patients with suspected NFPA to rule out growth hormone (GH) hypersecretion that might not be clinically suspected. (Level III) [9] Replacement for adrenal insufficiency and significant hypothyroidism is recommended in all patients preoperatively. (Level II) [9]
3. Surgery vs. non-surgery	Surgical resection is recommended as the primary treatment of symptomatic patients with NFPAs. (Level III) [7] There is insufficient evidence to make a recommendation for treatment versus observation of asymptomatic NFPAs. [7]
4. Endoscopic vs. microscopic transsphenoidal surgery 5. Medial cavernous sinus wall resection during surgery	Transsphenoidal microsurgery or endoscopic resection is recommended for symptomatic relief of nonfunctioning pituitary adenoma patients. (Level III) [8] The transsphenoidal approach is recommended for NFPA resection in ASA grade 1-3 elderly patients. (Level III) [8] Adequate bony exposure of the sphenoid and sellar regions is recommended to improve extent of NFPA resection. (Level III) [8] For select, invasive NFPAs with significant suprasellar, frontal, and/or temporal extension, the combined surgical strategy of transsphenoidal and transcranial approaches is recommended. (Level III) [8]
6. Intraoperative adjuncts	Although intraoperative MRI (low-field or high-field) helps improve immediate overall gross total resection of nonfunctioning pituitary adenomas, intraoperative MRI for estimating residual tumor is not recommended due to a reported variable false-positive rate. This false-positive rate may contribute to the higher rate of gross total resection occurring with intraoperative MRI (but at the cost of removing normal tissue) and underscores the importance of incorporating surgical experience in the interpretation of intraoperative MR imaging for surgical decision-making. (Level III) [8] There is insufficient evidence to recommend the use of neuronavigation as a useful adjunct for NFPA transsphenoidal surgery. [8] There is insufficient evidence to recommend the use of intrathecal saline or air introduction for suprasellar tumor delivery to augment NFPA resection. [8] There is insufficient evidence to recommend the use of perioperative CSF diversion to prevent postoperative CSF leak. [8] There is insufficient evidence to recommend the use of specific dural closure techniques to prevent postoperative CSF leak for NFPA resection[8]
7. Post-operative fluid restriction	There is insufficient evidence to make a recommendation on the detection and treatment of postoperative diabetes insipidus (DI). [4]

8. Postoperative care strategies aimed at decreasing length of stay and 30 day readmission	NEW-not included in 2016 guideline
9. Post-operative maintenance steroids	NEW-not included in 2016 guideline
10. Management of residual or recurrent NFPA	Radiosurgery and radiation therapy are recommended for treatment of residual or recurrent NFPAs to lower the risk of subsequent tumor progression. (Level II) [5] When no residual tumor is present or only a small intrasellar tumor exists postoperatively, serial neuroimaging studies are recommended. (Level II) [5] Radiosurgery using single-session doses of 12 or more Gy or radiation therapy with fractionated doses of 45 to 54 Gy is recommended for greater local tumor control rate of 90% or higher at 5 years after treatment. (Level II) [5] Assessment of NFPA proliferative index and ACTH staining to identify silent corticotrophic adenomas are recommended for providing guidance regarding the risk of adenoma progression and the benefit of earlier adjuvant radiation. (Level III) [5] Repeat resection is recommended for the treatment of symptomatic recurrent or residual NFPAs. (Level III) [5] Radiosurgery or radiation therapy for NFPAs is recommended when residual/recurrent sellar or parasellar tumor exists and(Level III) [5] the risk of a repeat resection is high.
11. Post-operative surveillance	**Radiologic evaluation** [4] The use of MRI with the addition of T2 and T1 Weighted Images with fat suppression sequences is recommended for radiologic follow-up of NFPAs after surgical or radiation treatment. (Level III) Long-term radiologic surveillance monitoring after surgical or radiation therapy treatment of NFPAs to evaluate for tumor recurrence or regrowth is recommended. There is insufficient evidence to make a recommendation on the length of time of surveillance. (Level III) It is recommended that patients who undergo radiologically proven gross total resection of the NFPA be followed less frequently than those undergoing subtotal resection. (Level III) It is recommended that the first radiologic study to evaluate the extent of resection of the NFPA be performed 3-4 months after surgical intervention. (Level III) There is insufficient evidence to make a recommendation regarding the frequency of radiologic surveillance follow-up after surgical or radiation treatment of patients with NFPAs.

	There is insufficient evidence to make a recommendation regarding the timing of initial radiologic follow-up after radiation therapy. **Endocrine evaluation** [4] Endocrine evaluation for pituitary dysfunction is recommended after surgery and/or radiation therapy in patients with NFPAs. (Level III) Postoperative evaluation of adrenal function on postoperative day 2, 6 weeks, and then 12 months after treatment is recommended to determine adrenal function in patients with NFPAs. (Level III) Corticosteroid supplementation in the perioperative period is recommended for NFPA patients with preoperative or immediate postoperative (day 2) hypocortisolemia. (Level III) Postoperative endocrinologic follow-up in patients with normal pituitary function beyond 1 year is not recommended, as it does not offer any further benefit. (Level III) Indefinite endocrinologic follow-up is recommended in all patients with abnormal pituitary function who undergo surgical resection of NFPAs. (Level III) Indefinite endocrine follow-up is recommended in patients who undergo radiation therapy for NFPAs for serial surveillance of their pituitary function. (Level III) Surveillance of serum sodium levels on the first 2 days after surgery and on postoperative days 7-8 is recommended to prevent symptomatic postoperative hyponatremia. (Level III) There is insufficient evidence to make a recommendation regarding the frequency of endocrinologic follow-up evaluation after surgery or radiation therapy. **Ophthalmic evaluation** [4] Postoperative ophthalmologic follow-up in patients undergoing surgical and/or radiation therapy treatment for NFPAs is recommended to evaluate the change in visual field and visual acuity postoperatively. There is insufficient evidence to make a recommendation on the length of time for this surveillance and the frequency. There is insufficient evidence to make a recommendation on how to integrate radiologic, ophthalmologic, and endocrinologic follow-up after surgical resection or radiation treatment of patients with NFPAs.
12. Post-operative hormone supplementation	NEW, not included in 2016 guideline

Summary of Selection Criteria Assessment

For this important topic with clinical uncertainty around management, we found multiple systematic reviews that covered some but not all of the questions, interventions and outcomes of interest. In addition, the reviews had a diversity of methods, inclusion criteria, and search dates which would pose a challenge to consolidate to inform a single guideline. We found studies that addressed most questions, with 1-6 studies per question. While a new systematic review is feasible, considering the large evidence base already identified in the previous review informing

the AANS/CNS guideline, if funded AHRQ should consider constraining the scope to ensure feasibility of completion under contractual timelines. Options include focusing on high-priority or controversial areas or commissioning multiple systematic reviews.

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Appendix A: Methods

We assessed the 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 conducted a search for existing systematic reviews. We searched for high-quality, completed or in-process evidence reviews published in the last three years August 2019 to August 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 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/

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 Medline search of primary literature published within the last five years from August 2016 through August 2022. We reviewed the entire search yield for relevance.

Search Strategies

Question 1a

(pituitary OR Pituitary Neoplasms[mesh]) AND adenomas AND (nonfunction* OR "non-functional" OR "non-functioning") AND ((computed tomography) OR Tomography, X-Ray Computed[mesh] OR "computerized tomography" OR "CT scan" OR "CT scans" OR Tomography, Emission-Computed, Single-Photon[mesh] OR "single photon emission computed tomography" OR "single photon emission computerized tomography" OR "single photon emission computer assisted tomography" OR "single photon emission CT scan" OR "single photon emission CT scans" OR "SPECT" OR Positron-Emission Tomography[mesh] OR "PET

scan” OR “PET scans” OR “positron-emission tomography” OR Diagnostic Imaging [Mesh:NoExp]) AND (Systematic Review[pt] OR Meta-Analysis[pt] AND Clinical Study[pt])
[3 citations retrieved. Only 1 citation when limiting to Systematic Reviews and Meta-Analysis.]

Question 1b
(pituitary OR Pituitary Neoplasms[mesh]) AND adenomas AND (nonfunction* OR “non-functional” OR “non-functioning”) AND (“visual assessment” OR “visual assessments” OR “ophthalmologic examination” OR “ophthalmologic examinations” OR Diagnostic Techniques, Ophthalmological[mesh] OR “ophthalmological diagnostic techniques” OR “ophthalmologic diagnostics” OR “optical coherence tomography” OR “OCT tomography” OR Tomography, Optical Coherence[mesh] OR “automated static perimetry”) AND (Systematic Review[pt] OR Meta-Analysis[pt] OR Clinical Study[pt])
[2 citations retrieved.]

Question 2
(pituitary OR Pituitary Neoplasms[mesh]) AND adenomas AND (nonfunction* OR “non-functional” OR “non-functioning”) AND (Preoperative Care[mesh] OR preoperative) AND (hormone replacement) AND (Systematic Review[pt] OR Meta-Analysis[pt] OR Clinical Study[pt])
[No citations retrieved.]

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(pituitary OR Pituitary Neoplasms[mesh]) AND adenomas AND (nonfunction* OR “non-functional” OR “non-functioning”) AND (Preoperative Care[mesh] OR preoperative) AND (hormone replacement)
[7 citations retrieved. Did not limit by publication type.]

Question 3
(pituitary OR Pituitary Neoplasms[mesh]) AND adenomas AND (nonfunction* OR “non-functional” OR “non-functioning”) AND surgery AND (Systematic Review[pt] OR Meta-Analysis[pt])
[17 citations retrieved. Including Clinical Study[pt] retrieves 33 citations.]

Question 4
(pituitary OR Pituitary Neoplasms[mesh]) AND adenomas AND (nonfunction* OR “non-functional” OR “non-functioning”) AND ("transsphenoidal surgery"[All Fields] OR "transsphenoidal surgeries"[All Fields]) AND (endoscopic OR microscopic OR endoscopy OR microscopy) AND (Systematic Review[pt] OR Meta-Analysis[pt] OR Clinical Study[pt])
[9 citations retrieved.]

Question 5
(pituitary OR Pituitary Neoplasms[mesh]) AND adenomas AND (nonfunction* OR “non-functional” OR “non-functioning”) AND (resection AND medial AND (cavernous sinus)) AND (Systematic Review[pt] OR Meta-Analysis[pt] OR Clinical Study[pt])
[No citations retrieved.]

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(pituitary OR Pituitary Neoplasms[mesh]) AND adenomas AND (nonfunction* OR “non-functional” OR “non-functioning”) AND (resection AND medial AND (cavernous sinus))
[3 citations retrieved. Did not limit by publication type.]

Question 6a
(pituitary OR Pituitary Neoplasms[mesh]) AND adenomas AND (nonfunction* OR “non-functional” OR “non-functioning”) AND (Intraoperative Care[mesh] OR Intraoperative Period[mesh] OR intraoperative) AND antibiotics
[No citations retrieved.]

Question 6b
(pituitary OR Pituitary Neoplasms[mesh]) AND adenomas AND (nonfunction* OR “non-functional” OR “non-functioning”) AND (Intraoperative Care[mesh] OR Intraoperative Period[mesh] OR intraoperative) AND steroids
[3 citations retrieved. No publication type limits.]

Question 6 c
(pituitary OR Pituitary Neoplasms[mesh]) AND adenomas AND (nonfunction* OR “non-functional” OR “non-functioning”) AND ("CSF diversion" OR "Cerebrospinal fluid diversion")
[1 citation retrieved. No publication type limits.]

Question 6d
(pituitary OR Pituitary Neoplasms[mesh]) AND adenomas AND (nonfunction* OR “non-functional” OR “non-functioning”) AND (Intraoperative Care[mesh] OR Intraoperative Period[mesh] OR intraoperative) AND ((magnetic resonance) OR MRI) AND (Systematic Review[pt] OR Meta-Analysis[pt] OR Clinical Study[pt])
[2 citations retrieved.]

Comment: Removing publication type limits retrieves 27 additional citations, some of which appear relevant.

Question 6e
(pituitary OR Pituitary Neoplasms[mesh]) AND adenomas AND (nonfunction* OR “non-functional” OR “non-functioning”) AND (Intraoperative Care[mesh] OR Intraoperative Period[mesh] OR intraoperative) AND fluoroscopy
[No citations retrieved.]

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(pituitary OR Pituitary Neoplasms[mesh]) AND adenomas AND (nonfunction* OR “non-functional” OR “non-functioning”) AND (Intraoperative Care[mesh] OR Intraoperative Period[mesh] OR intraoperative **OR surgery**) AND fluoroscopy
[No citations retrieved.]

Comment: 2 citations retrieved when not using publication date limits (2001 and 2016 articles).

Question 6f
(pituitary OR Pituitary Neoplasms[mesh]) AND adenomas AND (nonfunction* OR “non-functional” OR “non-functioning”) AND (Fluorescein Angiography[mesh] OR “fluorescence visualization”)
[1 citation retrieved. No publication type limits.]
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(pituitary OR Pituitary Neoplasms[mesh]) AND adenomas AND (nonfunction* OR "non-functional" OR "non-functioning") AND ((fluorescein angiography) OR (fluorescence visualization))
[9 citations retrieved. No publication type limits.]

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 U.S.?	Yes. Treatments for non-functioning pituitary adenomas are available in the US.
1b. Is the nomination a request for an evidence report?	The nominator is interested in guidance to assist in healthcare decision-making. Such guidance would ideally be supported by an evidence review.
1c. Is the focus on effectiveness or comparative effectiveness?	Yes. The nominator is interested in effectiveness and harms of treatment.
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	Pituitary adenomas comprise approximately 10-20% of intracranial tumors. Non-functioning pituitary adenomas (NFPAs) are benign tumors not associated with clinical evidence of hormonal hypersecretion. They represent between 22% to 54% of all pituitary adenomas.
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes, this affects health care decision-making around management and avoidance of interventions if not needed.
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
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	We identified multiple systematic reviews that partly cover the nomination scope. The reviews had a diversity of methods, inclusion criteria, and search dates which would pose a challenge to consolidate to inform a single guideline.
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)?	Guidance is available but since the 2016 AANS/CNS guideline newer approaches are in use, leading to clinical uncertainty about optimal management.
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 because of the use of newer interventions.
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 identified 20 studies relevant to the 12 questions of this nomination, with a range of 0-6 studies per question. Likely a review would be large, considering the large number of studies identified in support of the 2016 AANS/CNS guideline.
6. Value	

6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change	Yes
6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)	The nominator plans to develop a guideline based on the AHRQ systematic review. They are currently partnering with AHRQ on a systematic review.