

| 6.01.47 | Functional Magnetic Resonance Imaging of the Brain | | |
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| Section: | 6.0 Radiology | Page: | Page 1 of 16 |

Policy Statement

- I. Functional magnetic resonance imaging may be considered **medically necessary** in the preoperative evaluation of individuals with refractory epilepsy or brain tumors who are candidates for neurosurgery when the lesion is in close proximity to an eloquent area of the brain (e.g., controlling verbal or motor function) and testing is expected to have an important role in assessing the spatial relation between the lesion and eloquent brain area.
- II. Functional magnetic resonance imaging is considered **investigational** for all other applications.

NOTE: Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

Policy Guidelines

CPT coding specific to functional magnetic resonance imaging differentiates between circumstances when a provider does all of the functional testing and when the testing is done by other professionals.

- **70554:** Magnetic resonance imaging, brain, functional MRI; including test selection and administration of repetitive body part movement and/or visual stimulation, not requiring physician or psychologist administration
- **70555:** Magnetic resonance imaging, brain, functional MRI; requiring physician or psychologist administration of entire neurofunctional testing

The provider who administers the testing would use the following CPT code:

- **96020:** Neurofunctional testing selection and administration during noninvasive imaging functional brain mapping, with test administered entirely by a physician or other qualified health care professional (i.e., psychologist), with review of test results and report

Description

Functional magnetic resonance imaging (fMRI) is a noninvasive method for localizing areas of brain function and has been used for the presurgical evaluation of eloquent brain areas. Using this method, images are collected while specific activities are performed to assist in the localization of critical cortical areas, as well as the evaluation of language lateralization. Functional MRI is also being investigated in combination with diffusion tensor imaging and electroencephalography to identify seizure focus.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

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Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Several fMRI hardware (e.g., fMRI Hardware System; NordicNeuroLab AS) and fMRI software packages (e.g., BrainAcquireRx™/BrainProcessRx™ Data Suite; Kyron Clinical Imaging) have been cleared for marketing by the U.S. Food and Drug Administration through the 510(k) process for use with an MRI scanner to perform fMRI. FDA product code: LNH.

Rationale

Background

Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) is an activation method that uses sequences based on T2-weighted blood oxygen level-dependent response. These studies are often done on magnetic resonance scanners with field strengths of 1.5 tesla or greater. The interhemispheric difference between activated volumes in the left and right hemispheric regions of interest is calculated as the laterality index, which ranges from -1 to 1. A positive laterality index is considered left-dominant, while a negative laterality index is right-dominant. Laterality indexes determined by fMRI may be derived for several different functional areas (regions of interest) that include either the Broca area (language production) or the Wernicke area (language comprehension). Various thresholds (egg, -0.1 to +0.1, or -0.5 to +0.5) have been proposed to differentiate laterality from bilaterality. Bilateral activation patterns can result from the detection of the language-associated but not the language-essential cortex. Therefore, bilateral activation is not necessarily indicative of a bilateral distribution of the language-essential cortex and may be task-dependent. In addition, sensitivity and specificity may change with the application of different statistical thresholds.

Simultaneous electroencephalography (EEG) and fMRI are being investigated for the localization of seizures. Simultaneous EEG-fMRI combines the temporal resolution of EEG and the spatial resolution of fMRI. Simultaneous EEG-fMRI may allow for the detection of cerebral hemodynamic changes associated with seizures and interictal epileptiform discharges that are identified on scalp EEG. Another potential use of simultaneous EEG-fMRI is to facilitate the implantation strategy of invasive subdural electrodes.

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more

applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Presurgical Mapping of the Eloquent Cortex

Clinical Context and Test Purpose

Localization of certain areas of the brain (e.g., speech centers) before neurologic surgery for seizure disorders or resection of brain tumors is important because failure to do so can result in damage to language and motor centers; e.g., 25% to 60% of patients who undergo left anterior temporal lobectomy develop dysnomia (language/naming difficulties).

Finding these certain areas of the brain, often called "eloquent" areas, involves the use of the Wada test and direct electrical stimulation. Both the test and the stimulation are fairly invasive and require the expertise of various specialists. Direct intracortical electrical stimulation involves functional mapping of the exposed cortex with electrodes, which may elicit a motor or verbal response including the arrest of speech, random answering, or perseveration to stimulation. The Wada test is an inactivating method that blocks the function of 1 hemisphere by injecting amobarbital into the carotid artery, allowing functional testing of the reserve capacity of the nonanesthetized hemisphere.

The purpose of functional magnetic resonance imaging (fMRI) in individuals who have epilepsy or brain tumors is to provide a presurgical mapping of the eloquent cortex to minimize potential damage to language and motor centers during brain surgery.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with epilepsy or brain tumors who are undergoing presurgical mapping of the eloquent cortex.

Interventions

The intervention being considered is fMRI.

Comparators

The following tools and tests are currently being used to make decisions about preoperative management of brain surgery: the Wada test and intracortical mapping to evaluate postoperative language changes.

Outcomes

The general outcome of interest is clinical validity (e.g., sensitivity, specificity, predictive values). The primary outcomes of interest for clinical utility are morbid events (e.g., dysnomia), functional outcomes (e.g., change in the treatment plan, reduction of surgical time), and quality of life (QoL).

Functional MRI would be performed before surgery for mapping of the eloquent cortex. Determining clinical utility for fMRI would require longer-term follow-up.

Study Selection Criteria

For the evaluation of the clinical validity of fMRI, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Wada Testing as the Reference Standard

Systematic Review

Dym et al (2011) reported on a meta-analysis comparing fMRI-determined lateralization of language function with the Wada test.¹ Twenty-three studies (N=442) were included in the meta-analysis. Most studies did not specify whether evaluators were blinded to the results of the other test. With the Wada test as the reference standard, fMRI had a sensitivity of 84% and specificity of 88%. Specificity was significantly higher with the use of a word generation task (96%) than with a semantic decision task (70%). This analysis may have oversimplified the role of fMRI, which, in addition to providing information on hemispheric dominance, provides information on the localization of language and motor areas in relation to the tumor or lesion. It is also unlikely that current fMRI protocols use a single task (e.g., word generation) to evaluate the eloquent cortex. Tables 1 and 2 summarize the characteristics and results of the relevant systematic reviews.

Table 1. Characteristics of Systematic Reviews Assessing Clinical Validity With Wada Testing as the Reference Standard

| Study | Dates | Trials | Participants | N (Range) | Design | Duration |
|-------------------------------|-----------|--------|---|-----------|--------|----------|
| Dym et al (2011) ¹ | 1996-2008 | 23 | Patients who preoperatively underwent both a Wada test and fMRI | 442 (NR) | NR | NR |

fMRI: functional magnetic resonance imaging; NR: not reported.

Table 2. Results of Systematic Reviews Assessing Clinical Validity With Wada Testing as the Reference Standard

| Study | Sensitivity, % | Specificity, % | Sensitivity With a Word Generation Task, % | Sensitivity With a Semantic Decision Task, % |
|-------------------------------------|----------------|----------------|--|--|
| Dym et al (2011)¹ | | | | |
| fMRI | 83.5 | 88.1 | 95.6 | 79.5 |
| 95% CI | 80.2 to 86.7 | 87.0 to 89.2 | 93.9 to 97.3 | 66.5 to 72.5 |

CI: confidence interval; fMRI: functional magnetic resonance imaging.

Intracortical Mapping as the Reference Standard

Systematic Reviews

Weng et al (2018) published a systematic review and meta-analysis of studies directly comparing fMRI with direct cortical stimulation.² Ten studies were selected; 3 reported data on a per-patient basis and 7 on a per-tag basis (i.e., each direct cortical stimulation site [tag] was considered a separate data point across all patients). Per patient, the pooled sensitivity and specificity of fMRI were 44% and 80%, respectively; per tag, sensitivity and specificity were 67% and 55%, respectively. The study was limited by (1) bias inherent to the design of imaging studies, (2) heterogeneity across included studies; and (3) the lack of precision in sensitivity and specificity estimates. Tables 3 and 4 summarize the characteristics and results of the relevant systematic reviews.

Table 3. Characteristics of Systematic Reviews Assessing Clinical Validity With Intracortical Mapping as the Reference Standard

| Study | Dates | Trials | Participants | N (Range) | Design | Duration |
|--------------------------------|-----------|--------|--|---------------|--------|----------|
| Weng et al (2018) ² | 1997-2016 | 10 | Patients with brain tumors near the eloquent center undergoing resection | 214 (5 to 44) | NR | NR |

NR: not reported.

Table 4. Results of Systematic Reviews Assessing Clinical Validity With Intracortical Mapping as the Reference Standard

| Study | Sensitivity (95% CI), % | Specificity (95% CI), % |
|--------------------------------------|-------------------------|-------------------------|
| Weng et al (2018)² | | |
| Per patient | 44 (14 to 78) | 80 (54 to 93) |
| Per tag | 67 (51 to 80) | 55 (25 to 82) |

CI: confidence interval.

Prospective Studies

Bizzi et al (2008) reported on the sensitivity and specificity of fMRI for mapping language and motor functions using intraoperative intracortical mapping as the reference standard.³ Thirty-four consecutive patients with a focal mass adjacent to the eloquent cortex were studied. A site-by-site comparison between fMRI and intracortical mapping was performed with verb generation or finger tapping of the contralateral hand. A total of 251 sites were tested, 141 in patients evaluated with verb generation and 110 in patients evaluated with finger tapping. For hand motor function alone, the sensitivity and specificity were 88% and 87%, respectively. For language, sensitivity and specificity were 80% and 78%, respectively. Functional MRI for the Broca area showed 100% sensitivity and 68% specificity, while fMRI for the Wernicke area showed 64% sensitivity and 85% specificity. The sensitivity of fMRI decreased from 93% for World Health Organization grade II gliomas to 65% for grade IV gliomas.

In another study, Medina et al (2005), fMRI was concordant with direct electrical stimulation in 23 (88%) of 26 cases.⁴

Tables 5 and 6 summarize the characteristics and results of the relevant prospective studies.

Table 5. Characteristics of Observational Studies Assessing Clinical Validity With Intracortical Mapping as the Reference Standard

| Study | Study Type | Country | Dates | Participants | Treatment | Comparator | Follow-Up |
|---------------------------------------|-------------|---------|-----------|--|-------------|--|-----------|
| Bizzi et al (2008)³ | Prospective | Italy | 2002-2007 | Patients with a focal mass in or adjacent to the eloquent cortex of the language or motor system | fMRI (n=34) | Intraoperative electrocortical mapping (same individuals as treatment) | NR |

fMRI: functional magnetic resonance imaging; NR: not reported.

Table 6. Results of Observational Studies Assessing Clinical Validity With Intracortical Mapping as the Reference Standard

| Study | Sensitivity (95% CI), % | Specificity (95% CI), % |
|---------------------------------------|-------------------------|-------------------------|
| Bizzi et al (2008)³ | | |
| Overall | 80 (68 to 89) | 78 (67 to 86) |
| Broca area | 100 (78 to 100) | 68 (43 to 87) |
| Wernicke area | 64 (42 to 82) | 85 (65 to 96) |

CI: confidence interval.

Postoperative Language Changes as the Reference Standard

Janecek et al (2013) reported that 32 (14%) of 229 epilepsy patients showed discordance between fMRI and Wada testing, and that discordance was highest when either test indicated that language was bilateral.^{5,6} For 10 patients who had discordant results, underwent left temporal lobe surgery, and had preoperative and 6-month postoperative language testing, fMRI was more accurate in predicting naming outcomes in 7 patients; the Wada test was more accurate in 2 patients, and the 2 tests were equally accurate in 1 patient.⁶ Results from this small prospective study suggested that fMRI may be more accurate than the Wada test in predicting postsurgical language outcomes.

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Sabsevitz et al (2003) reported on a series of 24 consecutive patients who underwent both fMRI and Wada testing before left anterior temporal lobectomy for seizure disorders.⁷ While both tests were predictive of language changes, in this study, fMRI had a sensitivity of 100% and specificity of 57%, while results for the Wada test were 100% and 43%, respectively.

Tables 7 and 8 summarize the characteristics and results of the relevant retrospective studies.

Table 7. Characteristics of Observational Studies Assessing Clinical Validity With Postoperative Language Changes as the Reference Standard

| Study | Study Type | Country | Dates | Participants | Treatment | Comparator | FU |
|-------------------------------------|---------------|---------|-----------|---|--------------|---------------------------------|----|
| Janecek et al (2013) ^{5,6} | Retrospective | U.S. | 1993-2009 | Patients with epilepsy undergoing L-ATL | fMRI (n=229) | Wada testing (same individuals) | NR |
| Sabsevitz et al (2003) ⁷ | Retrospective | U.S. | NR | Patients with epilepsy undergoing L-ATL | fMRI (n=24) | Wada testing (same individuals) | NR |

fMRI: functional magnetic resonance imaging; FU: follow-up; L-ATL: left anterior temporal lobectomy; NR: not reported.

Table 8. Results of Observational Studies Assessing Clinical Validity With Postoperative Language Changes as the Reference Standard

| Study | Sensitivity, % | Specificity, % | PPV, % | Instances Where Test Had Greater Accuracy |
|-------------------------------------|----------------|----------------|--------|---|
| Janecek et al (2013) ^{5,6} | | | | |
| fMRI | | | 7 | |
| Wada | | | 2 | |
| Equivalent | | | 1 | |
| Sabsevitz et al (2003) ⁷ | | | | |
| fMRI | 100 | 57 | 63 | |
| Wada | 100 | 43 | 56 | |

fMRI: functional magnetic resonance imaging; PPV: positive predictive value.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs). No RCTs assessing the clinical utility of presurgical mapping of the eloquent cortex were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Systematic Reviews

Luna et al (2021) performed a systematic review and meta-analysis involving 68 observational studies that evaluated the overall postoperative morbidity among patients with brain tumors (N=3280) by using preoperative fMRI mapping versus surgery without this tool or with use of standard neuronavigation.⁸ Results revealed that functional deterioration was less likely to occur after a surgical procedure among patients with preoperative fMRI mapping (odds ratio [OR], 0.25; 95% CI, 0.12 to 0.53; p<.001) and postsurgical Karnofsky performance status scores were higher in

patients who underwent preoperative fMRI mapping ($p=.004$). Additionally, craniotomies for tumor resection performed with preoperative fMRI were associated with a reduced pooled adverse event rate as compared to those who did not undergo fMRI mapping (11% vs. 21%).

Prospective Studies

Wengenroth et al (2011) compared the localization of eloquent tumor-adjacent brain areas using fMRI or structural MRI in 77 consecutive patients with brain tumors of the central region.⁹ The motor hand area was localized in 76 (99%) of 77 patients by fMRI and in 66 (86%) of 77 patients by structural MRI. Motor areas of the foot and tongue were investigated in 70 patients and could be identified by fMRI in 96% (tongue representation) and 97% (foot representation) of patients. Morphologic landmarks for the motor hand area were found to be reliable in the unaffected hemisphere (97% success rate) but not in the tumor-affected hemisphere (86% success rate). After consideration of the clinical condition, tumor etiology, and fMRI results, the decision for neurosurgery was made in 52 (68%) patients. In 16 patients, the decision against surgery was based mainly on fMRI results, which provided evidence that major neurologic impairments would be expected after surgery. Functional MRI-based risk assessment before surgery had a high correlation with the clinical outcome and corresponded in 46 (88%) of 52 operative patients who had functional improvement or only minimal deficits postoperatively.

Petrella et al (2006) reported on the impact of fMRI preoperatively on 39 consecutive patients with brain tumors.¹⁰ Treatment plans differed in 19 patients after fMRI, with a more aggressive approach recommended after imaging in 18 patients. However, the impact of the altered treatment plans on outcomes was not assessed. Functional MRI resulted in reduced surgical time for 22 patients; it also led to decisions to perform craniotomy in 13 patients in whom less invasive approaches had been initially planned.

Medina et al (2005) evaluated 60 consecutive patients preoperatively.⁴ Language mapping was performed in 53 patients, motor mapping was done in 33, and visual mapping was in 7. The fMRI study revealed a change in anatomic location or lateralization of language reception (Wernicke) in 28% of patients and in language expression (Broca) in 21% of patients. In 38 (63%) patients, fMRI helped to avoid further studies, including the Wada test. In 31 (52%) and 25 (42%) patients, intraoperative mapping and surgical plans, respectively, were altered because of fMRI results. Others have reported that successful preoperative fMRI decreased intracortical mapping time from about 50 to 30 minutes and total operating time from an average of 8.5 to about 7 hours.¹¹

Tables 9 and 10 summarize the characteristics and results of the relevant prospective and retrospective studies.

Table 9. Characteristics of Observational Studies Assessing Clinical Utility

| Study | Study Type | Country | Dates | Participants | Treatment | Comparator | Follow-Up |
|--------------------------------------|---------------|---------|-----------|--|-------------|----------------|-----------|
| Wengenroth et al (2011) ⁹ | Retrospective | Germany | NR | Patients with brain tumors of the central region | fMRI | Structural MRI | NR |
| Petrella et al (2006) ¹⁰ | Prospective | U.S. | 2004-2005 | Patients referred for possible tumor resection | fMRI (n=39) | None | NR |
| Medina et al (2005) ⁴ | Prospective | U.S. | 2001-2003 | Patients who received language mapping | fMRI (n=53) | None | NR |

fMRI: functional magnetic resonance imaging; ; MRI: magnetic resonance imaging; NR: not reported.

Table 10. Results of Observational Studies Assessing Clinical Utility

| Study | Change in Lateralization, % | | Change in Treatment Plans, n (%) | Localization of Motor Hand Area, n/N (%) | | Identification of Motor Areas, n/N (%) |
|--|-----------------------------|------------|----------------------------------|--|------------|--|
| | Wernicke Area | Broca Area | | Foot | Tongue | |
| Wengenroth et al (2011)⁹ | | | | | | |
| fMRI | | | 76/77 (99) | | 68/70 (97) | 67/70 (96) |
| Structural MRI | | | 66/77 | | NR | NR |
| p | | | <.002 | | NR | NR |
| Petrella et al (2006) ¹⁰ | | 19 (49) | | | | |
| 95% CI | | 33 to 64.4 | | | | |
| Medina et al (2005) ⁴ | 28 | 21 | 42 | | | |

CI: confidence interval; fMRI: functional magnetic resonance imaging; MRI: magnetic resonance imaging; NR: not reported.

Case Series

Use of preoperative fMRI in combination with intraoperative MRI has been reported to permit more complete resection of tumors without affecting eloquent neurologic function. Hall et al (2009), in a case series of 29 patients, performed preoperative fMRI to identify and coregister areas of brain activation for motor, speech, and short-term memory before brain tumor resection.¹² Areas of brain activation that were identified preoperatively were superimposed on 1.5- or 3-tesla scanners during the operative procedure, allowing the surgeon to avoid brain areas where damage would result in a postoperative neurologic deficit. Postoperative neurologic morbidity was reported to be low in the 27 patients in whom a fMRI-guided tumor resection was possible. Tables 11 and 12 summarize the characteristics and results of the relevant case series.

Table 11. Characteristics of Case Series Assessing Clinical Utility

| Study | Country | Participants | Follow-Up |
|---------------------------------|---------|--|-----------|
| Hall et al (2009) ¹² | U.S. | Patients receiving preoperative fMRI before brain resection (n=29) | NR |

fMRI: functional magnetic resonance imaging; NR: not reported.

Table 12. Results of Case Series Assessing Clinical Utility

| Study | fMRI Accuracy, % | Transient Neurologic Deficits Resolved Within 1 mo, n (%) | Adverse Events |
|---------------------------------|------------------|---|----------------|
| Hall et al (2009) ¹² | 100% | 7 (26) | 0 |

fMRI: functional magnetic resonance imaging.

Section Summary: Presurgical Mapping of the Eloquent Cortex

The diagnostic accuracy of fMRI has been compared with the Wada test and with intracortical mapping to evaluate postoperative language changes. Sensitivity and specificity depend on the specific task but have been shown to be predictive of hemispheric dominance in a substantial percentage of patients. In a study that used postoperative language changes as the reference standard, both fMRI and the Wada test had high sensitivity and moderate specificity. When results were discordant between tests, fMRI was slightly more accurate. Evidence on health outcomes has suggested that, although bilateral activation patterns in fMRI cannot be conclusively interpreted, fMRI in patients who are to undergo neurosurgery for seizures or brain tumors may help to define eloquent areas, reduce surgical time, and alter treatment decisions.

Localization of Seizure Focus With Simultaneous Electroencephalography and Functional MRI Clinical Context and Test Purpose

The purpose of simultaneous electroencephalography (EEG) and fMRI in individuals who have epilepsy is to provide a presurgical mapping of areas of seizure focus to isolate target areas and to minimize potential damage to language and motor centers during brain surgery.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with epilepsy being evaluated for localization of seizure focus.

Interventions

The intervention of interest is simultaneous EEG and fMRI.

Comparators

The following test is currently being used to make decisions about managing seizure focus localization: intracranial EEG. Simultaneous EEG-fMRI may allow for the detection of cerebral hemodynamic changes associated with seizures and interictal epileptiform discharges that are identified on scalp EEG.

Outcomes

The outcome of interest is clinical validity (e.g., sensitivity, specificity, predictive values). The primary outcomes of interest for clinical utility are morbid events, functional outcomes, and QoL.

EEG-fMRI would be performed before surgery for localization of seizure focus. Determining clinical utility for EEG-fMRI would require longer-term follow-up.

Study Selection Criteria

For the evaluation of the clinical validity of simultaneous EEG-fMRI, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Observational Studies

Some small studies have evaluated surgical outcomes following the use of simultaneous EEG and fMRI to identify seizure focus. For example, van Houdt et al (2013) retrospectively compared presurgical EEG-fMRI with invasive electrocorticographic data and surgical outcomes in 16 patients.¹³ In each patient, at least 1 of the simultaneous EEG-fMRI areas was concordant with an interictally active electrocorticographic anatomic brain region. For areas covered with subdural grids, 76% of the blood oxygen level-dependent (BOLD) regions were concordant with interictally active electrocorticographic electrodes. However, due to limited spatial sampling, 51% of the active BOLD regions were not covered with electrodes. Simultaneous EEG-fMRI BOLD areas included the resected area in 93% of cases.

Moeller et al (2009) reported on an EEG-fMRI study for the workup of 9 patients with refractory frontal lobe epilepsy who did not have a clear lesion or seizure focus.¹⁴ The number of interictal discharges recorded during the fMRI session ranged from 9 to 744. There was concordance between

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spike localization and positive fMRI response in 8 patients; surgery was subsequently performed on 2 patients, 1 of whom was seizure-free at the time of publication.

Zijlmans et al (2007) assessed the preoperative localization of epileptic focus in 29 complex patients (unclear focus and/or multifocality) not deemed to be candidates for epilepsy surgery.¹⁵ In 8 (28%) patients, a robust fMRI response was considered to be topographically related to interictal electrical discharges. As a result of the testing, 4 (14%) patients were considered to be surgical candidates, and 1 of the 4 had undergone surgery at the time of publication.

Research is ongoing to improve the identification of seizure focus with simultaneous EEG-fMRI, including occasions without intrascaner interictal epileptic discharges.^{16,17}

Tables 13 and 14 summarize the characteristics and results of the relevant prospective and retrospective studies.

Table 13. Characteristics of Observational Studies Assessing Localization of Seizure Focus With Simultaneous EEG and fMRI

| Study | Study Type | Country | Dates | Participants | Treatment | Follow-Up |
|--------------------------------------|---------------|-------------|-----------|--|----------------------------|-----------|
| van Houdt et al (2013) ¹³ | Retrospective | Netherlands | 2007-2011 | Patients with refractory epilepsy | EEG-fMRI (n=16) | NR |
| Moeller et al (2009) ¹⁴ | Retrospective | Canada | 2007-2008 | Patients with nonlesional frontal lobe epilepsy | EEG-fMRI (n=9) | NR |
| Zijlmans et al (2007) ¹⁵ | Prospective | Netherlands | 2001-2006 | Surgical candidates considered ineligible because of an unclear focus and/or multifocality | EEG-correlated fMRI (n=29) | NR |

EEG: electroencephalography; fMRI: functional magnetic resonance imaging; NR: not reported.

Table 14. Results of Observational Studies With Simultaneous EEG and fMRI

| Study | IED Sets With Significant BOLD Response, n/N | Patients Considered for Surgery | Range of IEDs Recorded During fMRI | Concordance between Spike and Positive fMRI Response | Subsequent Localization and Positive fMRI Response | BOLD Regions Concordant With ECoG | Interictally Active ECoG Regions Missed | Brain Regions Correctly Identified as Inactive |
|--------------------------------------|--|---------------------------------|------------------------------------|--|--|-----------------------------------|---|--|
| van Houdt et al (2013) ¹³ | | | | | | 76% | 29% | 68% |
| Moeller et al (2009) ¹⁴ | | 744 | 8 patients | 2 patients | | | | |
| Zijlmans et al (2007) ¹⁵ | 26/46 | 4 (14%) | | | | | | |

BOLD: blood oxygen level-dependent; ECoG: electrocorticography; EEG: electroencephalography; fMRI: functional magnetic resonance imaging; IED: interictal epileptic discharge.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing the clinical utility of simultaneous EEG-fMRI for localization of seizure focus were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of simultaneous EEG-fMRI for isolating seizure focus has not been established, a chain of evidence supporting the clinical utility of this indication cannot be constructed.

Section Summary: Localization of Seizure Focus With Simultaneous Electroencephalography and Functional Magnetic Resonance Imaging

Several small studies identified have evaluated seizure focus with simultaneous EEG plus fMRI. This is a relatively recent area of research, which has followed the development of MRI-compatible EEG electrodes. Current research is attempting to improve the identification of seizure focus with this technique, particularly when there are no interictal epileptic discharges during the fMRI session. There are very few data on the effect of this procedure on health outcomes.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Neurology

In 2017, the American Academy of Neurology (AAN) published a guideline on the use of fMRI in the presurgical evaluation of patients with epilepsy.¹⁸ This guideline was reaffirmed on February 25, 2023. Table 15 presents a summary of the recommendations within this guideline.

Table 15. Summary of AAN Practice Guideline on the Use of fMRI in the Presurgical Evaluation of Patients With Epilepsy

| Recommendation | Evidence rating |
|---|----------------------|
| The use of fMRI may be considered an option in lateralizing language functions in place of the intracarotid amobarbital procedure (i.e., the Wada test) in patients with medial temporal lobe epilepsy, temporal epilepsy in general, or extratemporal epilepsy, although patients should be carefully advised of the risks and benefits of fMRI versus intracarotid amobarbital procedure during discussions of modality choice in each individual case. | Weak Insufficient |
| The evidence is unclear for patients with temporal neocortical epilepsy or temporal tumors | |
| The use of fMRI may be considered an option for predicting post surgical language outcomes after anterior temporal lobe resection for the control of temporal lobe epilepsy. | Weak |

| Recommendation | Evidence rating |
|---|-----------------|
| The use of fMRI may be considered as an option to lateralize memory functions in place of the intracarotid amobarbital procedure in patients with medial temporal lobe epilepsy. | Weak |
| Presurgical fMRI of verbal memory or of language encoding should be considered as an option to predict verbal memory outcome in patients with epilepsy who are undergoing evaluation for left medial temporal lobe surgery. | Moderate |
| Presurgical fMRI using nonverbal memory encoding may be considered as a means to predict visuospatial memory outcomes in patients with epilepsy who are undergoing evaluation for temporal lobe surgery. | Weak |
| Presurgical fMRI may be used instead of the intracarotid amobarbital procedure for language lateralization in patients with epilepsy who are undergoing evaluation for brain surgery. However, when fMRI is used for this purpose, task design, data analysis methods, and epilepsy type need to be considered. Of particular importance for patients with lesional epilepsy is the fact that only small numbers of participants with variable lesion size/location were included in studies. | Weak |
| fMRI of language and verbal memory lateralization may be an alternative to intracarotid amobarbital procedure memory testing for prediction of verbal memory outcome in medial temporal lobe epilepsy. fMRI is not yet established as an alternative to the intracarotid amobarbital procedure for prediction of global amnesia in patients who have undergone anterior temporal lobe surgery. | Weak |

AAN: American Academy of Neurology; fMRI: functional magnetic resonance imaging.

The American College of Radiology et al

The American College of Radiology, American Society of Neuroradiology, and Society for Pediatric Radiology (revised 2022) jointly published practice parameters which state that "Functional magnetic resonance imaging (fMRI) using blood oxygen level-dependent imaging (BOLD) technique is a proven and useful tool for localizing eloquent cortex in relation to a focal brain lesion, such as neoplasm or vascular malformation."¹⁹ The primary indications for fMRI included "presurgical planning and operative risk assessment, assessment of the eloquent cortex [...] in relation to a tumor or another focal lesion, surgical planning (biopsy or resection), therapeutic follow-up, evaluation of preserved eloquent cortex, assessment of eloquent cortex and language lateralization for epilepsy surgery, assessment of radiation treatment planning and post-treatment evaluation of eloquent cortex, [and] assessment of cerebral vascular reactivity for consideration of revascularization procedures" ..

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 16.

Table 16. Summary of Key Trials

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|----------------|---|--------------------|-----------------|
| <i>Ongoing</i> | | | |
| NCT01534104 | Using Functional MRI and Diffusion Imaging of Eloquent Brain Areas to Optimize Brain Tumor Resection Planning | 145 | Jun 2023 |
| NCT02107989 | Noninvasive Pre-surgical Evaluation of Patients With Focal Epilepsy and Establishment of a Normative Imaging Database | 500 | Mar 2028 |

NCT: national clinical trial.

References

1. Dym RJ, Burns J, Freeman K, et al. Is functional MR imaging assessment of hemispheric language dominance as good as the Wada test?: a meta-analysis. *Radiology*. Nov 2011; 261(2): 446-55. PMID 21803921
2. Weng HH, Noll KR, Johnson JM, et al. Accuracy of Presurgical Functional MR Imaging for Language Mapping of Brain Tumors: A Systematic Review and Meta-Analysis. *Radiology*. Feb 2018; 286(2): 512-523. PMID 28980887
3. Bizzì A, Blasi V, Falini A, et al. Presurgical functional MR imaging of language and motor functions: validation with intraoperative electrocortical mapping. *Radiology*. Aug 2008; 248(2): 579-89. PMID 18539893
4. Medina LS, Bernal B, Dunoyer C, et al. Seizure disorders: functional MR imaging for diagnostic evaluation and surgical treatment--prospective study. *Radiology*. Jul 2005; 236(1): 247-53. PMID 15987978
5. Janecek JK, Swanson SJ, Sabsevitz DS, et al. Language lateralization by fMRI and Wada testing in 229 patients with epilepsy: rates and predictors of discordance. *Epilepsia*. Feb 2013; 54(2): 314-22. PMID 23294162
6. Janecek JK, Swanson SJ, Sabsevitz DS, et al. Naming outcome prediction in patients with discordant Wada and fMRI language lateralization. *Epilepsy Behav*. May 2013; 27(2): 399-403. PMID 23541860
7. Sabsevitz DS, Swanson SJ, Hammeke TA, et al. Use of preoperative functional neuroimaging to predict language deficits from epilepsy surgery. *Neurology*. Jun 10 2003; 60(11): 1788-92. PMID 12796532
8. Luna LP, Sherbaf FG, Sair HI, et al. Can Preoperative Mapping with Functional MRI Reduce Morbidity in Brain Tumor Resection? A Systematic Review and Meta-Analysis of 68 Observational Studies. *Radiology*. Aug 2021; 300(2): 338-349. PMID 34060940
9. Wengenroth M, Blatow M, Guenther J, et al. Diagnostic benefits of presurgical fMRI in patients with brain tumours in the primary sensorimotor cortex. *Eur Radiol*. Jul 2011; 21(7): 1517-25. PMID 21271252
10. Petrella JR, Shah LM, Harris KM, et al. Preoperative functional MR imaging localization of language and motor areas: effect on therapeutic decision making in patients with potentially resectable brain tumors. *Radiology*. Sep 2006; 240(3): 793-802. PMID 16857981
11. Xie J, Chen XZ, Jiang T, et al. Preoperative blood oxygen level-dependent functional magnetic resonance imaging in patients with gliomas involving the motor cortical areas. *Chin Med J (Engl)*. Apr 05 2008; 121(7): 631-5. PMID 18466684
12. Hall WA, Kim P, Truwit CL. Functional magnetic resonance imaging-guided brain tumor resection. *Top Magn Reson Imaging*. Jan 2009; 19(4): 205-12. PMID 19148037
13. van Houdt PJ, de Munck JC, Leijten FSS, et al. EEG-fMRI correlation patterns in the presurgical evaluation of focal epilepsy: a comparison with electrocorticographic data and surgical outcome measures. *Neuroimage*. Jul 15 2013; 75: 238-248. PMID 23454472
14. Moeller F, Tyvaert L, Nguyen DK, et al. EEG-fMRI: adding to standard evaluations of patients with nonlesional frontal lobe epilepsy. *Neurology*. Dec 08 2009; 73(23): 2023-30. PMID 19996077
15. Zijlmans M, Huiskamp G, Hersevoort M, et al. EEG-fMRI in the preoperative work-up for epilepsy surgery. *Brain*. Sep 2007; 130(Pt 9): 2343-53. PMID 17586868
16. Hunyadi B, Tousseyen S, Dupont P, et al. A prospective fMRI-based technique for localising the epileptogenic zone in presurgical evaluation of epilepsy. *Neuroimage*. Jun 2015; 113: 329-39. PMID 25776215
17. Coan AC, Chaudhary UJ, Grouiller F, et al. EEG-fMRI in the presurgical evaluation of temporal lobe epilepsy. *J Neurol Neurosurg Psychiatry*. Jun 2016; 87(6): 642-9. PMID 26216941
18. Szaflarski JP, Gloss D, Binder JR, et al. Practice guideline summary: Use of fMRI in the presurgical evaluation of patients with epilepsy: Report of the Guideline Development,

Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. Jan 24 2017; 88(4): 395-402. PMID 28077494

19. American College of Radiology. ACR/ASNR/SPR practice parameter for the performance of functional magnetic resonance imaging (fMRI) of the brain. 2022; <https://www.acr.org/-/media/ACR/Files/Practice-Parameters/fmr-brain.pdf>. Accessed July 11, 2023.

Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
 - Reason for functional MRI of the brain
 - Plan for any related surgical procedure
- Previous imaging studies pertaining to request

Post Service (in addition to the above, please include the following):

- Functional MRI of the brain report

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

| Type | Code | Description |
|-------|-------|---|
| CPT® | 70554 | Magnetic resonance imaging, brain, functional MRI; including test selection and administration of repetitive body part movement and/or visual stimulation, not requiring physician or psychologist administration |
| | 70555 | Magnetic resonance imaging, brain, functional MRI; requiring physician or psychologist administration of entire neurofunctional testing |
| | 96020 | Neurofunctional testing selection and administration during noninvasive imaging functional brain mapping, with test administered entirely by a physician or other qualified health care professional (i.e., psychologist), with review of test results and report |
| HCPCS | None | |

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

| Effective Date | Action |
|----------------|--|
| 11/01/2016 | BCBSA Medical Policy adoption |
| 11/01/2017 | Policy revision without position change |
| 11/01/2018 | Policy revision without position change |
| 11/01/2019 | Policy revision without position change |
| 11/01/2020 | Annual review. No change to policy statement. Literature review updated. |

| Effective Date | Action |
|----------------|--|
| 11/01/2021 | Annual review. No change to policy statement. Literature review updated. |
| 11/01/2022 | Annual review. Policy statement and literature review updated. |
| 11/01/2023 | Annual review. No change to policy statement. Policy guidelines and literature review updated. |

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

| POLICY STATEMENT (No changes) | |
|---|---|
| BEFORE | AFTER |
| <p>Functional Magnetic Resonance Imaging of the Brain 6.01.47</p> <p>Policy Statement:</p> <p>I. Functional magnetic resonance imaging may be considered medically necessary in the preoperative evaluation of individuals with refractory epilepsy or brain tumors who are candidates for neurosurgery when the lesion is in close proximity to an eloquent area of the brain (e.g., controlling verbal or motor function) and testing is expected to have an important role in assessing the spatial relation between the lesion and eloquent brain area.</p> <p>II. Functional magnetic resonance imaging is considered investigational for all other applications.</p> | <p>Functional Magnetic Resonance Imaging of the Brain 6.01.47</p> <p>Policy Statement:</p> <p>I. Functional magnetic resonance imaging may be considered medically necessary in the preoperative evaluation of individuals with refractory epilepsy or brain tumors who are candidates for neurosurgery when the lesion is in close proximity to an eloquent area of the brain (e.g., controlling verbal or motor function) and testing is expected to have an important role in assessing the spatial relation between the lesion and eloquent brain area.</p> <p>II. Functional magnetic resonance imaging is considered investigational for all other applications.</p> |