

<b>6.01.47</b>		<b>Functional Magnetic Resonance Imaging of the Brain</b>	
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<b>Section:</b>	6.0 Radiology	<b>Page:</b>	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**

**Coding**

Current Procedural Terminology (CPT) coding specific to functional magnetic resonance imaging differentiates between circumstances when a provider or psychologist does all of the functional testing and when the testing is done by other professionals.

See the [Codes table](#) for details.

**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.

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.<sup>1</sup> 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) <sup>1</sup>	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) <sup>1</sup>				
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.<sup>2</sup> 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) <sup>2</sup>	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) <sup>2</sup>		
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.<sup>3</sup> 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.<sup>4</sup>

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) <sup>3</sup>	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) <sup>3</sup>		
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.<sup>5,6</sup> 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.<sup>6</sup> Results from this small prospective study suggested that fMRI may be more accurate than the Wada test in predicting postsurgical language outcomes. 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.<sup>7</sup> 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) <sup>5,6</sup>	Retrospective	U.S.	1993-2009	Patients with epilepsy undergoing L-ATL	fMRI (n=229)	Wada testing (same individuals)	NR
Sabsevitz et al (2003) <sup>7</sup>	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) <sup>5,6</sup>				
fMRI				7
Wada				2
Equivalent				1
Sabsevitz et al (2003) <sup>7</sup>				
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.<sup>8</sup> 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.<sup>9</sup> 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.<sup>10</sup> 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.<sup>4</sup> 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.<sup>11</sup>

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
<b>Wengenroth et al (2011)<sup>9</sup></b>	Retrospective	Germany	NR	Patients with brain tumors of the central region	fMRI	Structural MRI	NR
<b>Petrella et al (2006)<sup>10</sup></b>	Prospective	U.S.	2004-2005	Patients referred for possible tumor resection	fMRI (n=39)	None	NR
<b>Medina et al (2005)<sup>4</sup></b>	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
<b>Wengenroth et al (2011)<sup>9</sup></b>						
<b>fMRI</b>				76/77 (99)	68/70 (97)	67/70 (96)



Study	Change in Lateralization, %	Change in Treatment Plans, n (%)	Localization of Motor Hand Area, n/N (%)	Identification of Motor Areas, n/N (%)
Structural MRI			66/77	NR
p			<.002	NR
Petrella et al (2006) <sup>10</sup>		19 (49)		NR
95% CI		33 to 64.4		
Medina et al (2005) <sup>4</sup>	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.<sup>12</sup> 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) <sup>12</sup>	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) <sup>12</sup>	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 Magnetic Resonance Imaging 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.<sup>13</sup> 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.<sup>14</sup> The number of interictal discharges recorded during the fMRI session ranged from 9 to 744. There was concordance between 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.<sup>15</sup> 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 intrascanner interictal epileptic discharges.<sup>16,17</sup>

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) <sup>13</sup>	Retrospective	Netherlands	2007-2011	Patients with refractory epilepsy	EEG-fMRI (n=16)	NR
Moeller et al (2009) <sup>14</sup>	Retrospective	Canada	2007-2008	Patients with nonlesional frontal lobe epilepsy	EEG-fMRI (n=9)	NR
Zijlmans et al (2007) <sup>15</sup>	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 Localization and Positive fMRI Response	Subsequent Surgery Performed	BOLD Regions Concordant With ECoG	Interictally Active ECoG Regions Missed	Brain Regions Correctly Identified as Inactive
van Houdt et al (2013) <sup>13</sup>						76%	29%	68%
Moeller et al (2009) <sup>14</sup>			744	8 patients	2 patients			
Zijlmans et al (2007) <sup>15</sup>	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.<sup>18</sup> 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 (ie, 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
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
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

Recommendation	Evidence rating
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."<sup>19</sup> 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.

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## 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.
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.

Effective Date	Action
11/01/2024	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](http://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](mailto: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

## Functional Magnetic Resonance Imaging of the Brain 6.01.47

## 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.

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