Policy Statement

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

- Magnetoencephalography/Magnetic Source Imaging

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 (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 (e.g., -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.

**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 patients 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 question addressed in this evidence review is: Does the use of fMRI improve the net health outcome in individuals with epilepsy or brain tumors who require presurgical mapping of the eloquent cortex?

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

**Patients**
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. Presurgical mapping of the eloquent cortex with fMRI would be performed in the outpatient setting.

**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. The Wada test is performed in an outpatient setting; intracortical mapping is invasive and performed in a tertiary health care setting.

**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 functional MRI, 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.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on clinical validity and clinical utility.

Reproduction without authorization from Blue Shield of California is prohibited
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).

Wada Testing as the Reference Standard
Dym et al (2011) reported on a meta-analysis comparing fMRI-determined lateralization of language function with the Wada test. Twenty-three studies (total n=442 patients) were included in the meta-analysis. Most studies did not specify whether evaluators were blinded to 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Dates</th>
<th>Trials</th>
<th>Participants</th>
<th>N (Range)</th>
<th>Design</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dym et al (2011)</td>
<td>1996-2008</td>
<td>23</td>
<td>Patients who preoperatively underwent both a Wada test and fMRI</td>
<td>442 (NR)</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Sensitivity With a Word Generation Task, %</th>
<th>Sensitivity With a Semantic Decision Task, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dym et al (2011)</td>
<td>83.5</td>
<td>88.1</td>
<td>95.6</td>
<td>79.5</td>
</tr>
<tr>
<td>95% CI</td>
<td>80.2 to 86.7</td>
<td>87.0 to 89.2</td>
<td>93.9 to 97.3</td>
<td>66.5 to 72.5</td>
</tr>
</tbody>
</table>

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. Ten studies were selected; 3 reported data on a per-patient basis and 7 on a per-tag basis (ie, 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Dates</th>
<th>Trials</th>
<th>Participants</th>
<th>N (Range)</th>
<th>Design</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weng et al (2018)</td>
<td>1997-2016</td>
<td>10</td>
<td>Patients with brain tumors near the eloquent center undergoing resection</td>
<td>214 (5-44)</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR: not reported.
Table 4. Results of Systematic Reviews Assessing Clinical Validity With Intracortical Mapping as the Reference Standard

<table>
<thead>
<tr>
<th>Study</th>
<th>Sensitivity (95% CI), %</th>
<th>Specificity (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weng et al (2018)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per patient</td>
<td>44 (14 to 78)</td>
<td>80 (54 to 93)</td>
</tr>
<tr>
<td>Per tag</td>
<td>67 (51 to 80)</td>
<td>55 (25 to 82)</td>
</tr>
</tbody>
</table>

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. 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.

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

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

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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Sensitivity (95% Confidence Interval), %</th>
<th>Specificity (95% Confidence Interval), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>80 (68 to 89)</td>
<td>78 (67 to 86)</td>
</tr>
<tr>
<td>Broca area</td>
<td>100 (78 to 100)</td>
<td>68 (43 to 87)</td>
</tr>
<tr>
<td>Wernicke area</td>
<td>64 (42 to 82)</td>
<td>85 (65 to 96)</td>
</tr>
</tbody>
</table>

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. 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. 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. 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Country</th>
<th>Dates</th>
<th>Participants</th>
<th>Treatment</th>
<th>Comparator</th>
<th>FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janecek et al (2013)</td>
<td>Retrospective</td>
<td>U.S.</td>
<td>1993-2009</td>
<td>Patients with epilepsy undergoing L-ATL (n=229)</td>
<td>fMRI (n=229)</td>
<td>Wada testing (same individuals)</td>
<td>NR</td>
</tr>
<tr>
<td>Sabsevitz et al (2003)</td>
<td>Retrospective</td>
<td>U.S.</td>
<td>NR</td>
<td>Patients with epilepsy undergoing L-ATL (n=24)</td>
<td>fMRI (n=24)</td>
<td>Wada testing (same individuals)</td>
<td>NR</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>Instances Where Test Had Greater Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janecek et al (2013)</td>
<td>7</td>
<td></td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>fMRI</td>
<td>100</td>
<td>57</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Wada</td>
<td>100</td>
<td>43</td>
<td>56</td>
<td></td>
</tr>
</tbody>
</table>

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.

### 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. 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. 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. 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.

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**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Country</th>
<th>Dates</th>
<th>Participants</th>
<th>Treatment</th>
<th>Comparator</th>
<th>FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wengenroth et al (2011)†</td>
<td>Retrospective</td>
<td>Germany</td>
<td>NR</td>
<td>Patients with brain tumors of the central region</td>
<td>fMRI</td>
<td>Structural MRI</td>
<td>NR</td>
</tr>
<tr>
<td>Medina et al (2005)‡</td>
<td>Prospective</td>
<td>U.S.</td>
<td>2001-2003</td>
<td>Patients who received language mapping</td>
<td>fMRI (n=53)</td>
<td>None</td>
<td>NR</td>
</tr>
</tbody>
</table>

fMRI: functional magnetic resonance imaging; FU: follow-up; MRI: magnetic resonance imaging; NR: not reported.

**Table 10. Results of Observational Studies Assessing Clinical Utility**

<table>
<thead>
<tr>
<th>Study</th>
<th>Change in Lateralization, %</th>
<th>Change in Treatment Plans, n (%)</th>
<th>Localization of Motor Hand Area, n/N (%)</th>
<th>Identification of Motor Areas, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wemicke Area</td>
<td>Broca Area</td>
<td>Foot</td>
<td>Tongue</td>
</tr>
<tr>
<td>Wengenroth et al (2011)†</td>
<td>76/77 (99)</td>
<td>68/70 (97)</td>
<td>67/70 (96)</td>
<td></td>
</tr>
<tr>
<td>Structural MRI</td>
<td>66/77</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.002</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Petrella et al (2006)‡</td>
<td>19 (49)</td>
<td>33 to 64.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medina et al (2005)‡</td>
<td>28</td>
<td>21</td>
<td>42</td>
<td></td>
</tr>
</tbody>
</table>

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. 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Participants</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hall et al (2009)</td>
<td>U.S.</td>
<td>Patients receiving preoperative fMRI before brain resection (n=29)</td>
<td>NR</td>
</tr>
</tbody>
</table>

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

### Table 12. Results of Case Series Assessing Clinical Utility

<table>
<thead>
<tr>
<th>Study</th>
<th>fMRI Accuracy, %</th>
<th>Transient Neurologic Deficits Resolved Within 1 mo, n (%)</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hall et al (2009)</td>
<td>100%</td>
<td>7 (26)</td>
<td>0</td>
</tr>
</tbody>
</table>

fMRI: functional magnetic resonance imaging.

**Section Summary: Clinically Useful**

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 fMRI Clinical Context and Therapy Purpose**

The purpose of simultaneous EEG and fMRI in patients 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 question addressed in this evidence review is: Does the use of fMRI with EEG improve the net health outcome in individuals with epilepsy who are being screened to localize seizure focus?

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

**Patients**

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

**Interventions**

The intervention of interest is simultaneous EEG and fMRI. EEG-fMRI for localization of seizure focus is performed in the outpatient setting.

**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. Intracranial EEG is performed by a surgeon in a hospital setting.

**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 functional MRI, 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.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on clinical validity and clinical utility.

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).

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. 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. 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. 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.

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) | Retrospective | Netherlands | 2007-2011 | Patients with refractory epilepsy | EEG-fMRI (n=16) | NR |
| Moeller et al (2009) | Retrospective | Canada       | 2007-2008 | Patients with nonlesional frontal lobe epilepsy | EEG-fMRI (n=9) | NR |
Zijlmans et al (2007) 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

<table>
<thead>
<tr>
<th>Study</th>
<th>IED Sets With Significant BOLD Response, n/N</th>
<th>Patients Considered for Surgery</th>
<th>Range of IEDs Recorded During fMRI</th>
<th>Concordance between Spike Localization and Positive fMRI Response</th>
<th>Subsequent Surgery Performed</th>
<th>BOLD Regions Concordant With ECoG</th>
<th>Interictally Active ECoG Regions Missed</th>
<th>Brain Regions Correctly Identified as Inactive</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Houdt et al (2013)</td>
<td>744</td>
<td>8 patients</td>
<td>2 patients</td>
<td>76%</td>
<td>36%</td>
<td>68%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moeller et al (2009)</td>
<td>26/46</td>
<td>4 (14%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 randomized controlled trials.

No randomized controlled trials 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: Clinically Useful
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.

Summary of Evidence
For individuals who have epilepsy or brain tumors who are undergoing presurgical mapping of the eloquent cortex who receive fMRI, the evidence includes studies on diagnostic accuracy...
and clinical utility. Relevant outcomes are test accuracy, morbid events, functional outcomes, and quality of life. The diagnostic accuracy of fMRI has been compared with the Wada test and 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. According to findings from health outcomes, fMRI has several benefits for patients who are to undergo neurosurgery for seizures or brain tumors; these benefits include the potential to define eloquent areas (e.g., controlling verbal or motor function), and the ability to reduce surgery time and alter treatment decisions. Because of the highly detrimental impact of resecting the eloquent cortex, fMRI may be considered complementary to the Wada test and direct electrical stimulation when the lesion is in close proximity to an eloquent area of the brain. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have epilepsy who are being evaluated for localization of seizure focus who receive simultaneous electroencephalography and fMRI, the evidence includes a limited number of small studies. Relevant outcomes are test accuracy, morbid events, functional outcomes, and quality of life. The objective of current research is to improve the identification of seizure focus with this technique, particularly when there are no interictal epileptic discharges during an fMRI session. There are very few data on the effect of this procedure on health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Supplemental Information**

**Practice Guidelines and Position Statements**

**The American College of Radiology et al**

The American College of Radiology, American Society of Neuroradiology, and Society for Pediatric Radiology (2014; revised 2017) jointly published guidelines, 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." The guidelines' primary indications for functional magnetic resonance imaging 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), evaluation of preserved eloquent cortex, assessment of eloquent cortex for epilepsy surgery, assessment of radiation treatment planning and post-treatment evaluation of eloquent cortex" and therapeutic follow-up.

In 2017, the American Academy of Neurology (AAN) published a guideline on the use of fMRI in the presurgical evaluation of patients with epilepsy. 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**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Evidence rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>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 lobe 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.</td>
<td>Weak</td>
</tr>
<tr>
<td>The evidence is unclear for patients with temporal neocortical epilepsy or temporal tumors</td>
<td>Insufficient</td>
</tr>
<tr>
<td>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.</td>
<td>Weak</td>
</tr>
</tbody>
</table>
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. 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

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage decision specifically for functional magnetic resonance imaging.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 16.

Table 16. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td>National Study on the Interest of EEG-fMRI in the Presurgical Evaluation of Partial Epilepsies Drugs (ENERGY)</td>
<td>290</td>
<td>Apr 2020</td>
</tr>
<tr>
<td></td>
<td>Using Functional MRI and Diffusion Imaging of Eloquent Brain Areas to Optimize Brain Tumor Resection Planning</td>
<td>145</td>
<td>Feb 2021</td>
</tr>
<tr>
<td></td>
<td>Noninvasive Presurgical Evaluation of Patients With Focal Epilepsy and Establishment of a Normative Imaging Database</td>
<td>500</td>
<td>Mar 2026</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

References


**Documentation for Clinical Review**

**Please provide the following documentation:**
- History and physical and/or consultation notes including:
  - Reason for functional MRI of the brain
- 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. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>70554</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>70555</td>
<td>Magnetic resonance imaging, brain, functional MRI; requiring physician or psychologist administration of entire neurofunctional testing</td>
</tr>
<tr>
<td></td>
<td>96020</td>
<td>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</td>
</tr>
<tr>
<td>HCPCS</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

Policy History

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

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/01/2016</td>
<td>BCBSA Medical Policy adoption</td>
</tr>
<tr>
<td>11/01/2017</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>11/01/2018</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>11/01/2019</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>11/01/2020</td>
<td>Annual review. No change to policy statement. Literature review updated.</td>
</tr>
</tbody>
</table>

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 (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.

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.