Functional Magnetic Resonance Imaging of the Brain

Policy # 00447
Original Effective Date: 01/05/2015
Current Effective Date: 01/02/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Magnetoencephalography/Magnetic Source Imaging is addressed separately in medical policy 00082.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:
- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider functional magnetic resonance imaging (fMRI) as a complementary test in the preoperative evaluation of patients 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 relationship between the lesion and eloquent brain area to be eligible for coverage.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers functional magnetic resonance imaging (fMRI) for all other applications is considered to be investigational.*

Background/Overview
fMRI is a noninvasive method for localizing areas of brain function and has been used for the presurgical evaluation of eloquent brain areas. Images are collected while specific activities are performed to assist in the localization of critical cortical areas and evaluation of language lateralization. It is also being investigated in combination with diffusion tensor imaging, which measures white matter tract organization, and electroencephalogram (fMRI-EEG) to identify seizure focus.

Before neurologic surgery for seizure disorders or resection of brain tumors, localization of certain areas of the brain, such as speech centers, is important. For example, from 25% to 60% of patients who undergo left anterior temporal lobectomy develop dysnomia (language/naming difficulties). Most often these “eloquent” areas are assessed using the Wada test and direct electrical stimulation. Both of these tests are invasive and require involvement 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 arrest of speech, random answering, or perseveration to stimulation. The Wada test is an inactivating method that blocks the function of one hemisphere by injection of amobarbital into the carotid artery, allowing functional testing of the reserve capacity of the nonanesthetized hemisphere.

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Functional MRI is an activation method that uses sequences based on T2-weighted blood oxygen level-dependent (BOLD) 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 (LI), which ranges from -1 to 1. A positive LI is considered left-dominant, while a negative LI is right-dominant. LIs 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 language-associated, but not the language-essential cortex. Therefore, bilateral activation is not necessarily indicative of a bilateral distribution of language-essential cortex and may be task-dependent. In addition, sensitivity and specificity may change with the application of different statistical thresholds.

Simultaneous EEG and fMRI is 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.

**FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)
There are several fMRI hardware (e.g., fMRI Hardware System; NordicNeuroLab AS) and fMRI software packages (e.g., BrainAcquireRx™/BrainProcessRx™ Data Suite; Kyron Clinical Imaging) with 510(k) marketing clearance from the U.S. FDA for use in conjunction with a MRI scanner to perform fMRI. FDA Product Code: LNH

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage decision specifically for functional MRI. The national coverage decision on magnetic resonance imaging (MRI) (220.2) provides general guidelines or examples of what may be considered covered rather than as a restrictive list of specific covered indications. Imaging of cortical bone and calcifications, and procedures involving spatial resolution of bone and calcifications, are the only indications specifically listed as not covered.

**Rationale/Source**
fMRI might be thought of as a type of diagnostic test to determine the location of eloquent cortex or seizure focus. Assessment of a diagnostic technology typically focuses on 3 categories of evidence: technical performance, diagnostic accuracy, and impact on health outcomes.

- Technical performance refers to how well the technology measures and records the parameter(s) that it is purported to evaluate. Evaluation of technical performance may include various measures
of validity (e.g., criterion validity, construct validity) and reliability (e.g., test-retest reliability, agreement among multiple reviewers).

- Diagnostic accuracy is the ability of a test to accurately diagnose a clinical condition in relevant populations of patients compared to a reference standard. Measures of diagnostic accuracy include sensitivity, specificity, predictive values, likelihood ratios, and area under the curve analysis.
- Demonstration that the diagnostic information can be used to improve patient outcomes is essential to determining the utility of a diagnostic technology. In most cases, an indirect chain of evidence needs to be constructed to determine whether there is a tight linkage between the diagnostic technology and improvement in health outcomes.

For fMRI, comparators for language laterality may be the Wada test and intracortical mapping. Health outcomes can be directly assessed by the impact of the test on surgical outcomes.

Presurgical Mapping of Eloquent Cortex
Technical Performance
Some research has focused on establishing and improving standardized protocols and analysis for presurgical evaluation of the eloquent cortex. For example, Stippich et al has described a routine preoperative fMRI protocol in 81 consecutive patients (70 with tumors on the left side and 11 with tumors on the right side and language deficits). Patients were trained to recall simple sentences (picture cues) or to generate words in a category (word cues). The combination of tasks allowed localization of both the Broca (language expressive) and Wernicke (language receptive) areas and determination of hemispheric language dominance in 79 (98%) patients. Based on fMRI findings, surgical plans were modified in 9 (11%) patients. The authors noted that, although fMRI is capable of localizing the center of an area, resection borders cannot be reliably determined by this technique. Ruff et al (2008) found no optimal threshold for reliably determining the language LI. In addition to the statistical threshold, the language LI varied as a result of presence of tumor, prior surgery, and language task. In another report, Wellmer et al assessed whether currently recommended thresholds for the fMRI LI helped identify atypical dominant patients (i.e., not left-dominant) with sufficient safety for presurgical settings. Depending on the chosen LI threshold for unilateral language dominance, between 2 (9%) and 5 (23%) patients in this sample would have been misclassified as typical dominant.

Diagnostic Accuracy
Wada Testing as the Reference Standard
In 2011, Dym et al reported a meta-analysis of fMRI-determined lateralization of language function compared with the Wada test. Inclusion criteria were examination of the same patients with both fMRI and the Wada test; preoperative examination of at least 4 patients; and reporting of the concordance in individual patients. Twenty-three studies with a total of 442 patients were included in the meta-analysis. Language dominance for each patient was classified as typical (left hemispheric language dominance) or atypical (right hemispheric language dominance or bilateral language representation), with most studies using a LI threshold of 0.2. Sensitivity was defined as the ability of fMRI to depict atypical language representation, and specificity was the ability of fMRI to depict typical language representation. Most of the studies did not specify whether the evaluators were blinded to the results of the other test. With the Wada
test as the reference standard, fMRI had a sensitivity of 83.5% and specificity of 88.1%. Specificity was significantly higher with use of a word generation task (95.6%) than with a semantic decision task (69.5%). This analysis may oversimplify 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 utilize a single task (e.g., word generation) to evaluate the eloquent cortex.

**Intracortical Mapping as the Reference Standard**

Bizzi et al reported 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 eloquent cortex were included in the study. 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 291 sites were tested, 141 in patients evaluated with verb generation and 110 in patients evaluated with finger tapping. For hand motor function alone, sensitivity and specificity were 88% and 87%, respectively. For language, sensitivity and specificity were 80% and 78%, respectively. The fMRI for Broca area showed 100% sensitivity and 68% specificity, while the fMRI for Wernicke area showed 64% sensitivity and 85% specificity. Sensitivity of fMRI decreased from 93% for World Health Organization grade II gliomas to 65% for grade IV gliomas. In another study, fMRI was concordant with direct electrical stimulation in 23 of 26 (88%) cases.

**Postoperative Language Changes as the Reference Standard**

In 2003, Sabsevitz et al 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. In 2013, this group of investigators reported that 32 of 329 (14%) epilepsy patients showed discordance between fMRI and Wada testing and that discordance was highest when either of the tests indicated that language was bilateral. Ten of the 32 patients had discordant results, underwent left temporal lobe surgery, and had preoperative and 6-month postoperative language testing. Of the 10 patients, 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 suggest that fMRI may be more accurate than the Wada test in predicting postsurgical language outcomes.

**Effect on Health Outcomes**

Use of preoperative fMRI in combination with intraoperative MRI was reported in 2009 to allow more complete resection of tumors without affecting eloquent neurologic function. In this case series of 29 patients, preoperative fMRI was performed 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-T or 3-T 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 an fMRI-guided tumor resection was possible.
In a 2011 report, Wengenroth et al compared localization of eloquent tumor-adjacent brain areas by fMRI to 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 (66% 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 reported on the impact of fMRI preoperatively on 39 consecutive patients with brain tumors in 2006. 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. The fMRI 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 change in anatomic location or lateralization of language reception (Wernicke) in 28% of patients and in language expression (Broca) in 21%. In 38 (63%) patients, fMRI helped to avoid further studies, including the Wada test. In 31 (52%) and 25 (42%) of the 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 minutes to 30 minutes and total operating time from an average 8.5 hours to about 7 hours.

Section Summary: Presurgical Mapping of the Eloquent Cortex
The diagnostic accuracy of fMRI has been compared to the Wada test and to 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 suggests 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
Some small studies have evaluated surgical outcomes following use of simultaneous EEG and fMRI to identify seizure focus.
In a 2007 report, the preoperative localization of epileptic focus was assessed in 29 complex patients (unclear focus and/or multifocality) who had been rejected for epilepsy surgery. Patients were selected if they had no contraindications for MRI, had more than 10 interictal discharges in 40 minutes of a previously recorded EEG, and if the reason for denial of surgery was the inability to localize a single source with EEG. The results of the fMRI were considered robust if a consensus-defined interictal electrical discharge was associated with a significant fMRI response. 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.

Moeller et al (2009) reported 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.

A 2011 multicenter study compared presurgical interictal discharge-related BOLD signal changes with intracranial EEG and postoperative outcomes in 23 patients with refractory epilepsy. The 23 patients were selected based on a diagnosis of focal cortical dysplasia from structural MRI or histology. The EEG-fMRI results were not used in the planning of intracranial EEG or surgical resections. In the 11 patients with a BOLD response, fMRI results were concordant with the intracranial EEG-determined seizure onset zone in 5 (45%) patients. The other 6 of 11 patients had widespread or discordant regions of fMRI signal change, and 5 had either a poor surgical outcome or a widespread seizure onset zone that precluded surgery. It should be considered exploratory. Another 2011 study from many of the same investigators described a newer method to evaluate simultaneous EEG-fMRI results in the absence of visually identifiable interictal epileptiform spikes.

In a 2013 study, van Houdt et al conducted a retrospective comparison of presurgical EEG-fMRI with invasive electrocorticographic data and surgical outcomes in 16 patients. Patients were selected who had interictal epileptiform activity during fMRI acquisition, had acceptable quality of EEG and fMRI data, and were candidates for surgery. 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 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 the cases.

Research is ongoing to improve the identification of seizure focus with simultaneous EEG-fMRI, including occasions without intrascanner interictal epileptic discharges.

**Section Summary**

Several small studies identified have evaluated seizure focus with simultaneous EEG-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.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this policy are listed in Table 1.

Table 1. Summary of Key Trials

<table>
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<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td>NCT01534104</td>
<td>Using Functional MRI and Diffusion Imaging of Eloquent Brain Areas to Optimize Brain Tumor Resection Planning</td>
<td>250</td>
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<td>NCT02107989</td>
<td>Noninvasive Pre-surgical Evaluation of Patients With Focal Epilepsy</td>
<td>250</td>
<td>Jul 2020</td>
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<td>NCT02795338</td>
<td>Multi-modality Localization of Eloquent Brain Function-A</td>
<td>80</td>
<td>Oct 2021</td>
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<tr>
<td></td>
<td>Comparison of Technologies for Improved Applicability</td>
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NCT: national clinical trial.

- Denotes industry-sponsored or cosponsored trial.

Summary
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 to 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. Evidence on health outcomes has indicated that fMRI in patients who are to undergo neurosurgery for seizures or brain tumors may help to define eloquent areas (e.g., controlling verbal or motor function), reduce surgical 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 qualitatively 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.
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References

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10/02/2014 Medical Policy Committee review
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/08/2015 Medical Policy Committee review
10/21/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/06/2016 Medical Policy Committee review
10/19/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
10/05/2017 Medical Policy Committee review
10/18/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 10/2018

Coding
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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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<th>Code Type</th>
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<tr>
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<td>70554, 70555, 96020</td>
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<tr>
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| G40.B01-B40.B09 | G40.B11-G40.B19 |

**Investigational** – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
   1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
   2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
   3. Reference to federal regulations.

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A. In accordance with nationally accepted standards of medical practice;

B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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 that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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