



# CIGNA MEDICAL COVERAGE POLICY

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**Subject Magnetoencephalography (MEG)**

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- Functional Magnetic Resonance Imaging (fMRI), Brain
- Intracranial Electroencephalography (IEEG)
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- Nuclear Imaging including Single-Photon Emission Computer Tomography (SPECT)
- Positron Emission Tomography (PET)
- Quantitative Electroencephalography (QEEG)
- Somatosensory Evoked Potentials
- Transcranial Doppler (TCD) Ultrasonography
- Vagus Nerve Stimulation (VNS)
- Video Electroencephalographic (V-EEG) Monitoring

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## Coverage Policy

**CIGNA does not cover magnetoencephalography (MEG) or magnetic source imaging (MSI) for any condition because they are considered experimental, investigational or unproven.**

## General Background

Neurofunctional testing and functional imagings are used to map motor, sensory, language, and memory areas in neurosurgical patients (e.g., brain tumors, vascular lesions, and epilepsy). Localizing specific areas of the brain responsible for particular critical functions, such as thought, speech, movement and sensation, as well as white matter tracts connecting critical areas, is an essential component of the presurgical planning process

when treating brain disorders. The protection of functions that may be at risk during surgery is facilitated by functional mapping of critical eloquent areas.

Magnetoencephalography (MEG) is a complex, noninvasive functional brain imaging method that detects neuromagnetic signals produced by neuronal activity in the cortex of the brain. Magnetic activity measured outside the head is produced primarily by intracellular electrical currents within dendrites of cells in brain structures. With electroencephalogram (EEG), the secondary volume currents are detected outside the head; whereas, with MEG, the magnetic flux that is detected at the surface of the head penetrates the skull and tissues without significant distortion. The data with MEG is filtered and subjected to mathematical modeling to estimate the location, strength and orientation of the current sources in the brain that are associated with the magnetic fields.

Typical MEG recordings are made within a magnetically shielded room using a device that has 100—300 magnetometers or gradiometers (sensors). They are arranged in a helmet-shaped container called a Dewar. The Dewar is filled with liquid helium needed to produce superconductivity. The brain sources producing the magnetic field maps can be mapped and displayed on a co-registered magnetic resonance imaging (MRI) and is known as magnetic source imaging (MSI). This results in a visual display of normal brain activity such as the location of eloquent cortex for vision, touch, movement, or language. It displays abnormal brain activity such as epileptic discharges. Such depictions are proposed for pre-surgical brain mapping in patients with epilepsy, brain tumors, and vascular malformations (American Academy of Neurology [AAN], 2009). MEG has limitations, such as the cost of the device, the requirement for a purpose-built facility with magnetic shielding, and the need for frequent replacement of liquid helium. In addition, deep sources of activity cannot be readily detected, recordings are generally interictal (versus ictal), only tangentially oriented currents can be detected (not radially oriented), and patients must be cooperative (Hayes, 2008).

The most common proposed clinical applications of MEG are: evaluation of patients with medically refractory epilepsy; assessment of patients with brain masses such as tumors or arteriovenous malformations (AVMs); for psychiatric disorders such as schizophrenia and depression; learning disorders like dyslexia; and normal cognitive functions, underlying memory and language. Specific proposed uses of MEG include: (1) diagnosis of seizure disorders and mass lesions not definable by standard methods; (2) accurate and precise localization of epileptic foci to allow consideration of ablative therapy for resistant seizure disorders; and (3) preoperative mapping for mass lesions and vascular malformations prior to neurosurgical intervention to aid in designing surgical approach and surgical limitations; (4) determination of cerebral characteristics in patients with psychiatric disorders; (5) assessment of normal and abnormal language development (Hayes, 2008).

MEG has been investigated as an alternative or as an adjunct to other methods of locating epileptic foci and/or brain lesions. These other methods include scalp EEGs for evaluating the electrical activity of the brain; invasive EEGs requiring craniotomies, the gold standard; subdural electrocorticography (ECoG) and stereotactic electroencephalograph potentials (SEEP); functional neuroimaging procedures: positron emission tomography (PET), single-photon emission computed tomography (SPECT), and functional MRI (fMRI); and anatomic imaging modalities: MRI and computed tomography (CT) (AAN, 2009; Hayes, 2008).

Although accuracy data are lacking, intracranial electroencephalography (IEEG) has evolved into the standard of care for a subset of patients who are candidates for epilepsy surgery. IEEG is the established gold standard for defining epileptogenic zones prior to surgical intervention (Blue Cross Blue Shield Association [BCBSA] Technology Evaluation Center [TEC], 2009; Muzik, et al., 2005).

### **U.S. Food and Drug Administration (FDA)**

MEG machines are classified by the FDA as Class II devices. Class II devices are cleared through the FDA's 510(k) process and require special controls but do not require premarket application approval.

### **Literature Review**

The published evidence for MEG of the brain consists of a number of prospective uncontrolled case series, prospective controlled or comparative studies, retrospective studies, and systematic reviews. The proposed applications of MEG have not been assessed in detail with randomized control groups, including sham measurements to display effects on clinical outcome (Tharin, et al., 2007; Makela, et al., 2006; Papanicolaou, et al., 2005a).

**Epilepsy:** Due to the heterogeneity of etiologies of intractable epilepsy, lesions, extent of surgical resections, and outcomes, direct validation or strict proof of the utility or superiority of MEG, which is noninvasive, over the gold standard of IEEG is challenging. MEG's exact predictive value in surgical epilepsy has yet to be quantified. MEG is proposed as an adjunct rather than as a complete alternative to other seizure focus localization methods, such as IEEG.

In a prospective observational case series study (n=69), Sutherling et al. (2008) evaluated MEG's potential for making surgical decisions in neocortical epilepsy. The key questions were to what degree MSI changes surgical decision making and outcome. The key comparison was between the surgical conference decisions before and after presentation of the MSI results. A total of 69 patients met criteria with medically intractable partial seizures or partial secondary generalized seizures aged 8–66 years. Patients were not randomly assigned to receive or not receive MSI, because MSI is an accepted procedure in presurgical evaluation and it was believed unethical to deny patients this test. The patients diagnosed with partial epilepsy of suspected neocortical origin had video-EEG (V-EEG) and imaging protocol testing. Each patient had typical seizures on V-EEG. Neuropsychometric and sodium amytal testing were performed. Metabolic PET and ictal SPECT were performed when indicated. A patient met "skip" criteria for standard anterior temporal lobectomy if the V-EEG showed a focal temporal onset pattern, imaging showed ipsilateral mesial temporal sclerosis on MRI or focal temporal hypometabolism on PET, the patient passed the amytal test, and there were no conflicting data. Patients with a static lesion larger than 1.0 cm had "lesionectomy-plus" if the EEG was lateralizing and there were no conflicting data. All others were recommended for IEEG, either depth electrodes or subdural grids, if there was a reasonable hypothesis of a focal zone of seizure origin. At a surgical conference, a decision was made before and after presentation of MSI. Two decisions were made: the pre-MSI decision and the post-MSI decision. The clinical team was blinded to MSI at this time. The pre-MSI decision was made on IEEG, excisional surgery, or vagal nerve stimulation (VNS) and was documented. For the second decision, the MSI was then presented by a physician–scientist who had analyzed the MSI but did not vote. A second decision was then made either to alter or not to alter the first surgical decision in view of the information from MSI and was documented. Where MSI showed a location different from that indicated by the standard protocol, a decision was made to add intracranial electrodes over the MSI-indicated location. Additional electrodes were diagrammed over the location with the densest MSI spike cluster.

The results of the study state that MSI provided nonredundant information in 33% of the 69 patients (n=23). In the other 46 patients, MSI gave information similar to the standard noninvasive V-EEG and imaging protocol. MSI changed the decision to additional IEEG subdural strip electrodes (n=9), from no surgery to IEEG (n=2), from excision to IEEG (n=2), from IEEG to vagal nerve stimulator (n=4), and from bilateral to unilateral IEEG (n=3). MSI changed the second step in presurgical evaluation in three patients and reduced tests in one patient.

The reported outcomes state that 28 patients have had IEEG, 29 have had focal resections, and 14 have had VNS. Of those where the MSI changed the decision, ten have had focal resections and six have had VNS. The mean follow-up after resection is 17 months; only one patient has less than six months. The authors report that MSI benefited six patients, which represents 9% of the 69 patients who entered in the series and 21% of the 29 patients who have gone to resection to date. In the six patients, MSI influenced decisions by eliminating bilateral IEEG electrode coverage in two patients who are seizure free, indicating correctly a frontal seizure zone not apparent on the first IEEG in one who is seizure free, reducing tests in one who is seizure free, and prompting IEEG in two patients who have Engel class II and III outcomes. The authors reported no limitations with their study (Sutherling, et al., 2008). The study had a small sample size, lack of randomization and no long-term health outcomes data.

In a prospective observational study, Knowlton et al. (2008a) studied the predictive and prognostic value of MSI, 2-[18F] fluoro-2- deoxy-D-glucose positron emission tomography (18FDG-PET), and SPECT as compared with IEEG localization in epilepsy surgery. The study included patients with intractable seizures who had a standard workup with MRI and V-EEG. Those with normal MRI or insufficiently localized MRI findings entered the study. Of 160 patients enrolled over four years, 72 completed IEEG seizure monitoring. All 72 of these patients had MEG, 60 of them had FDG-PET, and 35 had ictal SPECT. Twenty-seven patients had all three noninvasive tests. The results of noninvasive tests and reasons for not proceeding to IEEG are not reported. Of the 72 patients having IEEG, 54 had positive studies, 18 had nonlocalized ictal patterns, and five studies were nondiagnostic in that no seizures were captured during recording. Sensitivity, specificity, and predictive values relative to IEEG were computed for each modality. Depending on patient subgroup pairs, sensitivity ranged from 58–64% (MSI), 22–40% (PET), and 39–48% (SPECT); specificity ranges were 79–88% (MSI), 53–63% (PET),

and 44–50% (SPECT). Gains in diagnostic yield were seen only with the combination of MSI and PET or MSI and ictal SPECT. Localization concordance with IEEG was greatest with MSI, but a significant difference was demonstrated only between MSI and PET. Moderate redundancy was seen between PET and ictal SPECT ( $k=0.452$ ;  $p=0.011$ ). The authors reported that positive MSI has a high predictive value for seizures localized with IEEG. Diagnostic gain may be achieved with addition of either PET or ictal SPECT to MSI. The authors reported that the first aim of this study was to determine whether any of the tests, alone or in combination, could serve as a noninvasive alternative to replace or supplement IEEG. Taking the results as is with only modest overall concordance rates, the answer would be no to replace; however, the answer truly remains unclear because of IEEG limitations in localization. As to the question to supplement IEEG, the answer is yes because of the cases with nonlocalized IEEG that had resection based on the imaging tests and became seizure free. The study does not identify the multiple potential imaging variables and criteria that best characterize potential skip cases. Only 72 of the 160 patients proceeded to have IEEG. It appears that whether to proceed to IEEG is an individualized decision based on all the results of prior tests up to IEEG. A clinical trial randomizing patients to IEEG or imaging-based surgery would be scientifically ideal, but this is not ethically possible (Knowlton, et al., 2008a). Results are inconclusive due to the variability in the sensitivity, specificity and predictive values of the diagnostic tests. It is not clear how MEG fits into the diagnostic process to improve patient outcomes. Due to the high drop out rate in this study, associations between the diagnostic tests and outcomes are biased.

The aim of the accompanying prospective study by Knowlton et al. (2008b) was to gain information on the value of MSI, FDG-PET, SPECT to predict seizure-free outcome following epilepsy surgery in patients who require IEEG. Of 160 patients enrolled and the 72 patients who had IEEG, 62 proceeded with surgical resection. The previous study reported 54 patients had positive IEEG. Eight patients proceeded to surgery despite a negative or nondiagnostic IEEG. Sixty-one percent resulted in an Engel I seizure-free outcome at a minimum of one-year follow-up (mean=3.4 years). Sensitivity, specificity, and predictive values were computed for each modality. MSI sensitivity for a conclusively localized study was 55% with a positive predictive value of 78%. Eliminating nondiagnostic MSI cases (no spikes captured during recording) yielded a corrected negative predictive value of 64%. With available comparison subgroups FDG-PET and ictal SPECT values were similar to MSI. The authors reported it is emphasized that the data from this study do not provide evidence that any of the tests should be used to replace IEEG. Rather, the results show that each test, if conclusively positive (unequivocally localized), can guide decision making toward successful surgical treatment. An important remaining question is whether, when combined, these noninvasive tests can also be validly used to guide patients away from surgery by indicating a low yield for seizure-free outcome. It is not clear how MEG fits into the diagnostic process to improve patient outcomes. Due to the high drop out rate in this study, associations between the diagnostic tests and outcomes are biased.

In a retrospective study, Ramachandran et al. (2008) studied clinical profiles, interictal MEG, IEEG findings from extraoperative intracranial invasive monitoring, surgical procedures, postoperative electrocorticography (ECoG), and pathology as to their relation to postsurgical seizure outcomes in a cohort of children ( $n=22$ ) with normal, subtle or nonfocal MRI findings, who underwent epilepsy surgery for intractable epilepsy. The authors hypothesized that in children with normal MRI and intractable localization-related epilepsy a single MEG cluster represented the epileptogenic zone. Seventeen children (77%) had a good postsurgical outcome (defined as Engel class IIIA or better), which included eight (36%) seizure-free children. All children with postsurgical seizure freedom had a MEG cluster in the final resection area. Postsurgical seizure freedom was obtained in none of the children who had bilateral MEG dipole clusters (3) or only scattered dipoles (1). All five children in whom ictal onset zones were confined to  $\leq 5$  adjacent intracranial electrodes achieved seizure freedom compared to three of 17 children with ictal onset zones that extended over  $>5$  electrodes ( $p=0.002$ ). None of six children with more than one type of seizure became seizure free, compared to eight of 16 children with a single seizure type ( $p=0.04$ ). Complete resection of the preoperatively localized epileptogenic zone resulted in seizure remission in 63% (5/8) and incomplete resections, in 21% (3/14) ( $p=0.06$ ). Age of onset, duration of epilepsy, number of lobes involved in resection, and pathology failed to correlate with seizure freedom. The author reported that seizure freedom was most likely to occur when there was concordance between EEG and MEG localization and least likely to occur when these results were divergent. A limitation of this study is the retrospective study design. MEG has not been assessed with a randomized control group.

In a retrospective study, Paulini et al. (2007) investigated the contribution of MEG in addition to long term V-EEG-monitoring in presurgical evaluation. The distribution of localization results to anatomical lobes was compared with special focus to MEG spike localization results in cases without or with ambiguous EEG findings. A total of 105 consecutive patients with intractable focal epilepsy and epilepsy surgery after investigation by V-

EEG-monitoring and MEG were included. The percentages of monolobar results were analyzed and compared, especially with respect to the resection lobe. Postoperative outcome was used for further validation. No spikes were recorded on MEG in 30% (32 of 105). In cases with a diagnostic finding by the respective method, MEG localized in 82% (60 of 73 patients) within one anatomical lobe. Ictal EEG localized within one lobe in 72% (66 of 92 patients), interictal EEG in 60% (59 of 98 patients). In 25 of 105 patients (24%) no clear localization within one lobe was found either in interictal or in ictal EEG. In 11 of these cases MEG localized within the resection lobe. Six patients of these became seizure-free; the other five had at least 50% reduction of their seizure rate one year after surgery. The authors reported that MEG is a useful tool in the routine workup for epilepsy surgery contributing information to focus hypothesis in addition to V-EEG. This study did not include data in patients who did not undergo surgery. This study does not address other diagnostic noninvasive tests that could have been included in the presurgical evaluation. The data does not clearly demonstrate whether MEG contributes to the health outcomes of patients.

Tuberous sclerosis complex (TSC) is a neurocutaneous disorder. Patients are most commonly first seen with seizures, and epilepsy occurs in > 90% of children with TSC. In many children, seizures cannot be managed with antiepileptic medications and may require surgery to relieve seizures. In a retrospective study, Iida et al. (2006) evaluated the use of MEG spike sources (MEGSSs) for localizing epileptic zones in TSC patients. The researchers characterized MEGSSs and correlated them to EEG and magnetic resonance imaging (MRI) results. Data was analyzed from seven children who underwent prolonged V-EEG monitoring, MEG, and MRI. MEGSSs were classified as clusters (six or more spike sources,  $\leq 1$  cm between sources) and scatters (fewer than six spike sources regardless of distance between sources; sources with  $> 1$  cm between sources regardless of number of sources). A single, unilateral cluster with additional scatters occurred in two patients; these predominantly lateralized dipoles correlated to prominent tubers on MRI and ictal/interictal EEG zones. Bilateral clusters with scatters existed in two patients; cluster locations partly overlapped multiple prominent tubers. These patients also had bilateral or diffuse interictal discharges, bilateral or generalized seizures, and changing seizure types and EEG findings. Only bilateral scatters occurred in three patients; scatters partly overlapped EEG interictal/ictal-onset regions; one patient had coexisting generalized seizures. In one patient with equally bilateral scatters, scatters overlapped a prominent tuber and interictal/ictal-onset zones (IOZs) in the right frontal region.

Wu et al. (2006) assessed whether MEG/MSI identified epileptogenic zones in patients with TSC. In six TSC children with focal seizures, ictal V-EEG predicted the region of resection with 56% sensitivity, 80% specificity, and 77% accuracy ( $p=0.02$ ), whereas interictal MEG/MSI fared better (100%, 94%, and 95%, respectively;  $p=0.0001$ ). The authors did emphasize this is a preliminary report, and their results are applicable to TSC patients with lateralized seizure onsets by V-EEG. The authors state their results may not be relevant for TSC patients with generalized or bilateral ictal seizure onsets; therefore, they emphasize a larger cohort of TSC patients undergoing epilepsy neurosurgery will be needed to verify their findings.

Jansen et al. (2006) compared epileptiform activity recorded with EEG and MEG in 19 patients with TSC and epilepsy. High-resolution (HR) EEG, HR-MEG, and 1.5-T MRI scans were performed. Epileptiform spikes were identified in EEG and MEG recordings offline by three observers. Spikes for which the interobserver agreement (spike consensus) was  $> 0.40$  were used for source localization with CURRYV 3.0 software. MUSIC analysis was performed. The distance between the source determined from EEG and MEG recordings and the border of the closest tuber was calculated and compared. It was found that consensus spikes ( $\kappa > 0.4$ ) were identified in 12 patients in the EEG recording and in 14 patients in the MEG recording. MEG sources were closer to tubers in all but one patient. Three patients underwent epilepsy surgery, two of whom are seizure-free after complete resection of the tuber.

Kamimura et al. (2006) researched the usefulness of MEG for diagnosis of the spatial relations between spike foci and suspicious epileptogenic tubers on MRI in patients with tuberous sclerosis (TS) and to compare MEG spike foci with SPECT findings. The researchers analyzed magnetic fields of epileptic spike discharges in 15 patients with TS and localization-related epilepsy (LRE) by using whole-head MEG. The spatial relation between the equivalent current dipoles (ECDs) of interictal spike discharges and visible cortical tubers on MRI were investigated. The results of MEG and MRI with SPECT findings were compared. MEG detected a cluster of ECDs around one cortical tuber in six of 15 patients and clusters of ECDs around two cortical tubers in five patients. Interictal SPECT was disappointing in detection of epileptic foci in TS. However, MEG spike foci showed spatial consistency with ictal hyperperfusion areas in two patients. Three patients with single ECD clusters underwent surgical treatment: two have been seizure-free, and one has obtained seizure reduction of >

90%. The authors stated, "The present study also suggests that interictal MEG could be substituted for ictal SPECT in epilepsy patients with TS; however, analysis of further similar cases is needed to confirm this."

Oishi et al. (2006) defined and compared locations of single and multiple clusters of ECDs for interictal spikes with MRI findings, ictal-onset zones (IOZs) from subdural electroencephalography (SDEEG), resected areas, and postsurgical outcomes of 20 patients who underwent cortical resection for medically intractable neocortical epilepsy. A total of 14 patients had single clusters, and six patients had multiple clusters. Overlap of clusters and IOZs defined group A (nine patients), in which a single cluster coincided with the IOZ; group B1 (four patients), in which a single cluster was within or partially overlapped the IOZ; group B2 (five patients), in which multiple cluster sections overlapped IOZs; group C (two patients—one single, one multiple), in which no overlap was seen. More single clusters (nine of 14) than multiple clusters (none of six) coincided with the IOZ ( $p=0.014$ ). More patients with single clusters (10 of 14) than patients with multiple clusters (one of six) had seizure-free outcomes ( $p=0.049$ ). Eight of nine patients in group A, versus three of 11 in groups B1, B2, and C, achieved seizure-free outcomes ( $p=0.0098$ ). Correlations between MRI findings and postsurgical outcomes were not statistically significant.

Knowlton et al. (2006) conducted a prospective study to compare MSI and IEEG localization in surgical candidates. Within their facility, 49 patients (age 1–61 years) were evaluated for surgical resection after surface EEG, V-EEG, MRI, flurodeoxyglucose-PET and ictal SPECT. The study included patients with medically intractable partial epilepsy. All patients agreed to have an MSI study conducted along with their IEEG mapping. During the epilepsy surgical consultation, after initial planning was completed for the placement of the intracranial electrodes, the results of the MSI were revealed. Localization results according to epilepsy type produced similar sensitivity outcomes (MSI, 65% and IEEG, 69%). The positive predictive value of MSI for seizure localization is 82–90% depending on whether computed against IEEG alone or in combination with surgical outcome. The MSI did not record seizure activity in 20% of the cases, while the IEEG was negative in 10% of the cases. For all 49 cases, 27 (55%) were localized, and the data was concordant between the MSI and IEEG; three cases (6%) were localized with both tests but differed on the site of activity; IEEG localized seven cases (14%), not localized by MSI; while MSI localized three cases (6%). The researchers concluded that additional studies are warranted to determine the feasibility of using MSI versus IEEG in a select population of patients prior to epileptic surgical resection. This study is limited by small sample size. The authors did not report postsurgical outcomes.

Wolff et al. (2005) conducted a case series study of 27 children to investigate the topographic relation between focal spikes and neuropsychological findings in children with benign partial epilepsy (BPE). All children in the study had an MEG/EEG and MRI. Psychological assessments, including language and motor performance, were also conducted. Of the 27 children, 20 had sufficient MEG data that could be used to evaluate the recorded findings versus the psychological test findings. The researchers saw a correlation between the interictal spikes that were recorded with MEG as compared to the other test findings. They concluded that high-level cognitive functions that depend on interaction of diverse cortical areas of the brain are particularly susceptible to interference by interictal discharges. They also concluded that these findings may have implications for therapeutic planning for children with BPE, but additional research is needed to verify these findings.

Papanicolaou et al. (2005b) compared the localization accuracy of interictal MEG with ictal and interictal invasive V-EEG in identifying the epileptogenic zone in epilepsy surgery patients. The study included 41 patients, 29 with temporal lobe epilepsy (TLE) and 12 with extratemporal lobe epilepsy (ETLE). Only patients with interictal changes during the MEG recordings were included. A comparison of the accuracy of invasive V-EEG and MEG seizure zone identification was based on the degree of overlap between the location of the actual surgical resection, the zone identified by each method, and the success of surgery in reducing seizure activity. No statistical differences were observed between the accuracy of invasive V-EEG and MEG in determining the location of the seizure zone across TLE and ETLE cases. Invasive V-EEG and MEG localization judgments were correct in 54% and 56% of the cases, respectively. Separate group analyses suggested that MEG may be less beneficial relative to invasive V-EEG in ETLE than TLE cases. MEG is of statistically equivalent accuracy to invasive V-EEG, despite the fact that its use has not reached optimal conditions. The authors predict that in the near future, MEG will replace the more invasive procedure for TLE cases, subsequent to the optimization of the conditions under which preoperative MEG is performed.

In a prospective comparative study, researchers evaluated the sensitivity and selectivity of interictal MEG versus prolonged ictal and interictal scalp V-EEG in order to identify patient groups that would benefit from preoperative MEG testing (Patarai, et al., 2004). The study included 113 consecutive patients with medically refractory epilepsy referred for presurgical evaluation. All patients had V-EEG monitoring, MRI and MEG. Some patients had additional testing, including SPECT, PET, and neuropsychological testing, and went on to surgery, including electrocorticography. Data from 31 patients were unsuitable due to artifacts or loss of clinical information. The final data set included complete clinical, scalp and invasive V-EEG data, and MEG results for 82 patients. The epileptogenic region predicted by interictal and ictal V-EEG and MEG was defined in relation to the resected area as perfectly overlapping, partially overlapping, or non-overlapping. Overall, MEG and V-EEG results were equivalent in 32.3% of the cases, and MEG yielded additional localization information in 40% of the patients. For identifying epileptogenic zone, sensitivity of 30-minute interictal MEG study was 79.2% (using V-EEG as gold standard). In following correspondence, the authors reiterate that a substantial proportion (40%) of patients with either non- or partially-localizable V-EEG results may benefit from an interictal MEG study. This information alone, provided that it is confirmed by later studies, will offer clinically significant input to the selection of candidates for noninvasive tests, including MEG. The authors stated that future studies with larger samples are needed to assess the additive advantage of MEG localization data for surgical outcome.

Stefan, et al., (2003) prospectively studied the accuracy of MEG in identifying epileptogenic zone compared with surgical findings in patients with medically intractable epilepsy (n=455). Patients received MSI using two different biomagnetic devices during two periods. The average sensitivity of MEG for specific epileptic activity was 70%. Among 131 patients who underwent surgical therapy in addition to antiepileptic drug medication, MSI identified the lobe to be treated in 89%, with results for extratemporal cases superior even to those who had temporal lobe surgery. When a measure was introduced to quantify the contribution of MSI to the general result of presurgical evaluation for 104 patients, the results showed that MSI supplied additional information in 35% and information crucial to final decision-making in 10%. The authors state that accuracy, as well as contribution findings, underlined MSI appropriateness even for extratemporal epilepsies, which otherwise frequently prove difficult with respect to focus localization. The data does not indicate whether MEG improved surgical outcomes beyond what they would have without MEG, nor whether MEG contributed to the decision to have surgery. This study lacked a control group.

Twenty patients with frequent or predictable seizures were studied to determine the utility of ictal MEG recordings in the presurgical evaluation of patients with epilepsy (Eliashiv, et al., 2002). Successful ictal MEG recordings were made in six of 20 patients with neocortical epilepsy. As determined by invasive EEG recording and postsurgical outcome, ictal MEG provided localizing information superior to that of interictal MEG in three of the six patients. Localization of ictal onset by MEG was at least as good as by invasive EEG in five of the six patients and was superior in two patients, as determined by postsurgical outcome. The researchers concluded that larger studies are necessary to confirm that, in patients with frequent or easily provoked neocortical seizures, ictal MEG recordings can contribute localizing information equivalent or superior to that of invasive EEG recording.

Evidence in the published, peer-reviewed scientific literature is primarily in the form of several small studies. While results to date appear promising for the future clinical application of magnetoencephalography (MEG) or magnetic source imaging (MSI) in epileptic patients, overall, insufficient evidence exists to support specific patient selection criteria. The ultimate clinical utility of MEG has yet to be defined in relation to invasive and noninvasive diagnostic testing. There is inadequate evidence to demonstrate that MEG or MSI can improve clinical outcomes by reducing or replacing invasive tests. More definitive data from large, randomized, prospective controlled studies will help evaluate MEG's/MSI's efficacy and clarify patient selection.

Textbook literature states that the basic approach in epilepsy surgery involves identification and precise localization of the epileptogenic zone, the region of the brain that is necessary and sufficient to cause clinical seizures; determining whether the patient possesses appropriate functional reserve for safe removal of that seizure focus; and subsequent operative resection of this area. A variety of investigations must be performed at specialized comprehensive epilepsy centers to determine if epilepsy surgery would be effective and safe for an individual patient. The most useful and important initial investigations are a high-resolution volumetric brain MRI (with thin cut coronal plane acquisition perpendicular to the hippocampal long axis) and inpatient prolonged ictal V-EEG monitoring that permits intimate correlation and offline, post hoc detailed analysis of the ictal behavior and EEG to localize the patient's habitual clinical seizures. Additional techniques that help localize the epileptic

focus preoperatively include functional imaging techniques such as SPECT, PET, MEG, and neuropsychological testing (St. Louis, et al., 2009).

**Brain Tumors:** There is limited evidence in the peer-reviewed literature for the use of MEG for predicting outcome and for presurgical planning in patients with brain tumors or AVMs. Additional research is required from large well-designed studies with long-term follow-up to determine the clinical utility of MEG for this application. While the results from the studies suggest that MEG can be useful in preoperative assessment of patients with brain tumors and that this information can help to guide surgery, additional studies are required to evaluate the role of MEG data in neuronavigation (Hayes, 2008).

In a prospective study, Korvenoja et al. (2006) compared MEG and functional magnetic resonance imaging (fMRI) with intraoperative cortical mapping in 15 patients with a lesion near the primary sensorimotor cortex (13 gliomas, one cavernous hemangioma, and one meningioma). Researchers utilized “the most widely applied paradigms for MEG and fMRI for primary sensorimotor cortex localization, which is a motor task at fMRI and an electric stimulation of a peripheral nerve at MEG.” Results indicated that MEG enabled more reliable localization of the central sulcus compared with fMRI. Specifically, in all 15 patients, MEG depicted the central sulcus correctly. In 11 (73%) patients, the area of primary activation at functional MR imaging was concordant with that at MEG and intraoperative mapping. The authors stated their results “emphasize that the limited temporal resolution must be appreciated when interpreting fMRI results. Because fMRI is more accessible than is MEG, it will likely remain the primary method used for noninvasive functional mapping. Ultimately, it may be beneficial to use both methods, if feasible, to achieve the most complete and reliable characterization of the functional anatomy.” Reported limitations of this study include small sample size and the variability in the types and locations of the lesions.

In a prospective study, Ganslandt et al. (2004) studied the potential utility of preoperative functional imaging with MEG for the selection of glioma patients who are likely to benefit from resective surgical treatment regarding postoperative morbidity. One hundred and nineteen patients with gliomas adjacent to sensorimotor, visual and speech related brain areas were investigated preoperatively with MEG. In each patient the pre-surgical evaluation was focused on the visual, sensorimotor cortex and/or of the speech related brain areas. A grading system was then used according to the distance of the MEG activation sources to the nearest tumor border to determine the further treatment. The therapeutic options consisted in conservative treatment, stereotactic biopsy and/or a radiation and chemotherapy, substantial cytoreduction and the gross total removal of the lesion. From 119 investigated patients, 55 patients (46.2%) were not considered for surgery due to tumor invasion to functional cortex. Sixty four patients (53.8%) were chosen for resective surgery. In the surgical group only four patients (6.2%) suffered from neurological deterioration. The authors reported that the question remains, if expensive methods for pre-surgical functional brain mapping like MSI warrant these results. Functional MRI may be an alternative more readily available but this method may not to be as accurate in localizing neuronal activity as MSI. Depending on the distance and direction in 3D-space a difference of up to 15mm between the major MEG- and fMRI-activity has been reported. These differences may result in fatal errors when trying to use these data in the operating room. Therefore, some groups emphasize the dual use and integration of both modalities.

In a retrospective case series study, Schiffbuer et al. (2001) studied the necessity of functional imaging in patients with cerebral tumors, particularly gliomas of different grades. Patients with intra-axial cerebral lesions located in the vicinity of eloquent brain cortex preoperatively underwent MSI. The major finding in this series of 106 patients harboring primary intra-axial neoplasms of and metastases to the brain is that 25% of the patients would have been at risk for some type of postoperative neurological deficit if neither preoperative functional imaging nor intraoperative mapping of the cortex had been applied, while attempting to achieve a complete tumor extirpation. The authors report that the results suggest that low-grade gliomas frequently show functional activity within the tumor extent defined by MRI, while high-grade tumors are more likely to show functional centers at the margins of the mass, possibly characteristic of anatomic displacement. To safely maximize tumor resection, preoperative functional imaging using MSI or other techniques and intraoperative electrophysiological mapping of the cerebral cortex and the white matter tracts is necessary. Although MSI should not be expected to be a substitute for intraoperative cortical mapping, it can be considered complementary. This study is limited by lack of randomization; small sample size; no control group; and no follow-up.

**Psychiatric Disorders and Learning Disorders:** Currently, there is insufficient evidence to determine the clinical utility of MEG in the evaluation of psychiatric or learning disorders. There is insufficient evidence to

conclude that MEG improves clinical outcomes in patients with neurologic disorders and psychiatric conditions (Hayes, 2008; Breier, et al., 2005; Fehr, et al., 2001; Lewine, et al., 1999; Reite, et al., 1997).

### **Technology Assessments/Reviews**

In 2009, The BlueCross BlueShield Association (BCBSA) published a Technology Evaluation Center Special Report on Magnetoencephalography and Magnetic Source Imaging for the Purpose of Presurgical Localization of Epileptic Lesions stating in their main results and conclusions that " The argument that MEG improves the diagnostic yield of intracranial electroencephalogram (IC-EEG) is often made, but it is difficult to identify studies that can support this argument. Studies that compare IC-EEG to MEG do not inform this particular question. On the other hand, given the gravity of this particular situation, there are some possible arguments to be made on behalf of MEG. Given that current decision making regarding who should receive surgery and what type of surgery is done with some uncertainty and lack of a true reference standard, an additional piece of information that is known to correlate with seizure focus could be arguably of some value in making difficult decisions. The diagnostic test is easy to perform and noninvasive. Also, IC-EEG and surgery are extremely invasive procedures that do not always provide diagnostic information. Information from MEG might influence a patient's decision to undergo the risks of further testing or surgery if the outcome can be slightly better estimated. However, given that one possible outcome of use of MEG may result in avoidance of tests and procedures that may benefit the patient, it is not possible to rule out harm from use of the test. The net effect of the use of MEG on patient outcomes for this indication remains to be determined" (BCBSA, 2009).

In a systematic review, Lau et al. (2008) determined the effectiveness of MEG/MSI in the presurgical evaluation of localization-related epilepsies. The authors searched MEDLINE, the Cochrane library, and EMBASE between 1987 and 2006 for English articles. Studies including a minimum of four patients with at least six months follow-up after surgery were reviewed. In each study, surgical outcome (seizure freedom) was correlated with the concordance of MEG source localization and resection area. Twenty-eight studies satisfied the inclusion criteria. Eleven of the 28 studies were excluded due to an inability to determine the concordance between the MEG epileptic focus and the resected area based on the published data. Data from the remaining studies found sensitivity (range: 0.20—1.0) values for all articles, and specificity (0.06—1.00) values, positive likelihood ratios (0.67—2.0) and negative likelihood ratios (0.40—2.13) for some studies. The authors concluded that as a primary diagnostic tool the sensitivity and/or specificity of MEG has not been consistently high. The authors noted that there are multiple sources of variation between studies, and the sample size of each population was fairly small. More controlled and consistent studies need to be done to determine whether MEG is an adequate replacement as a diagnostic tool for IEEG. There is insufficient evidence in the current literature to support the relationship between the use of MEG in surgical planning and seizure-free outcome after epilepsy surgery.

In September 2008, Hayes, Inc. conducted a review of the literature regarding the use of MEG and MSI of the brain. A total of 19 studies met inclusion criteria and were reviewed; ten studies for identification of epileptogenic foci and presurgical assessment of epilepsy patients; five studies for pretreatment assessment and operative planning in patients with brain lesions (tumors and arteriovenous malformations); and four studies for neuropsychiatric and learning disorders. The authors reported that "overall, evaluation of the effectiveness of MEG/MSI for epilepsy, structural brain lesions, and psychiatric and learning disorders was hampered by the lack of large, well-designed, randomized studies, lack of post-surgical outcomes, heterogeneity of study populations, and the diversity among both interventions and, outcome measures. The vast majority of studies involved adult patients, and there was very little evidence regarding the use of MEG/MSI in children. Most of the available studies failed to report any follow-up, although five studies reported follow-up of  $\geq$  one year. The reviewed studies did not examine the effect of MEG/MSI on patient management or disease outcomes. Therefore, there is currently no evidence that MEG/MSI reduce the morbidity or mortality associated with epilepsy, brain lesions, or neuropsychiatric or learning disorders" (Hayes, Inc., 2008).

In January 2007, the Ontario Health Technology Advisory Committee (OHTAC) reviewed the clinical utility of functional brain imaging (e.g., MEG) in the diagnosis or management of patients with epilepsy. The authors reported, "MEG provides a possible opportunity to replace the invasive EEG because it can potentially localize the seizure foci noninvasively. There is some limited observational data (five studies, n=190) to suggest that MEG may be as accurate as invasive EEG at localizing the seizure foci. MEG is not only non-invasive but the investigation is performed during a single examination." Based on the results of the health technology and policy assessment, the OHTAC recommendation for epilepsy states that a field evaluation needs to be conducted to determine the potential substitutive role of MEG versus IEEG.

## Professional Societies/Organizations

In May 2009, the Medical Economics and Management Committee (MEM) of The American Academy of Neurology (AAN) published a model medical policy for MEG. The policy states the following indications for MEG:

- Epilepsy—Pre-surgical evaluation in patients with intractable focal epilepsy to identify and localize area(s) of epileptiform activity. MEG can be valuable when discordance or continuing questions arise from amongst other techniques designed to localize a focus.
- Tumors and Arteriovenous Malformation Surgeries—Pre-surgical evaluation of brain tumors and vascular malformations. The aim is to identify, localize and preserve eloquent cortex during resective surgery.

The policy states the following limitations for MEG:

- MEG cannot replace, but may guide the placement of intracranial EEG (IEEG) and, in some patients, avoid an unnecessary IEEG.
- MEG is not the first order of test after clinical and routine EEG diagnosis of epilepsy. It is one of several advanced pre-surgical investigative technologies. The need for MEG is much lower than surface EEG and anatomical imaging studies.
- MEG is not a stand-alone test. To realize its optimum clinical potential a comprehensive team evaluation, such as that available in comprehensive epilepsy centers, is necessary. The team usually comprises a neurologist with expertise in epilepsy, a neurosurgeon, MEG-physicists, psychologists, nurses and staff experienced in treatment of seizure disorders.

The AAN policy reported the results of a number of clinical trials but do not provide an analysis of the quality of the studies. The model policy does not describe the process by which the evidence was used to reach conclusions. The AAN continues to develop an updated clinical practice guideline for MEG.

The American Academy of Neurology (AAN) and American Epilepsy Society (AES) practice parameters for the use of neuroimaging and EEG for evaluation of an apparent unprovoked first time seizure in adults recommends that brain imaging using CT or MRI should be considered as part of the neurodiagnostic evaluation of adults presenting with an apparent unprovoked first seizure. There is no mention of MEG/MSI in the practice parameter (Krumholz et al., 2007).

The American Clinical Magnetoencephalography Society (ACMEGS) Position Statement on the value of MEG/MSI in noninvasive presurgical evaluation of patient with medically intractable localization-related epilepsy states that after considering the entire body of published evidence through April 20, 2009, including what the ACEGS refers to as the most sophisticated clinical MEG studies designed and published internationally (Knowlton et al., 2008a,b; Sutherling, et al., 2008), the ACMEGS acknowledges that sufficient credible evidence has been published to support a position statement regarding the value of MEG in the presurgical evaluation of patients with medically intractable localization-related epilepsy. The ACMEGS intends to enhance the practice of clinical MEG/MSI further by developing practice parameters. The authors do not describe the process by which the evidence was used to reach conclusions. The ACMEGS supports (Bagic, et al., 2009):

- Routine clinical use of MEG/MSI in obtaining noninvasive, nonredundant localizing information in presurgical evaluation of patients with medically intractable localization-related epilepsy.
- Determination of MEG/MSI indications for an individual patient by an epileptologist or a clinical team associated with a National Association of Epilepsy Centers-designated epilepsy center.
- Routine use of MEG/MSI when traditional EEG methods and magnetic resonance imaging are implemented and provide insufficient localizing information.
- Uses for MEG/MSI indicated by accepted standards of clinical judgment and care and the rational utilization of resources without further restrictions.
- Further systematic clinical research that seeks to establish other clinical indications for MEG/MSI.

The American College of Radiology (ACR) Appropriateness Criteria™ for summary of literature for epilepsy states, “Only MEG and EEG are capable of measuring epileptic brain activity directly and with high temporal resolution. The temporal resolution of PET, single-emission computed tomography (SPECT), and functional MRI

(fMRI) is poor by comparison (seconds-minutes). Recent improvements in MEG technology now allow whole brain coverage and overlay of source information on MR or CT images (with MSI). Available data indicate that interictal MEG can be an effective tool for localization of seizure foci in patients with medical refractory partial epilepsy. Significant shortcomings include limited availability and assessment limited to relatively superficial and tangential sources. Nonetheless, MSI does provide unique, accurate, and useful information about epileptogenic regions in the brain and, where available, has a potential role in the diagnostic workup of most patients with epilepsy.” The ACR appropriateness criteria scale ranges from 1–9, with a score of 1 indicating the least appropriate imaging examination and a 9 indicating the most appropriate. The ACR gave MEG/MSI a rating of 2 for most variants. For the variant chronic epilepsy, poor therapeutic response and a surgery candidate, ACR gave MEG/MSI a rating of 5, stating the data is probably equivalent to blood oxygen level development (BOLD) and SPECT (Karis, et al., 2006). This criteria has not been updated since 2006.

The Report of the Quality Standards Subcommittee of the American Academy of Neurology (AAN) and the Child Neurology Society states that there is insufficient evidence to suggest a role for event-related potentials or MEG in the evaluation of autism (Filipek, et al., 2000). This report has not been updated since 2000.

### Summary

Evidence in the current, published, peer-reviewed scientific literature is primarily in the form of several small studies. While results to date appear promising for the future clinical application of magnetoencephalography (MEG) or magnetic source imaging (MSI) in epileptic patients, overall, insufficient evidence exists to support specific patient selection criteria. The ultimate clinical utility of MEG has yet to be defined in relation to invasive and noninvasive electroencephalography (EEG), interictal positron emission tomography (PET), interictal single-photon emission computed tomography (SPECT), magnetic resonance spectroscopy (MRS), and functional magnetic resonance imaging (fMRI). More definitive data from large, randomized, prospective controlled studies will help evaluate MEG's efficacy and clarify patient selection.

## Coding/Billing Information

**Note:** This list of codes may not be all-inclusive.

### Experimental/Investigational/Unproven/Not Covered:

CPT* Codes	Description
95965	Magnetoencephalography (MEG), recording and analysis; for spontaneous brain magnetic activity (e.g., epileptic cerebral cortex localization)
95966	Magnetoencephalography (MEG), recording and analysis; for evoked magnetic fields, single modality (e.g., sensory, motor, language, or visual cortex localization)
95967	Magnetoencephalography (MEG), recording and analysis; for evoked magnetic fields, each additional modality (e.g., sensory, motor, language, or visual cortex localization) (List separately in addition to code for primary procedure)

HCPCS Codes	Description
S8035	Magnetic source imaging

ICD-9-CM Diagnosis Codes	Description
	All codes

\*Current Procedural Terminology (CPT®) ©2008 American Medical Association: Chicago, IL.

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## Policy History

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<u>Pre-Merger Organizations</u>	<u>Last Review Date</u>	<u>Policy Number</u>	<u>Title</u>
CIGNA HealthCare	12/15/2007	0248	Magnetoencephalography (MEG)

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA's subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.