I. POLICY

Magnetoencephalography/magnetic source imaging for the purpose of determining the laterality of language function, as a substitute for the Wada test, in patients being prepared for surgery for epilepsy, brain tumors, and other indications requiring brain resection, may be considered medically necessary.

Magnetoencephalography/magnetic source imaging as part of the preoperative evaluation of patients with intractable epilepsy (seizures refractory to at least two first-line anticonvulsants) may be considered medically necessary when standard techniques, such as MRI and EEG, do not provide satisfactory localization of epileptic lesion(s).

Magnetoencephalography / magnetic source imaging is considered investigational for all other indications. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with these procedures.

Magnetic resonance spectroscopy is considered investigational, as there is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with these procedures.

Cross-reference

MP-2.304 Pervasive Developmental Disorders

II. PRODUCT VARIATIONS

[N] = No product variation, policy applies as stated
[Y] = Standard product coverage varies from application of this policy, see below

[N] Capital Cares 4 Kids
[N] PPO
[N] HMO
[N] SeniorBlue
[N] SeniorBlue PPO

[N] Indemnity
[N] SpecialCare
[N] POS
[Y] FEP PPO*

[Note: Final page is signature page and is kept on file, but not issued with Policy.]
III. DESCRIPTION/BACKGROUND

Magnetoencephalography

Magnetoencephalography (MEG) is a noninvasive functional imaging technique in which the weak magnetic forces associated with the electrical activity of the brain are recorded externally. Using mathematical modeling, the recorded data are then analyzed to provide an estimated location of the electrical activity. This information can be superimposed on an anatomic image of the brain, typically a magnetic resonance imaging (MRI) scan, to produce a functional/anatomic image of the brain, referred to as magnetic source imaging (MSI). The primary advantage of MSI is that while the conductivity and thus the measurement of electrical activity as recorded by the electroencephalogram (EEG) is altered by surrounding brain structures, the magnetic fields are not. Therefore, MSI permits a high-resolution image.

The technique is sophisticated. Detection of the weak magnetic fields depends on gradiometer detection coils coupled to a superconducting quantum interference device (SQUID), which requires a specialized room shielded from other magnetic sources. Mathematical modeling programs based on idealized assumptions are then used to translate the detected signals into functional images. In its early evolution, clinical applications were limited by the use of only one detection coil requiring lengthy imaging times, which, because of body movement, were also difficult to coordinate with the MRI. However, more recently the technique has evolved to multiple detection coils arranged in an array that can provide data more efficiently over a wide extracranial region.

One clinical application is localization of the pre- and postcentral gyri as a guide to surgical planning in patients scheduled to undergo neurosurgery for epilepsy, brain neoplasms, arteriovenous malformations, or other brain disorders. These gyri contain the "eloquent" sensorimotor areas of the brain, the preservation of which is considered critical during any type of brain surgery. In normal situations, these areas can be identified anatomically by MRI, but frequently the anatomy is distorted by underlying disease processes. In addition, the location of the eloquent functions is variable, even among
healthy patients. Therefore, localization of the eloquent cortex often requires such intraoperative invasive functional techniques as cortical stimulation with the patient under local anesthesia or somatosensory-evoked responses on electrocorticography (ECoG). While these techniques can be done at the same time as the planned resection, they are cumbersome and can add up to 45 minutes of anesthesia time. Furthermore, sometimes these techniques can be limited by the small surgical field. A preoperative test, which is often used to localize the eloquent hemisphere, is the Wada test. MEG/MSI has been proposed as a substitute for the Wada test.

Another related clinical application is localization of epileptic foci, particularly for screening of surgical candidates and surgical planning. Alternative techniques include MRI, positron emission tomography (PET), or single photon emission computed tomography (SPECT) scanning. Anatomic imaging (i.e., MRI) is effective when epilepsy is associated with a mass lesion, such as a tumor, vascular malformation, or hippocampal atrophy. If an anatomic abnormality is not detected, patients may undergo a PET scan. In a small subset of patients, extended electrocorticography (ECoG) or stereotactic electroencephalography EEG (SEEG) with implanted electrodes is considered the gold standard for localizing epileptogenic foci. MEG/MSI has principally been investigated as a supplement to or an alternative to invasive monitoring.

### Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) is a noninvasive technique that can be used to measure the concentrations of different chemical components within tissues. The technique is based on the same physical principles as magnetic resonance imaging (MRI) and the detection of energy exchange between external magnetic fields and specific nuclei within atoms. With MRI, this energy exchange, measured as a radiofrequency signal, is then translated into the familiar anatomic image by assigning different gray values according to the strength of the emitted signal. The principal difference between MRI and MRS is that in MRI the emitted radiofrequency is based on the spatial position of nuclei, while MRS detects the chemical composition of the scanned tissue. The information produced by MRS is displayed graphically as a spectrum with peaks consistent with the various chemicals detected. MRS may be performed as an adjunct to MRI. An MRI image is first generated, and then MRS spectra are developed at the site of interest, termed the voxel. While an MRI provides an anatomic image of the brain, MRS provides a functional image related to underlying dynamic physiology. MRS can be performed with existing MRI equipment, modified with additional software and hardware.

MRS has been studied most extensively in a variety of brain pathologies. In the brain, both 1-H (i.e., proton) and 31-P are present in concentrations high enough to detect and thus have been used extensively to study brain chemistry. For example, proton MRS of the healthy brain reveals 5 principal spectra:
• Arising from N-acetyl groups, especially N-acetylaspartate (NAA)

NAA intensity is thought to be a marker of neuronal integrity and is the most important proton signal in studying central nervous system (CNS) pathology. Decreases in the NAA signal are associated with neuronal loss.

• Arising from choline-containing compounds (Cho), such as membrane phospholipids (e.g., phosphocholine and glycerophosphocholine). Choline levels increase in acute demyelinating disease. Brain tumors may also have high signals from Cho.

• Arising from creatine and phosphocreatine

In the brain, creatine is a relatively constant element of cellular energetic metabolism and thus is sometimes used as an internal standard.

• Arising from lipid

• Arising from lactate

Normally this spectrum is barely visible, but lactate may increase to detectable levels when anaerobic metabolism is present. Lactate may accumulate in necrotic areas, in inflammatory infiltrates, and in brain tumors.

Different patterns of the above spectra and others, such as myoinositol and glutamate/glutamine, in the healthy and diseased brain are the basis of clinical applications of MRS. The MRS findings characteristically associated with non-necrotic brain tumors include elevated Cho levels and reduced NAA levels. The International Network for Pattern Recognition using Magnetic Resonance (Available online at: http://azizu.uab.es/INTERPRET/index.html) has developed a user-friendly computer program for spectral classification and a database of 300 tumor spectra with histologically validated diagnoses to aid radiologists in MRS diagnosis. All the findings reported in this policy refer to proton MRS, unless otherwise indicated.

One of the limitations of MRS is that it provides the metabolic composition of a given voxel, which may include more than 1 type of tissue.

For some applications, the voxels are relatively large (e.g., greater than 1 cm³), although they may be somewhat smaller using a 3T MRI machine versus a 1.5T magnet. The 3T technique creates greater inhomogeneities, however, which require better shimming techniques. There are two types of MRS data acquisition: single voxel or simultaneous multivoxel, also called chemical shift imaging. Reliable results are more difficult to obtain from some areas, e.g., close to the brain surface or in children with smaller brains because of the lipid signal from the skull. Some techniques are used to deal with these issues; various MRS techniques continue to be explored as well. A combination of MRS is often used with other MRI techniques, including diffusion-tensor imaging, susceptibility-
weighted imaging, etc., and possibly other types of imaging such as positron emission tomography (PET).

Peripheral applications of MRS include the study of myocardial ischemia, peripheral vascular disease, and skeletal muscle. Applications in non-CNS oncologic evaluation have also been explored. New nomograms for prostate cancer are being developed that incorporate MRI and MRS results.

Multiple software packages for performing proton MRS have received clearance by the U.S. Food and Drug Administration (FDA) through the 510(k) process since 1993.

IV. RATIONALE

Magnetoencephalography/Magnetic Source Imaging

Localization of Seizure Focus

This section is based on a 2008 TEC Special Report reviewing the evidence regarding MEG for localization of epileptic lesions. (1) MEG has been proposed as a method for localizing seizure foci for patients with normal or equivocal magnetic resonance imaging (MRI) and negative video-electroencephalogram (EEG) examinations, so-called “nonlesional” epilepsy. Such patients often undergo MEG, positron emission tomography (PET), or ictal-single photon emission computed tomography (SPECT) tests to attempt to localize the seizure focus. They then often undergo invasive intracranial EEG, a surgical procedure in which electrodes are inserted next to the brain. MEG would be considered useful if, when compared to not using MEG, it improved patient outcomes. Such improvement in outcomes would include more patients being rendered seizure-free, use of a less invasive and morbid diagnostic workup, and increased surgical success rates. This is a complicated array of outcomes that has not been thoroughly evaluated in a comprehensive manner.

Ideally, a randomized trial comparing the outcomes of patients who receive MEG as part of their diagnostic workup compared to patients who do not receive MEG could determine whether MEG improves patient outcomes. However, almost all of the studies evaluating MEG have been retrospective, where MEG, other tests, and surgery have been selectively applied to patients. Since patients often drop out of the diagnostic process before having intracranial EEG (IC-EEG), and many patients ultimately do not undergo surgery, most studies of associations between diagnostic tests and between diagnostic tests and outcomes are biased by selection and ascertainment biases. For example, studies that evaluate the correlation between MEG and IC-EEG invariably do not account for the fact that MEG information was sometimes used to deselect a patient from undergoing IC-EEG.
addition, IC-EEG findings only imperfectly correlate with surgical outcomes, meaning that it is an imperfect reference standard.

Numerous studies have shown associations between MEG findings and other noninvasive and invasive methods diagnostic tests, including IC-EEG, and between MEG findings and surgical outcomes. However, such studies do not allow any conclusions regarding whether MEG added incremental information to aid the management of such patients and whether patients’ outcomes were improved as a result of the additional diagnostic information.

A representative study of MEG by Knowlton and colleagues (2) demonstrates many of the problematic issues of evaluating MEG. In this study of 160 patients with nonlesional epilepsy, all had MEG, but only 72 proceeded to IC-EEG. The calculations of diagnostic characteristics of MEG are biased by incomplete ascertainment of the reference standard. However, even examining the diagnostic characteristics of MEG using the 72 patients who underwent IC-EEG, sensitivities and specificities were well below 90%, indicating the likelihood of both false-positive and false-negative studies. Predictive values based on these sensitivities and specificities mean that MEG can neither rule in nor rule out a positive IC-EEG, meaning that MEG cannot be used as a triage test before IC-EEG to avoid the potential morbidity in a subset of patients.

One study more specifically addresses the concept that MEG may improve the yield of IC-EEG, thus, allowing more patients to ultimately receive surgery. In a study by Knowlton et al., (3) out of 77 patients who were recommended to have IC-EEG, MEG results modified the placement of electrodes in 18 of the 77 cases. Seven cases out of the 18 had positive intracranial seizure recordings involving the additional electrodes placed because of the MEG results. It was concluded that 4 patients are presumed to have had surgery modified as a result of the effect of MEG on altering the placement of electrodes.

Several studies correlate MEG findings to surgical outcomes. Lau et al. (4) performed a meta-analysis of 17 such studies. In this meta-analysis, sensitivity and specificity have unorthodox definitions. Sensitivity is the proportion of patients cured with surgery in whom the MEG-defined epileptic region was resected, and specificity is the proportion of patients not cured with surgery in whom the MEG-defined epileptic region was not resected. The pooled sensitivity was 0.84, meaning that among the total number of cured patients, 14% occurred despite the MEG-defined region not being resected. Pooled specificity was 0.52, meaning that among 48% of patients not cured, the MEG-localized region was resected. These results are consistent with an association between resection of the MEG-defined region and surgical cure, but that it is an imperfect predictor of surgical success. However, it does not address the question as to whether MEG contributed original information to improve the probability of cure.
### MEDICAL POLICY

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Other studies imply a value to MEG, but it is difficult to make firm conclusions regarding its value. In a study by Schneider et al., (5) 14 patients with various findings on MEG, IC-EEG, and interictal SPECT underwent surgery for nonlesional neocortical focal epilepsy. Concordance of IC-EEG and MEG occurred in 5 patients, 4 of whom became seizure-free. This concordance of the 2 tests was the best predictor of becoming seizure-free. Although this was prognostic for success, whether this would actually change surgical decision making, such as declining to operate where there is not such concordance, is uncertain. A similar study by Widjaja et al. (6) shows that concordance of MEG findings with the location of surgical resection is correlated with better seizure outcomes. However, the authors admit that MEG is entrenched in clinical practice, and the decision to proceed further in diagnostic and therapeutic endeavors is based on the results of MEG and other tests.

The American Clinical MEG Society released a position statement that supports the routine clinical use of MEG/MSI for presurgical evaluation of patients with medically intractable seizures. (7) In this statement, they specifically cite a study by Sutherling et al. (8) as being a “milestone class I study.” Class I evidence usually refers to randomized comparisons of treatment. However, the study by Sutherling et al. is called by its authors a “prospective, blinded crossover-controlled, single-treatment, observational case series.” The study attempts to determine the proportion of patients in whom the diagnostic or treatment strategy was changed as a consequence of MEG. They concluded that the test provided nonredundant information in 33% of patients, changed treatment in 9% of surgical patients, and benefited 21% of patients who had surgery. There was no control group in this study. Benefit of MEG was inferred by assumptions of what might have occurred in the absence of the MEG result. Less than half of the 69 patients went on to receive IC-EEG; thus, there appears to be incomplete accounting for outcomes of all patients in the study. A similar study by De et al. (9) also attempted to determine the number of patients in whom management decisions were altered based on MEG results. They concluded that clinical management was altered in 13% of all patients.

**Conclusions.** There are no clinical trials demonstrating the utility of MEG in determining location of seizure focus and no high-quality studies of diagnostic accuracy. The available evidence on diagnostic accuracy is limited by ascertainment and selection biases because MEG findings were used to select and deselect patients in the diagnostic pathway thus, making it difficult to determine the role of MEG for the purpose of seizure localization. The evidence supporting the effect of MEG on patient outcomes is indirect and incomplete. Surgical management may be altered in a minority of patients based on MEG, but there is insufficient evidence to conclude that outcomes are improved as a result of these management changes. Trials with a control group are needed to determine whether good outcomes can be attributed to the change in management induced by knowledge of MEG findings.
Localization of Eloquent and Sensorimotor Areas

In a 2003 TEC Assessment of MEG, the evidence for this particular indication concluded that the evidence was insufficient to demonstrate efficacy. At that time, the studies reviewed had relatively weak study methods and very limited numbers of subjects. There are two ways to analyze the potential utility of MEG for this indication. MEG could potentially be a noninvasive substitute for the Wada test, which is a standard method of determining hemispheric dominance for language. The Wada test requires catheterization of the internal carotid arteries, which carries the risk of complications. The determination of the laterality of the language function is important to know to determine the suitability of a patient for surgery and what types of additional functional testing might be needed prior to or during surgery. If MEG provides concordant information with the Wada test, then such information would be obtained in a safe, noninvasive manner.

Several studies have shown high concordance between the Wada test and MEG. In the largest study, by Papanicolaou and co-workers, among 85 patients, there was concordance between the MEG and Wada tests in 74 (87%). In no cases were the tests discordant in a way that the findings were completely opposite. The discordant cases occurred mostly when the Wada test indicated left dominance and the MEG indicated bilateral language function. In an alternative type of analysis, where the test is being used to evaluate the absence or presence of language function in the side in which surgical treatment is being planned, using the Wada procedure as the gold standard, MEG was 98% sensitive and 83% specific. Thus, if the presence of language function in the surgical site requires intraoperative mapping and/or a tailored surgical approach, use of MEG rather than Wada would have “missed” one case where such an approach would be needed, and resulted in 5 cases where such an approach was unnecessary (false-positive MEG). However, it should be noted that the Wada test is not a perfect reference standard, and some discordance may reflect inaccuracy of the reference standard. In another study by Hirata et al., MEG and the Wada test agreed in 19/20 (95%) of cases.

The other potential use of MEG would be for the purpose of mapping the sensorimotor area of the brain, again to avoid such areas in the surgical resection area. Intraoperative mapping just before resection is generally done as the reference standard. Preoperative mapping as potentially done by MEG might aid in determining the suitability of the patient for surgery or for assisting in the planning of other invasive testing. Similar to the situation for localization of epilepsy focus, the literature is problematic in terms of evaluating the comprehensive outcomes of patients due to ascertainment and selection biases. Studies tend to be limited to correlations between MEG and intraoperative mapping. The intraoperative mapping would be performed anyway in most resection patients. Several of the studies evaluated in the 2003 TEC Assessment showed good to high concordance between MEG findings and intraoperative mapping.
assessment on functional brain imaging performed by the Ontario Ministry of Health reviewed 10 studies of MEG and invasive functional mapping and showed good to high correspondence between the two tests. (13) However, these studies do not demonstrate that MEG would replace intraoperative mapping or reduce the morbidity of such mapping by allowing a more focused procedure.

Recent studies of the use of MEG in localizing the sensorimotor area provide only indirect evidence of utility. A study by Niranjan et al. (14) reviewed the results of 45 patients in whom MEG was used for localizing somatosensory function. In 32 patients who underwent surgery, surgical access routes were planned to avoid regions identified as somatosensory by MEG. All patients retained somatosensory function. It is unknown to what extent MEG provided unique information not provided by other tests. In a study by Tarapore et al., (15) 24 patients underwent MEG, transcranial magnetic stimulation, and intraoperative direct cortical stimulation to identify the motor cortex. MEG and navigated transcranial magnetic stimulation were both able to identify several areas of motor function, and the median distance between corresponding motor areas was 4.71 mm. When comparing MEG to direct cortical stimulation, the median distance between corresponding motor sites (12.1 mm) was greater than the distance between navigated transcranial magnetic stimulation and direct cortical stimulation (2.13 mm). This study cannot determine whether MEG provided unique information that contributed to better patient outcomes.

Conclusions. There are no clinical trials that demonstrate the utility of using MEG for localization and lateralization of eloquent and sensorimotor regions of the brain. The available evidence consists of studies that correlate results of MEG with the Wada test, which is an alternative method for localization. The evidence generally shows that the concordance between MEG and the Wada test is high. Since MEG is a less invasive alternative to the Wada test, this evidence indicates that it is a reasonable alternative. There is also some evidence that the correlation of MEG with intraoperative mapping of eloquent and sensorimotor regions is high, but the test has not demonstrated sufficient accuracy to replace intraoperative mapping.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

In response to requests, input was received from 2 physician specialty societies (5 reviewers) and 2 academic medical centers while this policy was under review in 2011. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless
otherwise noted. There was support for use of MEG/MSI for both localization of language function and as part of the preoperative evaluation of intractable seizures. Those providing clinical input indicated that use of MEG/MSI in the preoperative evaluation leads to identification of additional individuals whose epilepsy may be cured using a surgical approach.

Summary

The published evidence on magnetoencephalography (MEG) is suboptimal, with no clinical trials demonstrating utility. The literature on diagnostic accuracy has methodologic limitations, primarily selection bias and ascertainment bias. The available studies report that this test has high concordance with the Wada test, which is currently the main alternative for localizing eloquent functions. Management is changed in some patients based on MEG testing, but it has not been demonstrated that these changes in management lead to improved outcomes. Clinical input obtained in 2011 indicated consensus for use of MEG as a substitute for the Wada test in determining the laterality of language function in patients being considered for surgery to treat epilepsy, brain tumors, and other structural brain lesions. Clinical input also demonstrated consensus on use of MEG as part of the preoperative evaluation of patients with intractable epilepsy when standard techniques, such as magnetic resonance imaging (MRI), are inconclusive.

Based on the available scientific literature, the results of clinical input, and a strong indirect chain of evidence that outcomes are improved, MEG/MSI (magnetic source imaging) may be considered medically necessary as a substitute for the Wada test for the purpose of determining laterality of language function. MEG may also be considered medically necessary as part of the preoperative evaluation of patients with intractable epilepsy when standard techniques such as MRI are inconclusive.

Magnetic Resonance Spectroscopy

Validation of a new imaging technique involves the following steps:

1. Demonstration of its technical feasibility, including assessment of its reproducibility and precision.
2. An understanding of normal and abnormal values as studied in different clinical situations. For accurate interpretation of study results, sensitivities, specificities, and positive and negative predictive values compared to a reference standard must be known.
3. The clinical utility of an imaging study is related to how the results of that study can be used to benefit patient management. The clinical utility of both true-positive and
true-negative tests must be assessed. Relevant outcomes of a negative test (ie, suspected pathology is not present) may be avoidance of more invasive diagnostic tests or avoidance of ineffective therapy. Relevant outcomes of a positive test (ie, suspected pathology is present) may also include avoidance of a more invasive test plus the institution of specific, effective therapy. Use of the imaging study should result in net health benefit.

The published data indicate that the second and third criteria have not been met for magnetic resonance spectroscopy (MRS). MRS has been investigated in a wide variety of clinical situations; key potential applications are discussed below.

**Literature Review**

There are a variety of potential indications for MRS, both for cancer and noncancer conditions. The clinical utility of MRS will be evaluated separately for each of these indications.

**Brain Tumors**

A TEC Assessment was completed in 2003 evaluating MRS for evaluation of suspected brain tumors. The 2003 TEC Assessment (4) used the following study selection criteria to identify studies for inclusion in the MRS assessment:

1. Sample sizes of 10 or more subjects;
2. A method to confirm the MRS diagnosis;
3. Specified criteria for a positive test; and

The Assessment identified 7 studies including a total of 271 subjects. MRS would be judged to produce a beneficial effect on a health outcome if MRS correctly determined the presence or absence of a tumor and avoided the need for a brain biopsy. The Assessment concluded that MRS did not meet TEC criteria for evaluation of suspected brain tumors. (4)

One study of 12 children treated with radiation for a brain tumor had an MRI suggestive of either progressive/recurrent tumor or delayed cerebral necrosis.(5) MRS identified 5 of 7 recurrent tumors, for a sensitivity of 71%. MRS identified 4 of 5 cases (80%) of delayed necrosis, and a fifth case was considered inconclusive.

Five studies that evaluated a heterogeneous group of patients, some with known prior tumor, some with unknown new masses, showed variable diagnostic test characteristics
for MRS with sensitivities ranging from 79% to 100% and specificity ranging from 74% to 100%. The positive predictive value ranged from 92% to 100%, while the negative predictive value ranged from 60% to 100%. The wide range reported for diagnostic performance in these studies may reflect heterogeneous groups of patients, differences in MRS protocols, or both.

One study evaluated 51 patients with intracranial cystic lesions. (11) MRS properly assigned the correct diagnosis in 47 of 51 patients (92%). However, MRS interpretation was based on investigator judgment, rather than on formal criteria.

The 2003 TEC Assessment concluded that the overall body of evidence did not provide strong and consistent evidence regarding the diagnostic test characteristics or clinical utility of MRS for any condition. Studies of diagnostic performance often included a heterogeneous mix of patients who had clinically important differences and did not clearly delineate how MRS information would be used to guide patient management. Furthermore, differences in MRS technique and methods of analysis across studies made it difficult to synthesize findings from different studies.

A systematic literature review on MRS for the characterization of brain tumors was performed in 2006. This review evaluated whether MRS could differentiate malignant from nonmalignant lesions; high-grade tumors from low-grade tumors; and metastatic from primary brain tumors. The review concluded that the evidence on MRS for characterizing brain tumors is promising but that additional high-quality studies are needed. (12) Many of the articles reviewed were flawed, in some cases because of research design and in other cases because key information needed to evaluate the study was not reported (eg, how many days elapsed between the imaging test and the biopsy, which served as the reference standard).

Other research has attempted to determine whether MRS can differentiate the type of brain tumor. In 2012, Vicente et al reported on a multicenter study to evaluate the ability of single voxel, proton MRS to differentiate 78 histologically confirmed pediatric brain tumors (29 medulloblastomas, 11 ependymomas and 38 pilocytic astrocytomas). (13) Significant metabolic differences in tumor types were identified by MRS when results from short and long echo times were combined, suggesting that MRS may provide noninvasive diagnostic information.

In 2012, Wilson et al evaluated MRS as a prognostic tool. This study reported on single voxel, proton MRS using short echo times to predict survival of patients with pediatric brain tumors in 115 patients followed for a median of 35 months. (14) Metabolic changes were identified that predicted survival. Poor survival was associated with lipids and
scyll-inositol while glutamine and N-acetylaspartate (NAA) were associated with improved survival (p<0.05).

Studies on the use of MRS to categorize newly diagnosed brain tumors (15); to distinguish between tumors and abscesses or other infectious processes (16); or to diagnose mitochondrial diseases (17) identify the MRS patterns associated with each type of lesion but, once again, do not include the necessary validation study or they report MRS findings that overlap across the categories of interest. Many are also retrospective.(16,18) Preliminary studies done in Asia with a 3T MRI machine for detecting tumor versus radiation injury reported diagnostic quality MRS studies in 26/28 (93%) cases, and the sensitivity and specificity for those 26 patients based on cutoffs identified in the study were 94.1% and 100%, respectively.(15) See also(19). Validation studies using the same cutoffs in larger samples are needed. (15)

A 2009 review on MRS in radiation injury concludes the following:

MR spectroscopy is presently one of the noninvasive radiologic methods used to distinguish recurrent tumor and radiation injury in patients previously treated with radiation for neoplasm. Still, despite a considerable volume of research in the field, no consensus exists in the community regarding ratio calculations, the accuracy of MR spectroscopy to identify radiation necrosis, and the accuracy of MR spectroscopy in differentiating radiation necrosis from tumor recurrence or the true value of the method in clinical decision making. (20)

For another review, see (21).

In a 2011 study, Amin et al compared MRS to single-photon emission computed tomography (SPECT) in the identification of residual or recurrent glioma versus radiation necrosis in 24 patients treated with surgery and radiotherapy. (22) MRS and SPECT results differed in 9 cases of recurrence and were more accurate with SPECT. Specificity and positive predictive value were 100% in both MRS and SPECT; however, sensitivity was 61.1% versus 88.8% and negative predictive value was 46.2% versus 75%, respectively. The use of a single voxel rather than multiple voxels is noted as a limitation in interpreting the MRS results in this study.

Section Summary

Although a number of studies have examined the use of MRS to differentiate between brain tumor recurrence and radiation necrosis, the cumulative evidence remains weak. The studies tend to have small sample sizes(23,24); they provide incomplete histopathologic data to serve as the reference standard(25); they find that combined imaging modalities,
such as MRS and perfusion MRI or diffusion-weighted MRI, outperform MRS by itself\(^\text{19,26}\); or they identify the patterns of interest and the cutoff values for making a diagnosis without providing validation studies.\(^\text{18,27}\) In some cases, a mixed reference standard is used, with histopathologic findings for lesions that are excised, undergo biopsy, or are reviewed at autopsy and longer follow-up for patients not undergoing surgery.\(^\text{18,19}\) Although having a mixed reference standard is not optimal, it may be the only feasible option in patients with brain tumors, some of which are located in parts of the brain not amenable to surgery. Some studies report mostly on primary brain tumors, \(^\text{15, and 19}\) while others focus mostly on metastases of cancers located in other parts of the body. \(^\text{23, 25}\)

**Dementia**

Research continues on using MRS to identify dementia, especially in its early stages. Tomato et al conducted a systematic review and meta-analysis of 29 studies on MRS for mild cognitive impairment (MCI). \(^\text{28}\) Included in the analysis were a total of 607 MCI patients and 862 healthy controls. Patterns in metabolite concentration, including NAA, creatine (Cr), choline (Cho), and myoinositol, in various regions of the brain were identified and associated with MCI. For example, levels of creatine were found to be significantly lower in the hippocampus and paratriginal white matter. NAA was found to be most associated with MCI, but other markers including myoinositol, Cho, and Cr may also contribute to MCI. A community-based study was conducted to evaluate whether MRS could distinguish between patients with normal cognition (group 1), dementia (group 2), or mci (group 3) in a population with a low Mini-Mental State Examination (MMSE) score.\(^\text{29}\) From an initial population of 215 with low MMSE scores, MRS results were obtained for 56 patients. Comparing MRS to clinical diagnoses, the results were mixed for MRS, with statistically significant differences in metabolic patterns between patients with dementia (group 2) and patients without dementia (group 1 and group 3) but not between patients with MCI and those with normal cognition (group 1 vs group 3). In a 2012 study, Shiino et al compared proton MRS in 99 patients with Alzheimer disease (AD), 31 patients with subcortical ischemic vascular dementia (SIVD) and 45 elderly controls.\(^\text{30}\) Differences in metabolic patterns were seen in both AD and SIVD patients. Especially notable were increases in myoinositol concentration in the hippocampus identified in AD but not in SIVD (0.95 area under the receiver operating characteristic [ROC] curve).

**Section Summary**

Although a number of studies have examined the use of MRS for identifying and monitoring cognitive impairment and dementia, the cumulative evidence is insufficient to determine any role for MRS outside of the research setting. There are no clear criteria for diagnosing cognitive impairment or dementia with MRS and insufficient data on
diagnostic comparators. Additionally, the impact of MRS imaging on clinical management and health outcomes is unknown.

**Breast Cancer**

MRS is being investigated to improve the specificity of MRI of the breast, which has a high false-positive rate. In 2013, Baltzer et al conducted a systematic review and meta-analysis of 19 studies on MRS for detecting benign versus malignant breast lesions. (31) The combined total number of patients in the studies reviewed was 1183 and included 452 benign and 773 malignant lesions. In the pooled estimates, sensitivity of MRS was 73% (556 of 761; 95% confidence interval [CI], 64% to 82%) and specificity was 88% (386 of 439; 95% CI, 85% to 91%). The area under the ROC curve for MRS detecting breast cancers versus benign lesions was 0.88. There was significant heterogeneity between studies and evidence of publication bias, limiting interpretation of findings.

Bartella et al conducted a preliminary study using MRS to evaluate suspicious lesions 1 cm or larger identified on MRI.(32) They found that the addition of MRS increased the specificity of MRI in the specific population examined to 88% (23/26) and could have prevented unnecessary biopsies; the sensitivity was 100% (31/31). As the authors note, these findings need to be confirmed in larger studies and with a more diverse set of lesions. In particular, their sample only included 1 ductal carcinoma in situ (DCIS), and other studies have suggested that the choline peak they used to indicate a positive MRS result may be less likely to occur with DCIS.

**Liver Disease**

MRS has been evaluated as a noninvasive alternative to liver biopsy in the diagnosis of hepatic steatosis. It has been compared to other noninvasive imaging procedures such as computed tomography (CT), dual-gradient echo magnetic resonance imaging (DGE-MRI), and ultrasonography; liver biopsy was the reference standard and a 3T MRI machine was used. In a prospective study of 161 consecutive potential living liver donors, DGE-MRI was reported to be the most accurate test for diagnosing hepatic steatosis. While DGE-MRI and MRS were similar for hepatic steatosis 5% or greater, DGE-MRI outperformed MRS for hepatic steatosis 30% or greater (especially regarding specificity) and on quantitative estimates. (33) See also (34). In a systematic review of imaging liver fat in children, Awai et al reviewed 5 MRI studies and found varying methodologies for measuring liver fat by MRI or MRS. Therefore, the available evidence was not sufficient to evaluate the utility of MRI or MRS for assessment of hepatic steatosis in children. (35)

**Prostate Cancer**
The utility of MRS has also been investigated for identifying whether prostate cancer is confined to the organ, which has implications for prognosis and treatment. In a 2013 Health Technology Assessment, Mowatt et al systematically reviewed 51 studies to evaluate image-guided prostate biopsy with MRS and other enhanced MRI techniques (ie, dynamic contrast-enhanced MRI and diffusion-weighted MRI) compared to T2-MRI and transrectal ultrasound (TRUS) in patients with suspicion of prostate cancer due to elevated prostate-specific antigen (PSA) levels, despite a previous negative biopsy. (36) MRS had the highest sensitivity in the meta-analysis of individual tests (92%; 95% CI, 86% to 95%), with an estimated specificity of 76% (95% CI, 61% to 87%). TRUS-guided biopsy had the highest specificity (81%; 95% CI, 77% to 85%).

Wang et al found that the addition of MRI findings, both endorectal MRI and MRS, improved the accuracy of the staging nomograms traditionally used to predict the likelihood of organ-confined prostate cancer. (37) Although the study was not ideally designed to assess the incremental value of MRS over MRI alone, it found that the area under the ROC curve was larger when MRS was included, but the difference was not statistically significant.

The results of the American College of Radiology Imaging Network study 6659 were published in April 2009. (38) This prospective, multicenter study compared the use of MRI with and without MRS to identify the extent of prostate cancer by sextant prior to prostatectomy in 134 patients. The results from centralized histopathologic evaluation of prostate specimens served as the reference standard; MRI and MRS images were independently reviewed by 8 readers. With complete data on 110 patients, no difference was found in the area under the ROC curve for MRI alone versus MRI and MRS combined. That is, the use of MRS provided no incremental value in identifying the extent of prostate cancer.

In a meta-analysis of 7 studies (of 140 screened) on using MRS to diagnose prostate cancer, the pooled weighted sensitivity was 0.82 (95% CI, 0.73 to 0.89); specificity, 0.68 (95% CI, 0.58 to 0.76); and the area under the curve, 83.40. (39) All of these results are based on a cutoff for identifying “definitive” tumor of 0.85 for the ratio of (choline plus creatine) to citrate.

A single-institution randomized controlled trial published in 2010 compared conducting a second randomly selected biopsy (group A) to a biopsy selected partly based on MRS and dynamic contrast-enhanced (DCE) MRI results (group B). (40) The participants were selected from 215 consecutive men with an elevated PSA (between 4 and 10 mg/mL), an initial negative biopsy result, and a negative digital rectal examination; 180 patients participated in the study. Cancer was detected in 24.4% of group A patients and 45.5% of group B participants. Fifty patients from group A with 2 negative biopsy results agreed to
undergo biopsy a third time using MRS and DCE MRI results; 26 more cancers were found. Overall, 61.6% of the cancers detected had Gleason scores 7 (4+3) or more. The cancers detected after using MRS and dynamic contrast-enhanced MRI imaging also lined up with the suspicious areas detected on imaging. The sensitivity and specificity of MRS were 92.3% and 88.2%, respectively; adding dynamic, contrast-enhanced MRI increased the sensitivity to 92.6%, and the specificity to 88.8%. Limitations of the study include that it was conducted at a single center, analysis was confined to the peripheral zone of the prostate gland, and more samples were drawn from group B patients than from group a patients (12.17 vs 10 cores, respectively). Furthermore, given the concerns about potential overtreatment among patients with early stage prostate cancer, the benefits of detecting these additional cancers need to be evaluated by examining clinical outcomes for these patients. Similar issues arise in Policy 7.01.121 on saturation biopsy of the prostate.

In a similar report from this institution by these authors, 150 patients with a negative prostate biopsy, despite PSA elevations, were randomized to MRS or MRS plus DCE-MRI to locate prostate cancer foci for a second targeted biopsy. (41) See also (42). The addition of DCE-MRI to MRS yielded increased sensitivity and specificity over MRS alone (93.7% and 90.7% vs 82.8% and 91.8%, respectively). Padron et al also reported on the combined use of MRS and DCE-MRI for prostate cancer in 106 patients in a prospective cohort study. (43) The authors reported combined MRS and DCE-MRI results yielded unacceptably low positive predictive value of 19%. Negative predictive value was 91%. Sensitivity was 71% and specificity was 48%. The authors indicated the combined MRS and DCE-MRI may be useful in avoiding biopsy, since the negative predictive value was 91%; however, further study is needed.

**Section Summary**

Although a number of studies have examined the use of MRS for localizing prostate cancer for biopsy and for monitoring of patients with prostate cancer, the cumulative evidence remains uncertain. Data comparing the diagnostic accuracy of MRS to alternative imaging strategies is limited. Additionally, the impact of MRS imaging compared to other imaging strategies on clinical management and health outcomes is unknown and further study is needed.

**Gauging Treatment Response**

The possibility of using MRS to track treatment response and failure has been explored. A small (n=16), preliminary study of tamoxifen treatment for recurrent gliomas found MRS patterns differed between responders and nonresponders.(44) Serial MRS demonstrated that metabolic spectra stabilized after initiation of therapy among responders and then changed in advance of clinical or radiologic treatment failure. In other words, MRS might
help predict imminent treatment failure. However, there are relatively few studies with small sample sizes assessing this possible use of MRS. In addition, a number of other types of imaging are being evaluated for the same use, including dynamic, contrast-enhanced MRI, diffusion-weighted MRI, and 18-fluorodeoxyglucose position emission tomography (FDG-PET). Additional studies are needed, including studies comparing modalities or evaluating multimodalities. (45, 46)

**Other Indications**

MRS has also been evaluated for other uses, such as tracking disease changes among patients with multiple sclerosis,(47,48) systemic lupus erythematos,(49) assessing carotid plaque morphology,(50) as biomarkers of traumatic brain injury,(51,52) predicting long-term neurodevelopmental outcome after neonatal encephalopathy,(53); see also(54,55) and other applications in children.(56,57) Additional evidence on these applications is needed. MRS has also been studied in a variety of psychiatric disorders in the research setting, but no studies on the clinical use of MRS for the treatment of psychiatric disorders were found. (58, 59)

**Ongoing Clinical Trials**

A search of online site ClinicalTrials.gov on November 20, 2013 identified many active studies using MRS including MRS imaging for brain tumors, cervical cancer, head and neck tumors, prostate cancer and neonatal hypoxic encephalopathy.

**Physician Specialty Society and Academic Medical Center Input**

In 2008, in response to requests, input was received from 3 physician specialty societies and 1 academic medical center while this policy was under review. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. The input received from these reviewers disagreed with the conclusions in the policy statement. In particular, information provided was in support of MRS in differentiating radiation necrosis from recurrent tumor and in the differential diagnosis of certain central nervous system tumors from nontumors.

**Summary**

Magnetic resonance spectroscopy (MRS) is a noninvasive technique that can be used to measure the concentrations of different chemical components within tissues. The available
studies do not provide strong and consistent evidence regarding the diagnostic test characteristics of MRS. Studies do not clearly delineate how MRS information would be used to guide patient management. Thus, it is not possible to determine whether MRS provides relevant clinical information that will safely influence diagnostic thinking and therapeutic choice. The scientific evidence at this time does not permit conclusions concerning the net effect of this technology on health outcomes. Therefore, the use of MRS is considered investigational.

Practice Guidelines and Position Statements

The National Comprehensive Cancer Network’s (NCCN) clinical practice guidelines on central nervous system cancers identifies MRS, along with MR perfusion or brain PET, as a modality that can be considered to rule out radiation necrosis, as compared to recurrence of brain tumors. (60) The authors also state that MRS may be helpful in grading tumors or assessing response and that the most abnormal area on MRS would be the best target for biopsy. The limitations include tumors near vessels, air spaces, or bone; the extra time required in an MRI machine; and the limitations occurring with any MRI, such as the exclusion of patients with implantable devices. The NCCN guidelines on prostate cancer mention MRS may be a part of a “more aggressive workup for local recurrence (eg, repeat biopsy, MR spectroscopy, endorectal MRI),” which is 1 possible element of salvage therapy for patients after radical prostatectomy with rising PSA or positive digital rectal examination after radical prostatectomy with a negative prostate biopsy and negative studies for metastases. (61) The NCCN guideline on breast cancer does not mention MRS.

The American College of Radiology updated its practice guideline on MRS of the CNS in 2013. (62) Most of the guideline is devoted to the actual performance of MRS, but it also lists 22 possible indications for MRS when MRI or computed tomography are inadequate for answering specific clinical questions.

V. Definitions

GYRI refer to one of the convolutions of the cerebral hemispheres of the brain.

MAGNETIC RESONANCE IMAGING is a type of diagnostic imaging that uses the characteristic behavior of protons (and other atomic nuclei) when placed in powerful magnetic fields to make images of tissues and organs.

NONINVASIVE refers to a device or procedure that does not penetrate the skin or enter any orifice in the body.
VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member’s contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. REFERENCES

Magnetoencephalography/Magnetic Source Imaging


Other:
Taber’s Cyclopedic Medical Dictionary, 19th edition.

Magnetic Resonance Spectroscopy

41. Panebianco V, Sciarra A, Ciccarello M et al. Role of magnetic resonance spectroscopic imaging ([1H]MRSI) and dynamic contrast-enhanced MRI (DCE-MRI) in identifying prostate cancer foci in patients with negative biopsy and high levels of prostate-specific antigen (PSA). Radiol Med 2010; 115(8):1314-29.

[Note: Final page is signature page and is kept on file, but not issued with Policy.]
### IX. Coding Information

**Note:** This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

**Covered when medically necessary:**

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**MEDICAL POLICY**

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| POLICY NUMBER | MP-5.011 |

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**Investigational and therefore not covered:**

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**The following ICD-10 diagnosis codes will be effective October 1, 2015:**

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*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.*
# Medical Policy

## Policy Title
Magnetoencephalography / Magnetic Source Imaging and Magnetic Resonance Spectroscopy

## Policy Number
MP-5.011

## X. Policy History

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