MAGNETIC RESONANCE SPECTROSCOPY (MRS)

Protocol: NEU026
Effective Date: October 8, 2012

Table of Contents

COMMERCIAL COVERAGE RATIONALE ................................................................. 1
MEDICARE & MEDICAID COVERAGE RATIONALE ........................................... 2
BACKGROUND .................................................................................................. 2
CLINICAL EVIDENCE ...................................................................................... 3
U.S. FOOD AND DRUG ADMINISTRATION (FDA) ......................................... 14
APPLICABLE CODES ....................................................................................... 15
REFERENCES .................................................................................................. 15
PROTOCOL HISTORY/REVISION INFORMATION ........................................... 23

INSTRUCTIONS FOR USE

This protocol provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificate of Coverage (COC) or Evidence of Coverage (EOC)) may differ greatly. In the event of a conflict, the enrollee's specific benefit document supersedes this protocol. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Protocol. Other Protocols, Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Protocols, Policies and Guidelines as necessary. This protocol is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the Milliman Care Guidelines®, to assist us in administering health benefits. The Milliman Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

COMMERCIAL COVERAGE RATIONALE

Magnetic resonance spectroscopy (MRS) is considered not medically necessary. There is a lack of evidence demonstrating that the use of MRS improves health outcomes such as increasing diagnosis rates, reducing the number of unnecessary biopsies, and improving care or treatment planning accuracy in patients with conditions such as psychiatric or neurological disorders, and prostate cancer. In addition, the techniques of acquiring the MRS spectra and interpreting the results are not well standardized. Further clinical trials that include well conducted randomized controlled trials and cohort studies are necessary to demonstrate the clinical usefulness of this procedure.
MEDICARE & MEDICAID COVERAGE RATIONALE

Medicare has a National Coverage Determination for Magnetic Resonance Spectroscopy (220.2.1) accessed August 2012. The National Coverage Determination is as follows:

Magnetic Resonance Spectroscopy (MRS) is an application of Magnetic Resonance Imaging (MRI). It is a non-invasive diagnostic test that uses strong magnetic fields to measure and analyze the chemical composition of human tissues. On March 22, 1994, Centers for Medicare and Medicaid Services considered MRS an investigational procedure and issued a national non-coverage determination for all indications of MRS.

Indications and Limitations of Coverage
Nationally Non-covered Indications

After thorough review and reconsideration of the existing national non-coverage determination for MRS, as well as the available evidence for the use of MRS as a diagnostic tool for distinguishing indeterminate brain lesions, and/or as an aid in conducting brain biopsies, CMS has determined that the evidence is not adequate to conclude that MRS is reasonable and necessary within the meaning of section 1862(a)(1)(A) of the Social Security Act, for use in the diagnosis of brain tumors. Therefore, CMS reaffirms its current national non-coverage determination for all indications of MRS.

There is no Local Coverage Determination for Nevada for Magnetic Resonance Spectroscopy. (Accessed August 2012)

For Medicare and Medicaid Determinations Related to States Outside of Nevada:
Please review Local Coverage Determinations that apply to other states outside of Nevada.
http://www.cms.hhs.gov/mcd/search

Important Note: Please also review local carrier Web sites in addition to the Medicare Coverage database on the Centers for Medicare and Medicaid Services’ Website.

BACKGROUND

Magnetic resonance spectroscopy (MRS) is a noninvasive technique that is used to measure the concentrations of different metabolites within body tissue. The basic scientific principle of MRS is identical to that of magnetic resonance imaging (MRI), except that, instead of anatomical images, radiofrequency waves are translated into biochemical composition of the scanned tissue. The metabolic profile that emerges is a reflection of underlying cellular integrity, proliferation, metabolism, and indicative of pathological status. Therefore, it is thought that MRS may be useful in identifying brain tumors; specifically in differentiating neoplastic from non-neoplastic, malignant from benign, primary from metastatic, and radiation injury from recurrence, as well as locating epileptic foci and/or brain lesions and ischemic stroke. MRS may also potentially be useful in grading tumors and in guiding the biopsy to the region of greatest malignancy.
Evidence reviewed for this policy focuses on the most commonly reported clinical applications of magnetic resonance spectroscopy (MRS). These include brain tumors, epilepsy, ischemic stroke, and prostate cancer. Almost all of the reviewed studies involved small, often heterogeneous study populations. Many provided surgical or histological confirmation of MRS findings, and used spectral data from healthy volunteers as a comparison. The imaging technique varied among the studies. Most studies evaluated proton MRS (1H MRS), as only a small number of patients have been studied using other spectroscopy modalities.

**Brain Tumors**

*MRS for Tumor Grading and Differentiating Tumor Types*

The evidence regarding the utility of MRS for tumor grading is inconclusive. Results of earlier studies suggest that MRS may be able to characterize brain tumors accurately (Krieger, 2003; Astrakas, 2004). A study by Stadlbauer et al. (2006) evaluated 26 patients suspected of having gliomas and 26 matched controls subjects who underwent proton MRS. The study results indicated that proton MRS imaging with high spatial resolution allows preoperative grading of gliomas. A study by Nafe et al. (2003) reported significant correlations between spectroscopic data and histological findings, but noted that the data were insufficient to determine if MRS can consistently differentiate grades within tumor types.

Bendini et al. (2011) assessed the diagnostic value of multivoxel proton MRS combined with perfusion MRI in the differential diagnosis and grading of brain tumors by comparing neuroimaging data with histopathological findings obtained after resection or biopsy. A total of 159 patients with a previous brain tumor diagnosis underwent multivoxel proton MRS and perfusion MRI. In the differential diagnosis between glioblastoma multiforme and metastases, proton MRS, combined with dynamic contrast enhanced MRI perfusion, reached high sensibility and specificity. In brain tumor grading, the same method reached high sensitivity and specificity in distinguishing grade III-IV gliomas but encountered difficulty in determining grades within the two main groups of primary brain tumors, especially where mixed gliomas were involved. The authors concluded that the systematic use of CSI spectroscopy and perfusion imaging has shown a high potential in the differential diagnosis and grading of brain tumors. However, further exploration into diagnostic procedures that can significantly distinguish between grade III-IV and grade II tumors is needed in order for MRS to be a clinically useful tool.

Zeng et al. (2011) evaluated whether metabolite ratios in multivoxel 3D proton MR spectroscopy (1H MRS) is different between low-grade and high-grade gliomas and may be useful for glioma grading. Thirty-nine patients suspected of having gliomas underwent 3D 1H MRS examinations. Receiver operating characteristic analysis demonstrated a threshold value of 2.04 for Cho/Cr ratio to provide sensitivity, specificity, PPV and NPV of 84.00%, 83.33%, 91.30% and 71.43%, respectively. Threshold value of 2.20 for Cho/NAA ratio resulted in sensitivity, specificity, PPV and NPV of 88.00%, 66.67%, 84.62% and 72.73%, respectively. Overall diagnostic accuracy was not statistically significantly different between Cho/Cr and Cho/NAA ratios. The investigators concluded that metabolite ratios of low-grade gliomas were significantly different from high-grade gliomas. Cho/Cr and Cho/NAA ratios could have the superior diagnostic performance in predicting the glioma grade.
These findings require confirmation in a larger study. It is also not clear how this information would be used in physician decision-making or to improve survival rates from glioma.

The studies evaluating MRS for differentiation of tumor types found that changes in metabolite levels correlated with histology results in both adult and pediatric patients with brain cancers of different types and grades. A large case series undertaken by Moller-Hartmann et al. (2002) evaluated 176 consecutive patients with brain tumors. The objective of the study was to test the clinical utility of proton MRS in conjunction with MRI to differentiate neoplastic and non-neoplastic brain lesions. Combined MRI and proton MRS led to a 15.4% greater number of correct diagnoses; 6.2% fewer incorrect and 16% fewer equivocal diagnoses than structural MRI alone. This study was limited by its heterogeneous patient population and case series design.

Fellow et al. (2010) evaluated the accuracy of proton MRS as an intervention limiting diagnostic tool for glioblastoma multiforme (GBM). Eighty-nine patients had clinical computed tomography (CT) and MR imaging and 1.5T single-voxel (SV) SE proton MRS for neuroradiological diagnosis and tumor classification with spectroscopic and automated pattern recognition analysis. Eighteen patients from a cohort of 89 underwent stereotactic biopsy. The 18 stereotactic biopsies revealed 14 GBM, 2 grade II astrocytomas, 1 lymphoma, and 1 anaplastic astrocytoma. All 14 biopsied GBMs were diagnosed as GBM by a protocol combining an individual radiologist and an automated spectral pattern recognition program. The investigators concluded that in patients undergoing stereotactic biopsy, combined neuroradiological and spectroscopic evaluation may diagnose GBM with accuracy that could replace the need for biopsy. According to the investigators, there may be a specific intervention limiting role for the use of (1)H-MRS in brain tumor diagnosis. Further research is needed to confirm this conclusion.

Porto et al. (2010) investigated whether in vivo proton magnetic resonance spectroscopic imaging, using normalized concentrations of total choline (tCho) and total creatine (tCr), can differentiate between WHO grade I pilocytic astrocytoma (PA) and diffuse, fibrillar WHO grade II astrocytoma (DA) in children. Data from 16 children with astrocytomas (11 children with PA and 5 children with DA) were evaluated retrospectively. MRS was performed before treatment in all patients with histologically proven low-grade astrocytomas. Based on the results of the study, the investigators concluded that choline as a single parameter is not reliable in the differential diagnosis of low-grade astrocytomas in children.

Garcia-Gomez et al. (2009) presented results from the multicenter eTUMOUR project (2004–2009), which builds upon previous expertise from the INTERPRET project (2000-2002). A total of 253 pairwise classifiers for glioblastoma, meningioma, metastasis, and low-grade glial diagnosis were inferred based on 211 SV short TE INTERPRET MR spectra obtained at 1.5 T (PRESS or STEAM, 20-32 ms) and automatically pre-processed. Afterwards, the classifiers were tested with 97 spectra, which were subsequently compiled during eTUMOUR. Accuracies of approximately 90% were achieved for most of the pair-wise discrimination problems. The exception was for the glioblastoma versus metastasis discrimination, which was below 78%. According to the investigators, a more clear definition of metastases may be obtained by other approaches, such as magnetic resonance spectroscopic (MRS) imaging plus MRI. The investigators concluded that the prediction of the tumor type of in-vivo MRS is possible using classifiers developed from previously acquired data, in different hospitals with different instrumentation under the same acquisition protocols. According to the investigators, this methodology
Magnetic Resonance Spectroscopy (MRS) may find application for assisting in the diagnosis of new brain tumor cases and for the quality control of multicenter MRS databases. However, this study was nonrandomized and not case controlled.

Fifty patients with intracranial cystic lesions (21 pyogenic abscesses, 23 tumor cysts, 3 epidermoid cysts, and 3 arachnoid cysts) were evaluated with conventional MRI, diffusion-weighted magnetic resonance imaging (DWI), and in vivo (1) H MRS. Preoperative diagnosis of the lesions was based on the results of DWI and in vivo MRS. Diagnostic accuracy of conventional MRI, DWI, and in vivo (1) H MRS was calculated with respect to a final diagnosis of brain abscess vs non-abscess cystic tumor. Diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of conventional MRI for the differentiation of brain abscess from non-abscess cystic tumor were 61.4%, 61.9%, 60.9%, 59.1%, and 63.6%, respectively, whereas they were 93.2%, 85.7%, 100%, 100%, and 88.5% with MRS; 95.5%, 95.2%, 95.7%, 95.2%, and 95.7% with DWI; and 97.7%, 95.2%, 100%, 100%, and 95.8% with MRS and DWI. Magnetic resonance imaging, when combined with in vivo MRS and DWI, accurately predicted the diagnosis in 47 (94%) of 50 and 48 (96%) of 50 of the cases, respectively. The investigators concluded that proton MRS and DWI are useful as additional diagnostic modalities in differentiating intracranial cystic lesions. Combination of DWI with calculated ADC values and metabolite spectrum acquired by MRS add more information to MRI in the differentiation of intracranial cystic mass lesions (Lai et al. 2007). The small size of the study population limits the validity of the conclusion of this study.

Chiang et al. (2009) compared the effectiveness of relative cerebral blood volume, apparent diffusion coefficient and spectroscopic imaging in differentiating between cerebral abscesses and necrotic tumors. In the prospective study, a 3-tesla MR unit was used to perform proton MR spectroscopy, diffusion and perfusion imaging in 20 patients with cerebral abscesses and 26 patients who had solitary brain tumors (14 high-grade gliomas and 12 metastases). The proton spectra obtained revealed amino acids only in the cerebral abscesses. Although the conventional MRI characteristics of cerebral abscesses and necrotic tumors may sometimes be similar, diffusion, perfusion-weighted and spectroscopic MRI enables distinction between the two. However, these findings require confirmation in a larger study.

Hourani et al. (2006) investigated whether in vivo proton magnetic resonance spectroscopic imaging (MRSI) can differentiate between 1) tumors and nonneoplastic brain lesions, and 2) high and low-grade tumors in children. Thirty-two children (20 males and 12 females, mean age = 10 +/- 5 years) with primary brain lesions were evaluated retrospectively. Nineteen patients had a neuropathologically confirmed brain tumor, and 13 patients had a benign lesion. Based in the results of the study, the investigators concluded that proton MRSI may have a promising role in differentiating pediatric brain lesions, and an important diagnostic value, particularly for inoperable or inaccessible lesions. However, the small size of the study population limits the validity of this conclusion.

**MRS for Discriminating Tumor Recurrence from Treatment-Related Changes**

According to Hayes, several prospective comparative studies evaluated the diagnostic accuracy of MRS in discriminating between tumor recurrence and treatment-related changes, comparing outcomes to that of histopathology. The sample sizes of these studies were fairly small, ranging from 25 to 55 patients. MRS demonstrated 89% to 90% sensitivity, 83% to 100% specificity, 100% positive predictive value, 83% negative predictive value, and an overall diagnostic accuracy ranging from 85.5% to 93% for discriminating tumor recurrence from treatment-related changes (Plotkin et al.,
In comparison, single photon emission computed tomography (SPECT) alone produced a sensitivity ranging from 90% to 95%, specificity of 100%, and overall diagnostic accuracy of 96% (Plotkin et al., 2004; Palumbo et al., 2006). MRS as an adjunct to SPECT produced 95% sensitivity, 100% specificity, 100% PPV, 90.9% negative predictive value, and an overall accuracy of 96.6% for distinguishing tumor recurrence. 3 T MRS, as an adjunct to diffusion weighted (DW)-MRI, was able to differentiate between tumor recurrence and radiation injury with accuracies of 93.8% and 100%, respectively, and with an overall diagnostic accuracy of 96.4%. Compared with MRS, diagnostic accuracy was significantly higher when MRS was used adjunctively with DW-MRI (Zeng et al., 2007). No significant differences were found between MRS and SPECT individually or when combined (Plotkin et al., 2004; Palumbo et al., 2006). While two studies observed patients only in the short term, up to 6 months after MRS, one study (Zeng et al., 2007) followed patients for 1 to 3 years after MRS to confirm final diagnoses in cases that biopsy was not performed. There is limited evidence indicating that MRS may provide useful diagnostic information that may complement the results of conventional imaging modalities in discriminating tumor recurrence from radiation injury. However, it remains to be proven whether MRS is sufficiently accurate to obviate the need for biopsy or can be used to modify treatment decisions in patients with suspected brain tumors (Hayes, 2008).

Proton MRS was not a useful modality for delineating secondary irradiation target volumes (Hall, 2001), nor was it helpful in evaluating short- and long-term neurotoxicity in children following cranial irradiation (Rutkowski, 2003). However, in one small study, proton MRS revealed widespread radiation-induced chemical pathology in the white matter of glioma patients after treatment compared with MRI (Virta, 2000).

In a consecutive series of 26 previously operated patients diagnosed with cerebral glioma, MRS, 2-((18)F) fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET), and perfusion MRI (MRP), were performed at follow-up to distinguish recurrence from radiation necrosis, and to identify tumour upgrading. Discrepancy between techniques was observed in 9 cases. The positive predictive value (PPV) and the negative predictive value (NPV) of each technique to detect the presence of high grade glioma was: MRI, PPV=50%; MRS, PPV=91.6%, NPV=100%; FDG-PET, PPV=75%, NPV=61.1%; MRP, PPV=100%, NPV=100%. In the selected group of nine cases studied to differentiate viable tumour from radiation necrosis, MRS and MRP reached a PPV and a NPV of 100%, whereas for FDG-PET, PPV and NPV were 66.6% and 60%, respectively. According to the investigators, MRS and MRP are superior to FDG-PET in discriminating tumour recurrence, grade increase and radiation necrosis (Prat et al. 2010). These findings require confirmation in a larger study.

Fink et al. (2012) compared 3 Tesla (3T) multi-voxel and single-voxel proton MRS, dynamic susceptibility contrast perfusion MRI (DSC), and diffusion-weighted MRI (DWI) for distinguishing recurrent glioma from postradiation injury. The authors concluded that 3T DSC and multi-voxel MRS Cho/Cr peak-area and Cho/NAA peak-height appear to outperform DWI for distinguishing glioma recurrence from posttreatment effects. The authors stated that single-voxel MRS parameters do not appear to distinguish glioma recurrence from posttreatment effects reliably, and therefore should not be used in place of multi-voxel MRS. Limitations of the study include its retrospective, single institution design with a small study population (n = 40). Prospective validation of these findings in a larger study population is needed.
Bobek-Billéwicz et al. (2010) evaluated the diagnostic effectiveness of perfusion-weighted imaging (PWI), diffusion-weighted imaging (DWI) and proton MRS in the differentiation of the tumor recurrence from radiation-related injury. The retrospective analysis included 11 contrast-enhancing lesions observed in 8 patients treated for gliomas with radiotherapy or radio chemotherapy. Based on the study results, PWI was the most reliable in differentiation between tumor regrowth/recurrence and radiation necrosis. Proton MRS and DWI did not differentiate analyzed groups with statistical significance.

Smith et al. (2009) developed a method using alterations in the ratios of standard brain metabolites—choline (Cho), creatine (Cr), and N-acetylaspartate (NAA)—to predict the probability of tumor recurrence in patients previously treated for brain tumors with new contrast-enhancing lesions. Thirty-three patients who had undergone treatment for primary brain tumors in whom routine MRI showed new contrast-enhancing lesions were retrospectively studied. The final diagnosis was assigned using histopathology (n = 13) or imaging follow-up (n = 20). Ratios of three metabolites (Cho, Cr, and NAA) were calculated, and the results were correlated with the final diagnosis using a Wilcoxon’s rank sum analysis. Elevations of the metabolic ratios Cho/Cr and Cho/NAA and a decrease in the ratio NAA/Cr were found in patients with recurrent tumor (n = 20) versus those with postradiation change (n = 13). A prediction model using the Cho/NAA ratio yielded a sensitivity of 85%, a specificity of 69.2%, and an area under the receiver operating characteristic curve of 0.92. The investigators concluded that the results of this study suggest that MR spectroscopy is a useful tool in assigning patients with nonspecific enhancing lesions to either invasive biopsy or conservative management. Further research is needed to confirm these results.

Quon et al. (2011) determined the correlation between MRS pattern of high-grade glioma before, during, and after radiotherapy (RT) with overall survival (OS) and progression-free survival (PFS). Twenty-six patients prospectively underwent surgery and RT. MRS was performed before RT, at week 4 of RT, and 2 months post-RT. Patients were analyzed for differences in OS and PFS. Significant decreases in tumor choline/N-acetyl-aspartate and normalized choline were observed from baseline to post-RT. After a median follow-up of 22.9 months, patients with >40% decrease in normalized choline from week 4 during RT to 2 months post-RT had a significantly worse median and PFS. The authors concluded that the change in normalized choline at 2 months post-RT was highly prognostic for PFS and OS. According to the authors, this may allow more individualized response-based treatment. However, further research is needed to confirm how this information would be used in physician decision-making or to improve survival rates from glioma.

The goal in the study by Lin et al. (1999) was to determine if proton MRS could be incorporated into the clinical management of patients with known or suspected brain tumors, in situations in which stereotactic biopsy might otherwise be employed. Prior to each MRS examination, one of the clinical investigators would define a treatment plan that would be carried out in the absence of a diagnostic MRS study, to determine if MRS directly impacted upon and altered clinical decision making. Proton MRS accurately predicted the pathological nature and clinical outcome of lesions in 15 of 16 regions of interest (ROIs). Interpretations directly influenced clinical decision-making in 12 patients, and altered surgery planning in 7 patients. This study was limited by the small number of patients and the vague description of controls. However, it is a pivotal study in that it clearly showed the positive impact on clinical decision-making in this patient population.
A Technology Assessment conducted by Tufts-New England Evidence-based Practice Center for the Agency for Healthcare Research and Quality (AHRQ) evaluated the use of MRS in brain tumors (Jordan, 2003). The conclusion stated that "human studies conducted on the use of MRS for brain tumors demonstrate that this non-invasive method is technically feasible and suggest potential benefits for some of the proposed indications. However, there is a paucity of high quality direct evidence demonstrating the impact on diagnostic thinking and therapeutic decision making. In summary, while there are a large number of studies that confirm MRS's technical feasibility, there are very few published studies to evaluate its diagnostic accuracy and whether it can positively affect diagnostic thinking and therapeutic choice. Those studies that do address these areas often have significant design flaws including inadequate sample size, retrospective design and other limitations that could bias the results" (Jordan, 2003).

**Epilepsy**

A meta-analysis performed by Willman et al. (2006) included 22 studies evaluating proton MRS for use in the preoperative assessment of epilepsy surgery. Only patients with intractable temporal lobe epilepsy were included in the meta-analysis. Sixty-four percent of all patients and 72% of patients with good outcome had an ipsilateral MRS abnormality concordant with the epileptogenic zone. The positive predictive value of patients with ipsilateral MRS abnormality for good outcome was 82%. The authors concluded that MRS still remains a research tool with clinical potential. Prospective studies limited to non-localized ictal scalp EEG or MRI-negative patients are required for validation of these data.

Doelken et al. (2007) conducted a study that compared intensive video electroencephalogram (EEG) monitoring, high-resolution MR imaging (MR imaging), proton MRS, and single-photon emission CT (SPECT) in 25 patients with temporal lobe epilepsy (TLE). Based on the results of the study, the authors concluded that multimodal imaging in patients with TLE improves lateralization of affected hemispheres, especially in patients without pathologic findings in MR imaging, and indicates bilateral effect, which is important to identify patients who will benefit from surgery. However, the small size of the study population limits the validity of this conclusion.

A study by Goncalves et al. (2006) assessed the value of 3 MRI quantitative modalities for presurgical screening of epilepsy. Ninety-two adults with temporal lobe epilepsy of which 28 underwent surgery and 34 matched controls were included in the study. High-resolution qMRI at 1.5 tesla, hippocampal volumetry with T2-relaxometry and multi-voxel spectroscopy were performed. The study results indicated that hippocampal structural damage is equivocally depicted by spectroscopy. For preoperative evaluation, volumetry and T2-relaxometry provide the most accuracy. This study is limited by a small sample size.

**Stroke and Carotic Artery Occlusion**

For stroke, MRS may identify biochemical signals of ischemia such as lactate (Parsons et al. 2002, Nicoli et al. 2003, Bakker et al. 2003), but the impact of MRS on patient management has not yet been adequately examined.

Zhang et al. (2011) evaluated the value of proton MRS in patients with stenosis or occlusion of the internal carotid artery (ICA) or middle cerebral artery (MCA). Fifty noninfarcted patients with stenosis or occlusion of unilateral ICA/MCA were included in the study. Twenty-five patients with cerebral
infarction and 25 healthy control subjects were also enrolled. All patients and healthy control subjects underwent proton MRS. Cerebral metabolic changes were studied in the noninfarcted patients and compared with the infarcted patients as well as healthy control subjects. In 50 noninfarcted patients N-acetylaspartate (NAA) decreased and choline increased in the ischemic hemisphere compared with the contralateral side and control subjects. The authors concluded that proton MRS can demonstrate abnormal metabolic changes in cerebral tissues with no infarction, while with ICA/MCA may show stenosis or occlusion at an early stage, which may help guide treatment decisions and preoperative evaluation. However, further research is needed to confirm how this information would be used in physician decision-making.

**Traumatic and Hypoxic Brain Injury**

For traumatic brain injury, MRS studies have detected neurochemical changes that appear to extend beyond the area of focal anatomic lesions seen on standard MRI (Shutter et al. 2004, Vagnozzi et al. 2010); however, there is no conclusive data regarding its ability to improve treatment outcome. Aaen et al. (2010) evaluated proton magnetic resonance spectroscopic imaging (MRSI) findings for children with traumatic brain injury attributable to non-accidental trauma (NAT) early after injury, to determine whether brain metabolite changes predicted outcomes. Proton MRSI (1.5 T) was performed (mean: 5 days after injury) through the level of the corpus callosum for 90 children with confirmed NAT. Regional N-acetylaspartate/total creatine, N-acetylaspartate/total choline, and choline/creatine ratios and the presence of lactate were measured. Data on long-term outcomes defined at $> or =6$ months were collected for 44 of 90 infants. The investigators concluded that reduced N-acetylaspartate levels (i.e., neuronal loss/dysfunction) and elevated lactate levels (altered energy metabolism) correlated with poor neurologic outcomes for infants with NAT. Elevated lactate levels may reflect primary or secondary hypoxic-ischemic injury, which may occur with NAT. According to the investigators, the data suggest that MRSI performed early after injury can be used for long-term prognosis. The study did not confirm the utility of such findings in improving care and outcome of patients.

**Demyelination or Dysmyelination Disorder**

While MRS may provide some information about the pathological changes of multiple sclerosis (Bellman-Strobl, 2009; Wattjes, 2008; Anik, 2011), there is no published research data indicating how MRS affects patient management compared to standard clinical assessment, including use of magnetic resonance imaging.

**Dementia and Alzheimer Disease**

For dementia and Alzheimer’s disease, MRS may identify biochemical signals of dementia (Jessen, 2009; Modrego, 2006; Garcia Santos, 2008), but the impact of MRS on patient management has not yet been adequately examined.

**Psychiatric Disorders**

MRS has been used in clinical trials to examine the neurochemistry of patients with psychiatric disorders (Chen, 2009; Batra, 2008; Hasler, 2007; Yoon, 2010; Bustillo, 2008). These studies do not address the impact of MRS on diagnostic accuracy and therapeutic decision making and often have significant design flaws including small sample sizes and retrospective design. Further clinical trials
demonstrating the clinical usefulness of MRS are necessary before it can be considered proven for these conditions.

Inborn Errors of Metabolism
Although MRS has been used to characterize a variety of inborn errors of metabolism including mitochondrial, peroxisomal, lysosomal, and amino and organic acid disorders (Scarabino et al. 2009, Tarnacka et al. 2009, Tarnacka et al. 2008, Eichler et al. 2002, Abe et al. 2004, Imamura, 2008 ), no studies have validated MRS findings with improved treatment outcomes. Further clinical trials demonstrating the clinical benefits of MRS are necessary before it can be considered proven for these conditions.

Prostate Cancer
In a randomized single center study, Sciarra et al. (2010) prospectively analyzed the role of magnetic resonance spectroscopy imaging (MRSI) and dynamic-contrast enhancement magnetic resonance (DCEMR) in the detection of prostate tumor foci. One hundred and eighty patients with persistently elevated prostate-specific antigen levels and prior negative random trans-rectal ultrasound (TRUS)-guided biopsy were included in the study. Patients in group A were submitted to a second random prostate biopsy, whereas patients in group B were submitted to a (1) HMRSI- DCEMR examination and samples targeted on suspicious areas were associated to the random biopsy. At the second biopsy, a prostate adenocarcinoma histologic diagnosis was found in 22 of 90 cases (24.4%) in group A and in 41 of 90 cases (45.5%) in group B. On a patient-by patient basis, MRSI had 92.3% sensitivity, 88.2% specificity, 85.7% positive predictive value (PPV), 93.7% negative predictive value (NPV), and 90% accuracy; DCEMR had 84.6 % sensitivity, 82.3% specificity, 78.5% PPV, 87.5% NPV, and 83.3% accuracy; and the association MRSI plus DCEMR had 92.6% sensitivity, 88.8% specificity, 88.7% PPV, 92.7% NPV, and 90.7% accuracy, for predicting prostate cancer detection. The investigators concluded that the combination of MRSI and DCEMR showed the potential to guide biopsy to cancer foci in patients with previously negative TRUS biopsy. To avoid a potential bias, represented from having taken more samples in group B (mean of cores, 12.17) than in group a (10 cores), in the future a MRSI/DCEMR directed biopsy could be prospectively compared with a saturation biopsy procedure. This analysis was limited to the peripheral zone of the prostate as MR and MRSI evaluation are both inadequate in the differential diagnosis between adenoma (benign) and adenocarcinoma (cancer) arising from the transition region of the prostate.

Umbehr et al. (2009) conducted a meta-analysis to evaluate the diagnostic accuracy of combined MRI/MRSI in prostate cancer and to explore risk profiles with highest benefit. A total of 31 test-accuracy studies (1765 patients) were identified; 16 studies (17 populations) with a total of 581 patients were suitable for meta-analysis. Nine combined MRI/MRSI studies (10 populations) examining men with pathologically confirmed prostate cancer (297 patients; 1518 specimens) had a pooled sensitivity and specificity on prostate subpart level of 68% and 85%, respectively. Compared with patients at high risk for clinically relevant cancer (six studies), sensitivity was lower in low-risk patients (four studies) (58% vs 74%); but higher for specificity (91% vs. 78%); .Seven studies examining patients with suspected prostate cancer at combined MRI/MRSI (284 patients) had an overall pooled sensitivity and specificity on patients level of 82% (59-94%) and 88% (80-95%). In the low-risk group (five studies) these values were 75% (39-93%) and 91% (77- 97%), respectively. The investigators concluded that a limited number of small studies suggest that MRI combined with MRSI
could be a rule-in test for low-risk patients. However, this finding needs further confirmation in larger studies.

In a prospective multicenter study conducted by the American College of Radiology Imaging Network (ACRIN), the incremental benefit of combined endorectal magnetic resonance (MR) imaging and MR spectroscopic imaging, as compared with endorectal MR imaging alone was evaluated for sextant localization of peripheral zone (PZ) prostate cancer. One hundred thirty-four patients with biopsy-proved prostate adenocarcinoma and scheduled to undergo radical prostatectomy were recruited at seven institutions. Complete data were available for 110 patients. MR imaging alone and combined MR imaging-MR spectroscopic imaging had similar accuracy in PZ cancer localization. AUCs for individual readers were 0.57-0.63 for MR imaging alone and 0.54-0.61 for combined MR imaging-MR spectroscopic imaging. The investigators concluded that in patients who undergo radical prostatectomy, the accuracy of combined 1.5-T endorectal MR imaging-MR spectroscopic imaging for sextant localization of PZ prostate cancer is equal to that of MR imaging alone. The study did not confirm that the addition of MR spectroscopic imaging to MR imaging would improve tumor localization (Weinreb et al. 2009).

Lawrentschuk and Fleshner (2008) published a systematic review of prospective studies of MRS for prostate cancer. They identified 6 studies of 215 men who had MRI/MRS after a negative biopsy conducted due to elevated PSA levels. For MRI or combined MRI/MRS, the sensitivity of predicting a positive repeat biopsy was 57% to 100% and the specificity was 44% to 96%.

Umbeher et al. (2008) also published a systematic review of the accuracy of the combination of MRI/MRS in diagnosing prostate cancer. The authors identified 9 case studies of 297 men with biopsy-confirmed prostate cancer and calculated for MRI/MRS a sensitivity of 68% (95% confidence interval [CI]: 56% to 78%) and a specificity of 85% (95% CI: 78 to 90%). The authors also identified 7 diagnostic cohort studies of 284 men suspected of having prostate cancer and calculated for combined MRI/MRS a sensitivity of 82% (95% CI: 59% to 94%) and a specificity of 88% (95% CI: 80% to 95%).

Villeirs et al. (2008) investigated the feasibility and diagnostic value of a whole prostate qualitative approach to combined magnetic resonance imaging and spectroscopy (MRI+MRS) in the detection of prostate cancer in patients with elevated PSA. Three hundred and fifty six subjects were examined with fast-T2-weighted images (MRI) and 3D-magnetic resonance spectroscopy (MRS). Prostate cancer was histopathologically proven in 220 patients and non-evidence of cancer was determined after at least 12 months clinical follow-up in 136 subjects. Receiver operating curve analysis revealed a significantly better diagnostic performance of MRI+MRS (A (z) =0.857) than MRI alone (A (z) =0.801) and MRS alone (A (z) =0.810). The sensitivity, specificity and accuracy of MRI+MRS for detection of prostate cancer were 72.3%, 92.6%, and 80.1%, respectively. The investigators concluded that spectral evaluation with a whole prostate qualitative approach is feasible in routine clinical practice. The combination of MRI and MRS yields superior diagnostic results than either modality alone. Further research is needed to confirm this conclusion.

Lagemaat et al. (2012) determined the reproducibility of 3D proton MRS of the human prostate in a multicenter setting at 1.5T. Fourteen subjects were measured twice with 3D point-resolved spectroscopy (PRESS) using an endorectal coil. The authors concluded that repeated measurements of
in vivo 3D proton MRS of the complete prostate at 1.5T produce equal and quantitative results. According to the authors, the reproducibility of the technique is high enough to provide it as a reliable tool in assessing tumor presence in the prostate. These findings require confirmation in a larger study.

According to a National Institute for Health and Clinical Excellence guideline for prostate cancer, magnetic resonance spectroscopy is not recommended for men with prostate cancer except in the context of a clinical trial (NICE 2008).

Other Conditions
MRS-detected biochemical abnormalities have been characterized for other diseases such as Parkinson’s disease (Lucetti, 2007), spinocerebellar ataxia (Boesch, 2007), brain abscess (Dev et al. 1998), heart disease (Schmidt, 2006), motor neuron disease (van der Graaff et al. 2010) and liver disease (Friedrich-Rush et al. 2010, Orlacchio, 2008). However, these MRS findings have not been translated into proven clinical practice demonstrating improved patient outcomes.

Professional Societies
American College of Radiology (ACR): The ACR in collaboration with the American Society of Neuroradiology (ASNR), recommend MRS as a proven and useful method for the evaluation, assessment of severity, and follow-up of diseases of the brain and other regions of the body. The guidelines, however, caution that MRS findings may be misleading and, therefore, should be interpreted by taking into consideration the results from other diagnostic studies, physical examination, clinical history, and laboratory results. According to the ACR practice guideline (developed through consensus; not evidence-based), when conventional imaging by magnetic resonance imaging (MRI) or computed tomography (CT) is inadequate to answer specific clinical questions, indications for MRS in adults and children include, but are not limited to, the following (ACR, 2008):

1. Evidence or suspicion of primary or secondary neoplasm (pretreatment and post treatment).
2. Grading of primary glial neoplasm, particularly high grade versus low grade glioma.
3. Evidence or suspicion of brain infection, especially cerebral abscess (pretreatment and post-treatment) and HIV-related infections.
4. Seizures, especially temporal lobe epilepsy.
5. Evidence or suspicion of neurodegenerative disease, especially Alzheimer’s disease, Parkinson’s disease, and Huntington’s disease.
6. Evidence or suspicion of subclinical or clinical hepatic encephalopathy.
7. Evidence or suspicion of an inherited metabolic disorder such as Canavan’s disease and other leukodystrophies.
8. Suspicion of acute brain ischemia or infarction.
9. Evidence or suspicion of a demyelination or dysmyelination disorder.
10. Evidence or suspicion of traumatic brain injury.
11. Evidence or suspicion of brain developmental abnormality and cerebral palsy.
12. Evidence or suspicion of other neurodegenerative diseases such as amyotrophic lateral sclerosis.
13. Evidence or suspicion of chronic pain syndromes.
14. Evidence or suspicion of chromosomal and inherited neurocutaneous disorders such as neurofibromatosis and tuberous sclerosis.
15. Evidence or suspicion of neurotoxicity disorders.
16. Evidence or suspicion of hypoxic brain injury.
17. Evidence or suspicion of spinal cord disorders such as tumors, demyelination, infection, and trauma.
18. Evidence of neuropsychiatric disorders such as depression, post-traumatic stress syndrome, and schizophrenia.
19. Differentiation between recurrent tumor and treatment related changes or radiation injury.
20. Differentiation of cystic lesions, e.g., abscess versus cystic metastasis or cystic primary neoplasm.
21. Evidence or suspicion of cerebral vasculitis, systemic lupus erythematosus (SLE), and neuropsychiatric systemic lupus erythematosus (NPSLE).

According to the ACR Appropriateness Criteria for pre-treatment staging of prostate cancer, improvements in diagnostic accuracy and staging have been reported with magnetic resonance spectroscopy imaging (MRSI) for prostate cancer. However, a recent clinical trial under the auspices of the American College of Radiology Imaging Network® (ACRIN®) showed no benefit of MR spectroscopy for localizing prostate cancer over standard MRI alone (Weinreb 2009). Thus, MRSI cannot yet be considered a routine diagnostic tool (ACR, 2009).

The ACR Appropriateness Criteria for dementia and movement disorders states that MRS is investigational and does not appear to clinically help establish a diagnosis of vascular dementia or mixed vascular dementia and Alzheimer’s disease. The ACR appropriateness criteria for dementia and movement disorders indicates ratings of 4 or less for MRS except for suspected prion disease (Creutzfeld-Jakob, iatrogenic CJ or variant CJ) which is assigned a rating of 5 for MRS. The ACR appropriateness criteria for focal neurological deficits indicates ratings of 4 or less for MRS. The ACR appropriateness criteria for cerebrovascular disease indicates a rating of 1 for all criteria. The ACR appropriateness criteria for ataxia indicates ratings of 2 or less for MRS except for acute or subacute ataxia as a manifestation of suspected infection (adult or child) which is assigned a rating of 6 for MRS. (ACR Rating Scale: 1=least appropriate, 9=most appropriate). (ACR Appropriateness Criteria)

American Academy of Neurology (AAN): The AAN guideline for Utility of MRI in Suspected Multiple Sclerosis states that new imaging technologies, such as magnetization transfer ratios (MTR), MRS, diffusion tensor imaging, tractography, and brain atrophy measurements will undoubtedly facilitate a better understanding of the extent and dynamic aspects of disease pathology in MS. Each of these new MRI techniques will need to be evaluated for sensitivity and specificity in detecting tissue injury in MS and for predicting the development of MS in the future (Frohman, 2003).

The AAN guideline Neuroimaging of the Neonate states that for diagnostic assessment, MRI should include MRS if single-voxel proton MRS is available for infants with neonatal encephalopathy (Ment, 2002).

American Urological Association (AUA): In a best practice statement for prostate-specific antigen the AUA states that endorectal coil MRI together with magnetic resonance spectroscopy (MRS) for characterization of cancer stage and volume is still considered an investigational procedure, but has shown promise in preliminary studies (Greene et al. 2009).
National Comprehensive Cancer Network (NCCN): NCCN practice guidelines (2012) for central nervous system cancers states that MRS spectroscopy can be considered to rule out radiation-induced necrosis or pseudo-progression.

The NCCN practice guideline for prostate cancer indicates that a more aggressive workup such as repeat biopsy, MR spectroscopy, and endorectal MRI may be done for post-radiation therapy recurrence of prostate cancer (NCCN, 2012).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Magnetic resonance spectroscopy (MRS) devices are regulated by the FDA as Class II devices. Several MRS devices have been approved via the FDA 510(k) process and include:

- ACS NT (K991568) - approved July 19, 1999
- Magnetom Symphony (K050199) - approved February 18, 2005
- Magnetom Vision (K945517) - approved October 17, 1995
- ProBE (Proton Brain Exam) (K930265) - approved April 25, 1995
- Signa Advantage (K941666) - approved December 22, 1995
- Signa Excite (K945779) - approved June 17, 2004


Use the following product codes:
- Product code LNI (system, nuclear magnetic resonance spectroscopic)
- Product code LNH (system, nuclear magnetic resonance imaging)
- Product code MOS (coil, magnetic resonance specialty)

The FDA cautions that magnetic resonance examination is contraindicated for patients who have metallic implants or electrically, magnetically or mechanically activated implants (e.g., cardiac pacemakers) because the magnetic and electromagnetic fields may produce strong attraction and/or torque to the implant or may interfere with the operation of these devices. This applies also to patients who rely on electrically, magnetically or mechanically activated life support systems. Scanning patients with intracranial aneurysm clips is contraindicated unless the physician is certain that the clip is not magnetically active. Scanning patients with intracranial aneurysm clips is contraindicated unless the physician is certain that the clip is not magnetically active. See the following Web site for more information: http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm135362.htm. (Accessed August 2012)

Additional Products
- Elscint 2T Prestige; 1.5T Infinion, 1.5T Intera; 1.5T Signa MR/i; Proton Spectroscopy Package for use with EXCELART™ with Pianissimo; Signa VH/i Magnetic Resonance System with SW version VH2; Picker MR Spectroscopy Package
APPLICABLE CODES

The codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the benefit document. This list of codes may not be all inclusive.

<table>
<thead>
<tr>
<th>CPT® Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>76390</td>
<td>Magnetic resonance spectroscopy</td>
</tr>
</tbody>
</table>

*CPT® is a registered trademark of the American Medical Association.*

REFERENCES


ECRI Institute. Health Technology Forecast Database. Ultrahigh-field-strength magnetic resonance imaging (MRI) with field strengths greater than 3.0T. April 2010.


Lawrentschuk, N, Fleshner, N. The role of magnetic resonance imaging in targeting prostate cancer in patients with previous negative biopsies and elevated prostate-specific antigen levels. BJU Int. 2009. Jan 14.


## PROTOCOL HISTORY/REVISION INFORMATION

<table>
<thead>
<tr>
<th>Date</th>
<th>Action/Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>08/23/2012</td>
<td></td>
</tr>
<tr>
<td>08/25/2011</td>
<td></td>
</tr>
<tr>
<td>10/28/2010</td>
<td></td>
</tr>
<tr>
<td>05/21/2010</td>
<td></td>
</tr>
<tr>
<td>05/22/2009</td>
<td>Corporate Medical Affairs Committee</td>
</tr>
</tbody>
</table>

The foregoing Health Plan of Nevada/Sierra Health & Life Health Operations protocol has been adopted from an existing UnitedHealthcare coverage determination guideline that was researched, developed and approved by the UnitedHealthcare Coverage Determination Committee.