Magnetic Resonance Spectroscopy (MRS) for Evaluation of Neurological Disorders

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NON-COVERAGE POLICY AND RATIONALE

Magnetic resonance spectroscopy (MRS) is 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.
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.

Clinical Evidence:
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
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.

Proton MRS allowed for the differentiation of gliomatosis cerebri from low-grade glioma (Galanaud, 2003); based on unique spectral patterns, proton MRS differentiated primary central nervous system lymphoma from glioma (Harting, 2003; Utriainen, 2003). These findings have strong implications for patient management, although MRS results were not used to inform clinical decision-making in these studies.

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.

Fellow et al. (2010) evaluated the accuracy of (¹H-MR spectroscopy ((¹H-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 SV SE (¹H-MRS with PRESS localization 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. It is also not clear how this information would be used in physician decision-making or to improve survival rates from glioblastoma multiforme.

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, fibrillary 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. Metabolite concentrations of tCho and tCr were normalized to the respective concentration in contralateral brain tissue. The Mann-Whitney U test was performed to evaluate differences between these two groups. Normalized tCho did not show any statistically significant difference between the two groups. There was a strong trend toward higher values of normalized tCr in the DA group. For 3 of 5 children with DA, lactate was detectable, but only 1 of 11 children with PA showed lactate. 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 pair-wise 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 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.

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.

The evidence regarding the utility of MRS for tumor grading is inconclusive. Results of some 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.

Hourani et al. (2008) investigated whether proton MR spectroscopic imaging (1H-MRSI) can aid in differentiating between tumors and nonneoplastic brain lesions, and whether perfusion MR imaging can improve the classification in a retrospective study of 69 adults with untreated primary brain lesions (brain tumors (n = 36); benign lesions (n = 10); stroke (n = 4); demyelination (n = 10); and stable lesions not confirmed on pathologic examination (n = 9). MR imaging and 1H-MRSI were performed at 1.5T before biopsy or treatment. MRSI and perfusion MR imaging had similar discriminatory capabilities in differentiating tumors from nonneoplastic lesions. According to the investigators, these results suggest a promising role for 1H-MRSI and perfusion MR imaging in the distinction between brain tumors and nonneoplastic lesions in adults.

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. All patients had previously been treated for high-grade glioma with surgery, radiation therapy, or chemotherapy alone or in combination. The new lesions were considered tumor recurrence if they met either of the following criteria: subsequent histopathologic evidence of
active tumor by biopsy or surgical resection; or followup MR image showing mass effect and steady growth of enhancement. Lesions were classified as radiation injury if they met either of the following criteria: later histopathologic verification of radiation injury without tumor, by biopsy, or surgical resection; or stable and/or resolving regions of enhancement on subsequent MR image. MRS demonstrated 89% to 90% sensitivity, 83% to 100% specificity, 100% PPV, 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., 2004; Palumbo et al., 2006; Zeng et al., 2007). 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 (Hayes, 2008).

In a consecutive series of 26 previously operated patients diagnosed with cerebral glioma, magnetic resonance spectroscopy (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. It is also not clear how this information would be used in physician decision-making or to improve survival rates from glioma.

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.

Two-dimensional chemical shift imaging (CSI) MR spectroscopy was performed in 29 consecutive patients who had a new contrast-enhancing lesion in the vicinity of a previously diagnosed and treated brain neoplasm. Clinical and imaging follow-up, and histopathology in 16 patients, were used as indicators of the identity of a lesion. Diagnostic-quality spectra were obtained in 97% of the patients. The Cho/Cr (choline/creatine) and Cho/NAA (choline/N-acetyl aspartate) ratios were significantly higher, and the NAA/Cr ratios significantly lower, in tumor than in radiation injury. The
Cho/Cr and Cho/NAA ratios were significantly higher in radiation injury than in normal-appearing white matter, whereas NAA/Cr ratios were not different. Mean Cho/Cr ratios were 2.52 for tumor, 1.57 for radiation injury, and 1.14 for normal-appearing white matter. Mean Cho/NAA ratios were 3.48, 1.31, 0.79, and mean NAA/Cr ratios were 0.79, 1.22, and 1.38, respectively. When values greater than 1.8 for either Cho/Cr or Cho/NAA ratios were considered evidence of tumor, 27 of 28 patients could be correctly classified. According to the investigators, two-dimensional CSI MR spectroscopy can differentiate tumor from radiation injury in patients with recurrent contrast-enhancing intracranial lesions. In these lesions, the Cho/NAA and Cho/Cr ratios may be the best numeric discriminators (Weybright et al., 2005). These findings require confirmation in a larger study.

Steffen-Smith et al. (2008) conducted a study to detect abnormalities and identify relationships between brain metabolic ratios determined by proton magnetic resonance spectroscopic imaging ((1)H-MRSI) and neuropsychological (NP) function in cancer patients at risk for neurotoxicity. Thirty-two patients received (1)H-MRSI using a multi-slice, multi-voxel technique on a 1.5T magnet. Cho/NAA, NAA/Cr, and Cho/Cr ratios were identified in seven pre-determined sites without tumor involvement. A battery of age-appropriate NP tests was administered within 7 days of imaging. Relationships were examined between test scores and metabolite ratios. According to the investigators (1)H-MRSI may be useful in early detection of neurotoxic effects, but prospective longitudinal studies in a homogeneous population are recommended to determine the prognostic value.

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). Lichy et al. (2006) evaluated 34 patients with histologically proven gliomas who underwent MRS after radiation therapy. A sensitivity of 93.8% and specificity of 85.7% were achieved in the differentiation of progressive tumors from non-progressive tumors by MRS. The investigators concluded that MRS allows for the evaluation of radiotherapy response.

Bobek-Billewicz et al. (2010) evaluated the diagnostic effectiveness of perfusion-weighted imaging (PWI), diffusion-weighted imaging (DWI) and 1HMRS 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 radiochemotherapy. Based on the study results, PWI was the most reliable in differentiation between tumor regrowth/recurrence and radiation necrosis. Proton MR spectroscopy (1HMRS) and DWI did not differentiate analyzed groups with statistical significance.

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
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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.

Intensive video electroencephalogram (EEG) monitoring, high-resolution MR imaging (MR imaging), proton MR spectroscopy ((1)H-MR spectroscopy) and single-photon emission CT (SPECT) were compared in 25 patients with temporal lobe epilepsy (TLE) to evaluate lateralization of affected hemisphere with regard to bilateral affection and postoperative outcome. (1)H-MR spectroscopy indicated concordant lateralization to EEG in 82% of MR imaging-positive patients and 71% of MR imaging-negative patients and to SPECT in 84% of MR imaging-positive patients and 67% of MR imaging-negative patients with TLE. In unilateral TLE, the concordance rate of both modalities was 74% in MR imaging-positive patients and 67% in MR imaging-negative patients. Contralateral findings to EEG focus were found in 28% by (1)H-MR spectroscopy and in 27% by SPECT. Concordant findings to the operated side of different modalities revealed a clear tendency for a better postoperative outcome compared with bitemporal or contralateral findings. According to the investigators, this study demonstrates 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 (Doelken et al. 2007). The small size of the study population limits the validity of the conclusion of this study.

Lantz et al. (2006) evaluated 15 patients with temporal lobe epilepsy who underwent preoperative and postoperative proton MRS. The study identified 2 factors (extensive preoperative MRS abnormalities and right-sided focus) that predict postoperative normalization of contralateral MRS abnormalities. The investigators suggested that both factors indicate a more generalized epileptic disease. This study did not demonstrate how this information would affect patient management.

A study by Goncalves et al. (2006) assessed the value of 3 MRI quantitative modalities for pre-surgical 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

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.

Ross et al. (2006) evaluated the potential of proton MRS for predicting cognitive decline in stroke patients. Structural MRI and single-voxel proton MRS were performed in 49 stroke patients and 60 controls. The investigators concluded that the MRS measures were better predictors of cognitive decline than structural measures. This study is limited by a small study population.

Karaszewski et al. (2006) used MRS to measure cerebral temperature in 40 stroke patients and found that temperature was elevated in the acutely ischemic brain. The authors concluded that MRS could be used to evaluate temperature after brain injury to monitor interventions. The MRS results in this study were not used for clinical 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.
Aanen et al. (2010) evaluated proton magnetic resonance spectroscopic imaging (MRSI) findings for children with traumatic brain injury attributable to nonaccidental 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 ≥ 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.

Tollard et al. (2009) evaluated whether multimodal magnetic resonance imaging can provide a reliable outcome prediction of the clinical status, focusing on consciousness at 1 year after severe traumatic brain injury (TBI) in a single center prospective cohort. Forty-three TBI patients not responding to simple orders after sedation cessation and 15 healthy controls were included in the study. A multimodal magnetic resonance imaging combining morphologic sequences, diffusion tensor imaging (DTI), and H proton magnetic resonance spectroscopy (MRS) was performed 24 +/- 11 days after severe TBI. The ability of DTI and MRS to predict 1-year outcome was assessed by linear discriminant analysis (LDA). After 1 year, 19 (44%) patients had unfavorable outcomes (death, persistent vegetative state, or minimally conscious state) and 24 (56%) favorable outcomes (normal consciousness with or without functional impairments). Unfavorable outcome was predicted with up to 86% sensitivity and 97% specificity; these values were better than those obtained with DTI or MRS alone. This study did not validate MRS findings with improved treatment outcomes.

**Demyelination or Dysmyelination Disorder**

Bellmann-Strobl et al. (2009) assessed magnetic resonance imaging (MRI)-based lesion load assessment with clinical disability in early relapsing remitting multiple sclerosis (RRMS). Seventeen untreated patients (ten women, seven men; mean age 33 years) with the initial diagnosis of RRMS were included for cross-sectional as well as longitudinal (24 months) clinical and MRI-based assessment in comparison with age-matched healthy controls. Conventional MR sequences, MR spectroscopy (MRS) and magnetisation transfer imaging (MTI) were performed at 1.5 T. Lesion number and volume. MRS and MTI measurements for lesions and normal appearing white matter (NAWM) were correlated to clinical scores. According to the investigators, MTI and MRS were useful for initial disease assessment in normal appearing white matter. MTI and MRS correlated with clinical scores, indicating potential for monitoring the disease course and gaining new insights into treatment-related effects. The study did not confirm the utility of such findings in improving care and outcome of patients.

Wattjes et al. (2008) prospectively investigated metabolic changes in the normal-appearing white matter (NAWM) of patients presenting with clinically isolated syndromes (CIS) suggestive of multiple sclerosis (MS) and correlated these changes to conventional MR imaging findings in terms of MR imaging criteria. Multisequence MR imaging of the brain and (1)H-MR spectroscopy of the parietal NAWM were performed in 31 patients presenting with CIS and in 20 controls using a 3.0 T MR system. According to the investigators, as assessed by (1)H-MRS a significant axonal damage already occurs during the first demyelinating episode in patients with CIS. Conventional MR imaging in terms of diagnostic imaging criteria does not significantly reflect NAWM disease activity in terms of metabolic alterations detected by (1)H-MR spectroscopy. This study did not validate MRS findings with improved treatment outcomes.

Mader et al (2000) compared the absolute concentrations of total creatine (Cr), N-acetylaspargtate (NAA), choline (Cho), and myo-inositol between patients treated with a placebo or 15 +/- deoxyxysperguain (DSG) and between clinical groups with relapsing-remitting or secondary-progressive MS. Sixteen patients, recruited from a pharmacological study of DSG, and 11 healthy control subjects were investigated by a stimulated-echo acquisition mode sequence. The
investigators concluded that the contradictory time courses of Cr and NAA show that an absolute quantification in proton MR spectroscopy in MS is necessary to avoid a false interpretation of reduced NAA/Cr ratios. The increase in Cr is probably due to remyelination. The initial dip and later recovery of NAA seem to be related to diminishing edema and remyelination. The study did not confirm the utility of such findings in improving care and outcome of patients.

While MRS may provide some information about the pathological changes of multiple sclerosis, 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
Jessen et al. (2009) conducted a (1)H-MRS study in patients with mild dementia and mild cognitive impairment (MCI) at four sites to investigate the multicenter feasibility of (1)H-MRS. In total, 130 patients with dementia (98 Alzheimer disease (AD), 32 non-AD), 136 subjects with MCI (70 of AD type, 66 of non-AD type), and 45 unimpaired control subjects were included. Single-volume (1)H-MRS of the left medial temporal lobe was performed at long and short echo times. Metabolites were quantified and metabolic ratios were determined. A significant reduction of N-acetyl aspartate (NAA) concentration was found in patients with AD as compared to healthy volunteers and compared to patients with MCI of AD type. According to the investigators, this study demonstrated the multicenter feasibility of proton magnetic resonance spectroscopy ((1)H-MRS) of the medial temporal lobe in mild dementia and mild cognitive impairment, which is a prerequisite for the application of (1)H-MRS in large-scale clinical trials. However, this study did not translate abstract research data into clinical guidelines that can be used to improve physician decision-making and patient care.

Modrego et al. (2006) assessed the effect of rivastigmine on metabolite levels in different areas of the brain, and whether changes in metabolite levels correlate with clinical outcome, in patients with Alzheimer's disease compared with untreated patients with Alzheimer's disease. Twenty-four consecutive patients with mild or moderate Alzheimer's disease were enrolled in the study and were treated with rivastigmine. A comparison group of ten consecutive untreated patients with Alzheimer's disease with similar cognitive impairment to the treatment group were also enrolled. Each patient underwent single-voxel MRS of the frontal, parietal and occipital cortices of the brain to assess levels of brain metabolites (NAA, creatine, choline and myo-inositol) and their ratios to creatine. Treatment with rivastigmine showed modest neuronal functional recovery in the frontal cortex only (being able to reverse disease-related decreases in NAA/creatinic and myo-inositol/creatine ratio in this area but unable to affect the disease-related increase in myo-inositol/creatine ratio in any cortex). The investigators concluded that since the modest clinical changes correlated with the small changes in the metabolite rates, MRS could be useful in monitoring response to current or future treatments for Alzheimer's disease. The small study population limits the validity of the conclusion of this study.

Garcia Santos et al. (2008) evaluated (1)H-labelled magnetic resonance spectroscopy (MRS) in 56 patients with a low Mini Mental State Examination (MMSE) score identified during a dementia community-based survey. Two single-voxel sequences (TR 1,500, TE 35/144 ms) were carried out in the posterior cingulate gyrus of each individual, and the ratios N-acetylaspartate (NAA)/creatine (Cr), choline (Cho)/Cr, myo-inositol (mI)/Cr, NAA/ml and NAA/Cho were compared statistically. The ability of MRS to distinguish clinical groups was assessed by receiver-operating characteristics analysis. Cognition effects on metabolite ratios were estimated, with gender and cognition as categorical variables and age as a continuous covariate. NAA/Cr and NAA/Cho ratios were lower in dementia or Alzheimer's disease than in MCI and normal groups. The NAA/Cr ratio at TE 35 ms performed best when distinguishing dementia or Alzheimer's disease from non-demented subjects. MRS could not distinguish between MCI patients and normal subjects. Dementia was an independent predictor of metabolite values. According to the investigators, conventional MRS still proved to be a useful tool for dementia discrimination, but it is potentially far less useful as a surrogate marker for MCI. Based upon this study, it is not clear how MRS would be used to treat patients with suspected dementia.
Paul et al. (2007) performed magnetic resonance spectroscopic and neuropsychological evaluations on 61 patients with AIDS dementia complex (stages 1-3) and 39 HIV-positive neurologically asymptomatic individuals. N-acetylaspartate, a marker of mature neurons, choline and myoinositol, both markers of gliosis, and creatine, a reference marker, were measured in the basal ganglia, frontal white matter, and parietal cortex. According to the investigators, this study provides convincing evidence that neuropsychological impairment is associated with reduced markers of mature neurons and increased markers of gliosis in the basal ganglia and frontal white matter. Neural changes as reflected by these metabolite levels may prove useful in identifying individuals at risk for neuropsychological impairment but more studies are needed.

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)H-MRSI-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.

Umbehrr 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).

Seitz et al. (2009) systematically reviewed the literature and concluded that a limited number of small studies suggest that functional MRI may improve the diagnosis and staging of prostate cancer; However according to the authors, further confirmation in larger studies is needed.

Lawrentschuk and Fleschner (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%).

Wang et al. (2008) published a systematic review of MRS for diagnosis of prostate cancer. The authors of the review concluded that MRS had a better applied value compared to other common modalities.

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.

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 (2011) for central nervous system cancers states the following regarding MRS:

- Assesses metabolites within tumors and normal tissue
- Optimal use is to differentiate tumor from radiation necrosis; may be helpful in grading tumors or assessing response.
- Area most abnormal should be the best place to target for a biopsy.
- Limitations: tumors near vessels, air spaces, or bone.

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, 2011).

Additional Search Terms
Electrocorticography, electroencephalography, frontal cortex, NMR, TIA

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
Additional information is available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. Accessed May 2011. 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 May 2011.

**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

**PAYMENT GUIDELINES**

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 Member’s plan of benefits or Certificate of Coverage. This list of codes may not be all inclusive.

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**REFERENCES**

The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by UnitedHealthcare Medical Technology Assessment Committee. [2011T0063H].


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### Policy History/Revision Information

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