

## Medical Policy



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### **Title:       Magnetic Resonance Spectroscopy**

#### **Professional**

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#### **DESCRIPTION**

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

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

- Arising from N-acetyl groups, especially n-acetylaspartate (NAA)
- NAA intensity is thought to be a marker of neuronal integrity and is the most important proton signal in studying central nervous system (CNS) pathology. Decreases in the NAA signal are associated with neuronal loss.
- Arising from choline-containing compounds (Cho) such as membrane phospholipids (e.g., phosphocholine and glycerophosphocholine). Choline levels increase in acute demyelinating disease. Brain tumors may also have high signals from Cho.
- Arising from creatine and phosphocreatine

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

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

Different patterns of the above spectra, in both the healthy and diseased brain, are the basis of clinical applications of MRS. The MRS findings characteristically associated with non-necrotic brain tumors include elevated choline (Cho) levels and reduced N-acetylaspartate (NAA) levels. The International Network for Pattern Recognition using Magnetic Resonance (<http://azizu.uab.es/INTERPRET/index.html>) has developed a user-friendly computer program for spectral classification and a database of 300 tumor spectra with histologically validated diagnoses to aid radiologists in MRS diagnosis. (1)

Peripheral applications of MRS include the study of myocardial ischemia, peripheral vascular disease, and skeletal muscle. Applications in non-CNS oncologic evaluation have also been explored. New nomograms for prostate cancer are being developed that incorporate MRI and MRS results. (2)

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

### **POLICY**

Magnetic resonance spectroscopy is considered **experimental / investigational**.

### **RATIONALE**

While MRS has been investigated in a wide variety of clinical situations, there are limited studies specifically focusing on its sensitivity and specificity in specific clinical situations. No studies demonstrate that patient management based on the results of MRS improves patient outcomes. For example, MRI is a sensitive tool for identifying space-occupying CNS lesions, but it is relatively nonspecific in distinguishing between benign and malignant lesions. MRS can provide a chemical profile of the lesions that may help in this determination. However, there are not sufficient data detailing the sensitivity and specificity of MRS in distinguishing benign and malignant lesions. (3, 4) In known malignancies, MRS has been used to assess tumor histology before resection. (5-8) However, this information may not always influence treatment decisions. For example, the standard approach to CNS tumors is complete surgical resection—exact tumor histology may not be necessary. (9) In this setting, a high negative predictive value is probably the most critical statistic, so there is a minimal chance of missing a diagnosis of

malignancy. After initial treatment, the distinction between tumor recurrence or radiation necrosis is frequently a difficult clinical issue. However, there are not sufficient data about whether MRS can be used to make this distinction. (10)

Lack of definitive studies demonstrating clinical value of MRS extends to its use in multiple sclerosis, cerebrovascular injury, prostate cancer, breast cancer, and mitochondrial disorders.

A 2003 TEC Assessment concluded that MRS does not meet TEC criteria for evaluation of suspected brain tumors. (11) The Assessment identified 7 studies including a total of 271 subjects. MRS would be judged to produce a beneficial effect on a health outcome if MRS correctly determines the presence or absence of a tumor and avoids the need for a brain biopsy.

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

Five studies evaluating a heterogeneous group of patients, some with known prior tumor, some with unknown new masses, showed variable diagnostic test characteristics for MRS with sensitivities ranging from 79% to 100% and specificity ranging from 74% to 100%. (13-18) The positive predictive value ranged from 92% to 100%, while the negative predictive value ranged from 60% to 100%. The wide range reported for diagnostic performance in these studies may reflect heterogeneous groups of patients, differences in MRS protocols, or both.

One study evaluated 51 patients with intracranial cystic lesions. (18) MRS properly assigned the correct diagnosis in 47 of 51 patients (92%). However, MRS interpretation was based on investigator judgment, rather than on formal criteria.

### **2005 Update**

A search for pivotal publications on the use of MRS for several conditions did not find any studies for the use of MRS for any condition that provide strong evidence for clinical utility.

### **Summary**

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

**2006 Update**

A search for key publications on the use of MRS did not find any studies that provide strong evidence for the clinical utility of MRS. A recent systematic literature review on MRS for the characterization of brain tumors concluded that the evidence on MRS for characterizing brain tumors is promising, but that additional high-quality studies are needed (19). Many of the articles reviewed were flawed, in some cases because of research design and in other cases key information needed to evaluate the study was not reported (e.g., how many days elapsed between the imaging test and the biopsy, which served as the reference standard). A search of studies published after the period covered by the systematic review (2005–2006) (e.g., 20, 21) did not identify any that provided sufficient evidence to alter the conclusions of this policy. A trial on staging brain tumors with MRS and MR perfusion is in development by the American College of Radiology Imaging Network (22). Other trials on MRS are also under way, as reported at [clinicaltrials.gov](http://clinicaltrials.gov).

The utility of MR spectroscopy has also been investigated for identifying whether prostate cancer is confined to the organ, which has implications for prognosis and treatment. Wang et al. (23) found that the addition of MRI findings—both endorectal MRI imaging and MR spectroscopy—improved the accuracy of the staging nomograms traditionally used to predict the likelihood of organ-confined prostate cancer. Although the study was not ideally designed to assess the incremental value of MRS spectroscopy over MR alone, it found that the area under the ROC curve was larger when MR spectroscopy was included, but the difference was not statistically significant. More information on this issue may be forthcoming when the results of a clinical trial conducted by the American College of Radiology Imaging Network (#6659) are released (22). This study specifically evaluates the incremental value of MRS. Data collection has been completed, and analysis and preparation of publications are currently underway.

Another use of MRS that is being investigated is to improve the specificity of MRI of the breast. One of the weaknesses of MRI of the breast is that it has a high false-positive rate. Bartella et al conducted a preliminary study using MRS to evaluate suspicious lesions 1 cm or larger identified on MR imaging. (24) They found that the addition of MRS increased the specificity of MRI in the specific population examined to 88% (23/26) and could have prevented unnecessary biopsies; the sensitivity was 100% (31/31). As the authors note, these findings need to be confirmed in larger studies and with a more diverse set of lesions. In particular, their sample only included one ductal carcinoma in situ (DCIS), and other studies have suggested that the choline peak they used to indicate a positive MRS result may be less likely to occur with DCIS.

**2008 Update**

Preliminary results from ACRIN Protocol 6659 (annual meeting of the Radiological Society of North American, abstract No. SSJ05-06, November 28, 2006, Chicago, IL) did not indicate any statistically significant improvement in prostate cancer localization due to the addition of MRS to MRI results (although other studies had different results [25]). Peer-

reviewed publication of the results of the ACRIN trial will provide further evidence on this issue.

Although a number of studies have examined the use of MRS to differentiate between brain tumor recurrence and radiation necrosis, the cumulative evidence is weak. The studies tend to have small sample sizes (26, 27); they provide incomplete histopathological data to serve as the reference standard (28); they find that combined imaging modalities, such as MRS and perfusion MRI or diffusion-weighted MRI outperform MRS by itself (29, 30); or they identify the patterns of interest and the cutoff values for making a diagnosis without providing validation studies (31, 32). In some cases, a mixed reference standard is used, with histopathological findings for lesions that are excised, biopsied, or reviewed at autopsy and longer follow-up for patients not undergoing surgery (29, 31). Although having a mixed reference standard is not optimal, it may be the only feasible option in patients with brain tumors, some of which are located in parts of the brain not amenable to surgery. Some studies report mostly on primary brain tumors (29, 33), while others focus mostly on metastases of cancers in other parts of the body (26, 28). Studies on the use of MRS to categorize newly diagnosed brain tumors (1); to distinguish between tumors and abscesses or other infectious processes (34); or to diagnose mitochondrial diseases (35) identify the MRS patterns associated with each type of lesion but once again do not include the necessary validation study or report MRS findings that overlap across the categories of interest. Many are also retrospective (e.g., 31, 34) Preliminary studies done in Asia with a 3T MRI machine for detecting tumor versus radiation injury reported diagnostic quality MRS studies in 26/28 (93%) cases, and the sensitivity and specificity for those 26 patients based on cutoffs identified in the study were 94.1% and 100%. (33; see also 29). Validation studies using the same cutoffs in larger samples are needed. (33)

### **Medicare Policy**

In January 2004, Medicare issued a decision memorandum for MRS for brain tumors that reaffirmed its national non coverage determination. (36) After reviewing updated literature, a technology assessment it commissioned from the Agency for Healthcare Research and Quality, and the BCBSA TEC Assessment, Medicare found that there was not adequate evidence to conclude that MRS is reasonable and necessary for the diagnosis of brain tumors.

**CODING**

**The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.**

**CPT/HCPCS**

76390      Magnetic resonance spectroscopy

**REVISIONS**

06-16-2009	Added policy to bcbsks.com web site.
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