

Medical Policy



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Populations	Interventions	Comparators	Outcomes
Individuals: • With brain tumors	Interventions of interest are: • Magnetic resonance spectroscopy	Comparators of interest are: • Magnetic resonance imaging alone	Relevant outcomes include: • Test accuracy • Change in disease status • Morbid events • Functional outcomes
Individuals: • With breast cancer	Interventions of interest are: • Magnetic resonance spectroscopy	Comparators of interest are: • Magnetic resonance imaging alone	Relevant outcomes include: • Test accuracy • Change in disease status • Morbid events
Individuals: • With prostate cancer	Interventions of interest are: • Magnetic resonance spectroscopy	Comparators of interest are: • Magnetic resonance imaging alone	Relevant outcomes include: • Test accuracy • Change in disease status • Morbid events
Individuals: • With dementia	Interventions of interest are: • Magnetic resonance spectroscopy	Comparators of interest are: • Observation	Relevant outcomes include: • Test accuracy • Change in disease status • Morbid events

Populations	Interventions	Comparators	Outcomes
Individuals: • With liver disease	Interventions of interest are: • Magnetic resonance spectroscopy	Comparators of interest are: • Liver biopsy	Relevant outcomes include: • Test accuracy • Change in disease status • Morbid events
Individuals: • With multiple sclerosis	Interventions of interest are: • Magnetic resonance spectroscopy	Comparators of interest are: • Observation	Relevant outcomes include: • Test accuracy • Change in disease status • Morbid events

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.

Objective

The objective of this evidence review is to evaluate whether magnetic resonance spectroscopy improves health outcomes in patients with brain tumors, breast cancer, prostate cancer, and various noncancer indications.

Background

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 MR image is first generated, and then MRS spectra are developed at the site of interest, at the level of the voxel (3-dimensional volume X pixel). The voxel of interest is typically a cube or rectangular prism with a dimensional pixel with a volume of 1 to 8 cm³. While an MRI provides an anatomic image of the brain, MRS provides a functional image related to underlying dynamic physiology. MRS can be performed with existing MRI equipment, modified with additional software and hardware, which are provided with all new MRI scanners. Imaging time in the scanner is increased by 15 to 30 minutes.

MRS has been studied most extensively in a variety of brain pathologies. In the brain, both 1-H (ie, proton) and 31-P are present in concentrations high enough to detect and

thus have been used extensively to study brain chemistry. Proton MRS of the brain reveals 6 principal spectra:

1. Arising from *N*-acetyl groups, especially *N*-acetylaspartate (NAA): NAA is an amino acid that is generated by mitochondria and is present almost exclusively in neurons and axons in the adult central nervous system (CNS). 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, damage to neuronal structures, and/or reduced neural metabolism.
2. Arising from choline-containing compounds (Cho), such as membrane phospholipids (eg, phosphocholine and glycerophosphocholine): an increase in Cho is considered a marker of pathologic proliferation/degradation of cell membranes and demyelination. Cho levels can increase in acute demyelinating disease, but an increase in Cho levels is most commonly associated with neoplasms. Cho levels can also be affected by diet and medication.
3. 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.
4. Arising from myo-inositol: myo-inositol is a polyalcohol present at high concentration in glial cells. An increase in the ratio of myo-Inositol to NAA suggests gliosis and regional neuronal damage.
5. Arising from lipid.
6. 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 these spectra and others (eg, myo-inositol, glutamate / glutamine) in the healthy and diseased brain are the basis of clinical applications of MRS. The MRS findings characteristically associated with non-necrotic brain tumors include elevated Cho levels and reduced NAA levels. The International Network for Pattern Recognition using Magnetic Resonance¹ 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.^{2,3}

One of the limitations of MRS is that it provides the metabolic composition of a given voxel, which may include more than 1 type of tissue. For some applications, the voxels are relatively large (eg, $>1 \text{ cm}^3$), although they may be somewhat smaller using a 3-tesla MRI machine versus a 1.5-tesla magnet. High-field strength increases the signal to noise ratio and spectral resolution. The 3-tesla technique creates greater inhomogeneities, however, which require better shimming techniques.⁴ There are 2 types of MRS data acquisition: single-voxel or simultaneous multivoxel, also called chemical shift imaging. Reliable results are more difficult to obtain from some areas, eg, close to the brain surface or in children with smaller brains because of the lipid signal from the skull. Some techniques are used to deal with these issues; various MRS

techniques continue to be explored as well. A combination of MRS is often used with other MRI techniques (eg, diffusion-tensor imaging, susceptibility-weighted imaging) and other types of imaging such as positron emission tomography (PET).

Peripheral applications of MRS include the study of myocardial ischemia, peripheral vascular disease, and skeletal muscle. Applications in non-central nervous system oncologic evaluation have also been explored. Nomograms for prostate cancer are being developed that incorporate MRI and MRS results.⁵

All the findings reported in this policy refer to proton MRS, unless otherwise indicated.

Regulatory Status

Multiple software packages for performing proton MRS have been cleared for marketing by the U.S. Food and Drug Administration through the 510(k) process since 1993. Single-voxel MRS is available on all modern MR scanners. FDA product code: LNH.

POLICY

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

RATIONALE

The evidence review has been updated with searches of the MEDLINE database. The most recent literature update was performed through July 9, 2018. This review was informed in part by a TEC Assessment (2003).⁶

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Brain Tumors

Clinical Context and Test Purpose

The purpose of magnetic resonance spectroscopy (MRS) in patients with brain tumors is to differentiate malignant from nonmalignant tumors, evaluate tumor grade, and distinguish metastatic from primary brain tumors.

The question addressed in this evidence review is: Does the use of MRS improve the net health outcome of patients with brain tumors?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is patients being evaluated for brain tumors.

Interventions

The intervention of interest is MRS.

Comparators

The following practice is currently being used to make decisions about managing brain tumors: standard evaluation with magnetic resonance imaging (MRI).

Outcomes

The outcomes of interest are sensitivity and specificity and the impact of the diagnosis on health outcomes.

Timing

The time of interest is at biopsy, surgical resection, or clinical follow-up.

Setting

MRS would be administered in an outpatient setting.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews

Wang et al (2014) reported on a meta-analysis of 24 studies (615 cases, 408 controls) assessing the diagnostic performance of MRS for detecting or grading of brain tumors.⁷ Twenty-two studies assessed gliomas, and 2 studies assessed ependymomas and primitive neuroectodermal tumors. Seven studies evaluated recurrence, 9 evaluated the tumor grade, 5 evaluated the detection of tumors, 1 evaluated residual tumors, and 2 assessed tumor metastases. The meta-analysis found the overall sensitivity and specificity of MRS were 80.1% and 78.5%, respectively. The area under the receiver operating characteristics curve was 0.78.

Diagnosis of Pediatric Brain Tumor Type

Pediatric brain tumors are histologically more diverse than adult brain tumors and include tumor types such as embryonal tumors, germ cell tumors, pilocytic astrocytoma, and ependymomas.

Manias et al (2018) reported on a multicenter U.K. study that retrospectively evaluated MRS for the noninvasive diagnosis of brain tumors.⁸ This study analyzed 64 consecutive children who had MRI, MRS, and histopathology. The clinical information was reviewed by a tumor board, which included pediatric oncologists, pediatric radiologists specializing in neuroradiology, clinical oncologists, neurosurgeons, and histopathologists, who arrived at consensus diagnosis and treatment planning. The reference standard was the diagnosis by the tumor board, verified

through clinical course. MRI alone was correct in 38 (59%) of 64 patients. The addition of MRS increased diagnostic accuracy to 47 (73%) out of 64, with 17 cases incorrectly diagnosed by MRI plus MRS.

Combined MRI and MRS to diagnose the type of pediatric brain tumors were reported by Shiroishi et al (2015) in a study from multiple children's hospitals in the United States.⁹ MRI and MRS were performed in 120 pediatric patients as part of the usual presurgical workup, followed by biopsy or resection. For the first 60 patients (from 2001 to 2004), MRS was performed, but was considered experimental and not used for diagnosis. For the next 60 patients (2005 to 2008), radiologists used information from both MRI and MRS. The percentage of correct diagnoses was reported for the first 60 patients using only MRI (63% correct). MRI scans were re-evaluated at the time of the study (71% correct), and the diagnosis at the second MRI reading did not differ significantly from the first MRI reading. These results were compared with blinded diagnosis using MRI plus MRS (87% correct, $p < 0.05$). For the second group of 60 patients who were diagnosed using MRI plus MRS, tumor type was correctly identified in 87% of patients ($p < 0.005$ vs initial diagnosis with MRI alone). Together, the results indicated an improvement (from 71% to 87% correct) in the diagnosis of tumor type when MRS was combined with MRI.

Vicente et al (2013) reported on a multicenter study that evaluated the ability of MRS to differentiate 78 histologically confirmed pediatric brain tumors (29 medulloblastomas, 11 ependymomas, 38 pilocytic astrocytomas).¹⁰ Significant metabolic differences in tumor types were identified by MRS when results from short and long echo times were combined, suggesting that MRS might provide noninvasive diagnostic information. MRS has also been evaluated as a prognostic tool.

In another study, Wilson et al (2013) reported on single-voxel, proton MRS to predict survival in 115 patients with pediatric brain tumors who were followed for a median of 35 months.¹¹ Poor survival was associated with lipids and scyllo-inositol while glutamine and *N*-acetylaspartate (NAA) were associated with improved survival ($p < 0.05$).

Differentiating Glioma Recurrence From Radiation Necrosis

A systematic review by Zhang et al (2014) assessed the use of MRS in the differential diagnosis of glioma recurrence from radiation necrosis; it included 18 studies (total N=455 patients).¹² Only 3 studies were prospective. Fourteen of the studies used both pathology and clinical plus radiologic follow-up as the reference standard. Twelve studies examined the choline (Cho)/creatinine (Cr) ratio, 9 studies calculated the Cho/NAA ratio, 5 studies calculated the NAA/Cr ratio, and 3 studies calculated the Cho/Cr ratio. Meta-analysis showed moderate diagnostic performance for MRS using the Cho/Cr and Cho/NAA ratios.

The largest prospective study included in the review was by Amin et al (2012).¹³ This study compared MRS with single-photon emission computed tomography (SPECT) in the identification of residual or recurrent glioma vs radiation necrosis in 24 patients treated with surgery and radiotherapy. MRS and SPECT results differed in 9 cases of recurrence and were more accurate with SPECT. The specificity and positive predictive value (PPV) were 100% in both MRS and SPECT; however, the sensitivity was 61.1% vs 88.8%, and negative predictive value (NPV) was 46.2% vs 75%, respectively. The use of a single voxel rather than multiple voxels was noted as a limitation in interpreting the MRS results in this study.

Differentiating High-Grade From Low-Grade Glioma

Wang et al (2016) reported on a systematic review of 30 studies (total N=228 patients) evaluating the diagnostic performance of MRS in differentiating high- from low-grade gliomas.¹⁴

The articles included used pathology or clinical follow-up as the reference standard for the identification of high-grade gliomas. Only 5 studies were prospective, sample sizes ranged from 7 to 160 patients, and there was considerable variability in the thresholds used to identify high-grade gliomas. There was also evidence of publication bias. The pooled sensitivity and specificity in the meta-analysis were 75% and 60% for the Cho/Cr ratio, 80% and 76% for Cho/NAA ratio, and 71% and 70% for NAA/Cr ratio. The areas under the receiver operating characteristic curve were 0.83, 0.87, and 0.78, respectively. Thus, MRS had moderate diagnostic accuracy in distinguishing high-grade from low-grade gliomas in the published studies.

Gauging Treatment Response

The possibility of using MRS to track treatment response and failure has been explored. A small (N=16), preliminary study by Sankar et al (2008) assessed tamoxifen treatment for recurrent gliomas and found MRS patterns differed between responders and nonresponders.¹⁵ Serial MRS demonstrated that metabolic spectra stabilized after initiation of therapy among responders and then changed in advance of clinical or radiologic treatment failure. In other words, MRS might help predict imminent treatment failure. However, there are relatively few studies with small sample sizes assessing this possible use of MRS. Additionally, other types of imaging are being evaluated for the same use, including dynamic contrast-enhanced (DCE) MRI (DCE-MRI), diffusion-weighted MRI, and fluorine 18 fluorodeoxyglucose positron emission tomography. Other studies are needed, including those comparing modalities or evaluating multimodalities.^{16,17}

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

No RCTs were identified that support the clinical utility of MRS for this indication. The retrospective study by Manias et al (2018), discussed above, did report that patient management was influenced by MRS in 13 cases, including avoidance of biopsy in 10 cases, appropriate management in 1 case, and alerting to high-grade lesions in 2 cases.⁸

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of MRS has not been established for this indication, a chain of evidence cannot be constructed.

Section Summary: Brain Tumors

Several systematic reviews have evaluated the performance of MRS for the diagnosis and evaluation of brain tumors. A number of small studies have assessed detection, characterization, grading, prognosis, and differentiation of tumor recurrence vs necrosis. Most studies included in the meta-analyses were small, retrospective, and used various ratios of MRS spectra. The largest prospective study found that combining MRS with MRI resulted in a greater percentage of correct diagnoses of pediatric brain tumor type. This report offered limited information on the specific MRS spectra associated with the different tumor types. Prospective studies are needed to define

better the spectra associated with tumor characteristics, to evaluate the diagnostic accuracy, and to determine the effect on health outcomes.

Breast Cancer

Clinical Context and Test Purpose

The purpose of MRS in patients with breast cancer is to improve the specificity of breast imaging, which has a high false-positive rate.

The question addressed in this evidence review is: Does the use of MRS improve the net health outcome of patients with breast cancer?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is patients being evaluated for breast cancer.

Interventions

The intervention of interest is MRS.

Comparators

The following practice is currently being used to make decisions about managing breast tumors: standard evaluation with MRI.

Outcomes

The outcomes of interest are sensitivity and specificity and the effect on health outcomes.

Timing

The time of interest is at biopsy, surgical resection, or clinical follow-up.

Setting

MRS would be administered in an outpatient setting.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Baltzer et al (2013) conducted a systematic review and meta-analysis of 19 studies on MRS for detecting benign vs malignant breast lesions.¹⁸ The total number of patients in the studies reviewed was 1183 and included 452 benign and 773 malignant lesions. In the pooled estimates, the sensitivity of MRS was 73% (556/761; 95% confidence interval [CI], 64% to 82%) and the specificity was 88% (386/439; 95% CI, 85% to 91%). The area under the receiver operating characteristic curve for MRS detecting breast cancers vs benign lesions was 0.88. There was significant heterogeneity between studies and evidence of publication bias.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs were identified that support the clinical utility of MRS for this indication.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of MRS has not been established for this indication, a chain of evidence cannot be constructed.

Section Summary: Breast Cancer

The evidence on MRS to determine whether breast lesions are benign or malignant includes a systematic review. Pooled estimates of sensitivity and specificity were 73% and 88%, respectively. There was evidence of publication bias, limiting interpretation of findings.

Prostate Cancer**Clinical Context and Test Purpose**

The purpose of MRS in patients with prostate cancer is to improve the evaluation of prostate cancer. There are several potential applications of MRS for prostate cancer, including diagnosis, recurrence assessment, and localization for biopsy and treatment planning.

The question addressed in this evidence review is: Does the use of MRS improve the net health outcome of patients with prostate cancer?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is patients being evaluated for prostate cancer.

Interventions

The intervention of interest is MRS.

Comparators

The following practice is currently being used to make decisions about managing prostate cancer: standard evaluation with MRI.

Outcomes

The outcomes of interest are sensitivity and specificity and the effect on health outcomes.

Timing

The time of interest is the initial evaluation, prior to biopsy, and following treatment for prostate cancer.

Setting

MRS would be administered in an outpatient setting.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews

In a health technology assessment, Mowatt et al (2013) systematically reviewed 51 studies to evaluate image-guided prostate biopsy with MRS and other enhanced MRI techniques (ie, dynamic contrast-enhanced MRI, diffusion-weighted MRI) compared with T2-MRI and transrectal ultrasound.¹⁹ In these studies, the patients had a suspicion of prostate cancer due to elevated prostate-specific antigen levels, despite a previous negative biopsy. MRS had the highest sensitivity in the meta-analysis of individual tests (92%; 95% CI, 86% to 95%), with an estimated specificity of 76% (95% CI, 61% to 87%). The transrectal ultrasound-guided biopsy had the highest specificity (81%; 95% CI, 77% to 85%).

Randomized Controlled Trials

A single-institution RCT published by Sciarra et al (2010) compared a second randomly selected biopsy (group A) with a biopsy selected partly based on MRS and DCE-MRI results (group B).²⁰ The participants were selected from 215 consecutive men with an elevated prostate-specific antigen level (between 4 ng/mL and 10 ng/mL), an initial negative biopsy result, and a negative digital rectal examination; 180 patients participated in the study. Cancer was detected in 24.4% of group A patients and 45.5% of group B participants. Fifty patients from group A with 2 negative biopsy results agreed to undergo biopsy a third time using MRS and DCE-MRI results; 26 more cancers were found. Overall, 61.6% of the cancers detected had Gleason scores of 7 (4+3) or more. The cancers detected after using MRS and DCE-MRI also aligned with the suspicious areas detected on imaging. The sensitivity and specificity of MRS were 92.3% and 88.2%, respectively; adding DCE-MRI increased the sensitivity to 92.6%, and the specificity to 88.8%. Trial limitations included its single-center design, analysis confined to the peripheral zone of the prostate gland, and greater sample volume from group B patients (12.17 cores) than from group A patients (10 cores). Furthermore, given the concerns about potential overtreatment among patients with early-stage prostate cancer, the benefits of detecting these additional cancers must be evaluated by examining clinical outcomes for these patients.

In a similar report from the same institution and author group, 150 patients with a negative prostate biopsy, despite prostate-specific antigen elevations, were randomized to MRS or MRS plus DCE-MRI to locate prostate cancer foci for a second targeted biopsy²¹ (see also Panebianco et al [2012]²²). The addition of DCE-MRI to MRS yielded increased sensitivity over MRS alone (93.7% and 90.7% vs 82.8% and 91.8%, respectively).

Prospective Studies

Lahoti et al (2017), in a study from India, prospectively evaluated the diagnostic accuracy of ultrasonography, MRI, and a combination of MRI plus MRS in 66 patients with a strong clinical

suspicion of prostate pathologies.²³ All patients underwent ultrasonography, MRI, and MRS, followed by a biopsy. Diagnostic accuracy of the 3 tests is shown in Table 1. Of 41 patients with malignant lesions, MRI identified 39 as malignant and MRI plus MRS identified 40 as malignant. Of 25 patients with benign lesions, MRI identified 21 as benign and MRI plus MRS identified 23 as benign.

Table 1. Clinical Validity of Technologies to Identify Malignant Prostate Lesions

Test	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Ultrasonography	78.0	88.0	91.4	71.0
MRI	95.1	84.0	90.7	91.3
MRI plus MRS	97.6	92.0	95.2	95.8

Adapted from Lahoti et al (2017).²³

MRI: magnetic resonance imaging; MRS: magnetic resonance spectroscopy; NPV: negative predictive value; PPV: positive predictive value.

Pedrona et al (2013) also reported on the combined use of MRS and DCE-MRI for assessing prostate cancer in 106 patients in a prospective cohort study.²⁴ The authors reported that combined MRS and DCE-MRI results yielded unacceptably low PPV of 19%. The NPV was 91%. Sensitivity was 71%, and specificity was 48%. The authors indicated the combined MRS and DCE-MRI may be useful for avoiding biopsy because the NPV was 91%; however, further study is needed.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs were identified that support the clinical utility of MRS for this indication.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of MRS has not been established for this indication, a chain of evidence cannot be constructed.

Section Summary: Prostate Cancer

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

Noncancer Indications

Clinical Context and Test Purpose

The purpose of MRS in patients with noncancer indications is to improve the diagnosis and management of a variety of conditions.

The question addressed in this evidence review is: Does the use of MRS improve the net health outcome of patients with noncancer indications?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant populations of interest are patients being evaluated for dementia, liver disease, multiple sclerosis, or other noncancer indications.

Interventions

The intervention of interest is MRS.

Comparators

The following practice is currently being used to make decisions about managing various condition: observation for patients with dementia or multiple sclerosis and liver biopsy for patients with liver disease.

Outcomes

The outcomes of interest are sensitivity and specificity and the effect on health outcomes.

Timing

The time of interest is in the initial evaluation.

Setting

MRS would be administered in an outpatient setting.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Dementia

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Research continues on the use of MRS to identify dementia, especially in its early stages. In a review, Zhang et al (2014) identified 30 studies since 2007 on low-field (<1.5 tesla) MRS and 27 studies on high-field (>3.0 tesla) MRS that compared results from patients with Alzheimer disease, mild cognitive impairment (MCI), and healthy controls.²⁵ While metabolite changes are heterogeneous across brain regions, most studies focused on detecting changes in individual metabolites or their ratios. Reviewers concluded that to characterize Alzheimer disease—associated with neurochemical changes effectively, future approaches should interactively analyze multiple quantifiable metabolites from different brain regions.

Tumati et al (2013) conducted a systematic review and meta-analysis of 29 studies on MRS for MCI.²⁶ Included in the analysis were 607 MCI patients and 862 healthy controls. Patterns in metabolite concentration, including NAA, Cr, Cho, and myo-inositolin, were identified in various regions of the brain; they were associated with MCI. For example, levels of Cr were found to be significantly lower in the hippocampus and paratrigrinal white matter. NAA was found to be most

associated with MCI, but other markers including myo-inositolin, Cho, and Cr may also contribute to MCI.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs were identified that support the clinical utility of MRS for this indication.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of MRS has not been established for this indication, a chain of evidence cannot be constructed.

Section Summary: Dementia

Although a number of studies have examined the use of MRS for identifying and monitoring cognitive impairment and dementia, the cumulative evidence does not support any role for MRS outside of the research setting. There are no clear criteria for diagnosing cognitive impairment or dementia with MRS, and there are insufficient data on diagnostic comparators. Additionally, the impact of MRS on clinical management and health outcomes is unknown.

Liver Disease

MRS has been evaluated as a noninvasive alternative to liver biopsy in the diagnosis of hepatic steatosis. It has been compared with other noninvasive imaging procedures such as computed tomography, dual-gradient echo MRI (DGE-MRI), and ultrasonography; liver biopsy was the reference standard, and a 3-tesla MRI machine was used.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

In a prospective study of 161 consecutive potential living liver donors, DGE-MRI was reported to be the most accurate test for diagnosing hepatic steatosis. While DGE-MRI and MRS were similar for hepatic steatosis 5% or greater, DGE-MRI outperformed MRS for hepatic steatosis 30% or greater (especially regarding specificity) and on quantitative estimates²⁷ (see also Taouli et al [2009]²⁸). In a systematic review of imaging liver fat in children, Awai et al (2014) reviewed 5 MRI studies and found varying methodologies for measuring liver fat by MRI or MRS.²⁹

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs were identified that support the clinical utility of MRS for this indication.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of MRS has not been established for this indication, a chain of evidence cannot be constructed.

Section Summary: Liver Disease

The available evidence does not support the utility of MRS or MRI for assessment of hepatic steatosis in children.

Multiple Sclerosis

Multiple sclerosis is a chronic disease with a variable prognosis and clinical course. Predictors of future disease course might help select patients who would benefit most from disease-modify treatments.³⁰

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Llufriu et al (2014) published a study assessing the use of MRS in a preliminary data set of 59 patients with multiple sclerosis and 43 healthy controls, and in a confirmatory independent data set of 220 patients.³¹ Change in brain volume and measures of disability were obtained annually. The myo-inositol: NAA ratio in the normal-appearing white matter was found to be a predictor of brain volume change over 4 years ($p=0.02$) and of clinical disability (eg, a decrease in the Multiple Sclerosis Functional Composite evolution scale of -0.23 points annually, $p=0.01$). Effect sizes in this study were low, indicating that the measure is not sufficiently reliable to predict the future disease course in individual patients.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs were identified that support the clinical utility of MRS for this indication.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of MRS has not been established for this indication, a chain of evidence cannot be constructed.

Section Summary: Multiple Sclerosis

Future research is needed that includes larger cohorts with progressive multiple sclerosis, serial measurements of outcomes, and complementary measures of disease activity.³⁰

Other Indications

MRS has also been evaluated for other uses, such as tracking disease changes among patients with systemic lupus erythematosus,³² assessing carotid plaque morphology,³³ identifying biomarkers of traumatic brain injury,^{34,35} and predicting long-term neurodevelopmental outcome after neonatal encephalopathy.³⁶⁻³⁸ MRS has also been used to evaluate pediatric patients with seizures,³⁹ and other applications in children.⁴⁰ Additional evidence on these applications is needed. MRS has also been studied in a variety of psychiatric disorders in the research setting, but no studies on the clinical use of MRS for the treatment of psychiatric disorders were found.^{41,42}

Summary of Evidence

For individuals who have brain tumors who receive MRS, the evidence includes a number of small studies and systematic reviews. Relevant outcomes are test accuracy, change in disease status, morbid events, and functional outcomes. Small studies have evaluated detection, characterization, grading, prognosis, and differentiation of tumor recurrence vs necrosis. Most studies included in the meta-analyses were small, retrospective, and used various ratios of MRS spectra. The largest prospective studies found that combining MRS with MRI resulted in a greater percentage of correct diagnoses of pediatric brain tumor type. These reports had limited information on the specific MRS spectra associated with the different tumor types. Additional study is needed to define better the spectra associated with tumor characteristics, to evaluate the diagnostic accuracy, and to determine the effect on health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have breast cancer, prostate cancer, dementia, liver disease, or multiple sclerosis who receive MRS, the evidence includes prospective studies on diagnostic accuracy and systematic reviews. Relevant outcomes are test accuracy, change in disease status, morbid events, and functional outcomes. A number of studies have examined the use of MRS for localizing prostate cancer for biopsy, for diagnosis, and for the monitoring of patients with prostate cancer. However, the cumulative evidence remains uncertain. Data comparing the diagnostic accuracy of MRS with alternative imaging strategies is limited. A systematic review of MRS to identify dementia concluded that to characterize Alzheimer disease–associated neurochemical changes effectively, future approaches need to analyze interactively multiple quantifiable metabolites from different brain regions. A study of MRS as a noninvasive alternative to liver biopsy indicated that dual-gradient echo MRI outperforms MRS. Data on use of MRS in multiple sclerosis has indicated that the measure is not sufficiently reliable to predict the future disease course. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 3 physician specialty societies and 1 academic medical center while this policy was under review in 2008. Input received disagreed with the conclusions in the policy statement. In particular, information provided supported use of magnetic resonance spectroscopy in differentiating radiation necrosis from recurrent tumor and in the differential diagnosis of certain central nervous system tumors from nontumors.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

The National Comprehensive Cancer Network's (NCCN) clinical guidelines on central nervous system cancers (v.1.2018) identifies magnetic resonance spectroscopy (MRS), as a modality that can be considered to rule out radiation necrosis, as compared with a recurrence of brain tumors.⁴³ The guidelines also state that MRS may be helpful in grading tumors or assessing response and that the most abnormal area on MRS would be the best target for biopsy. The limitations include tumors near vessels, air spaces, or bone, and the extra time required in a magnetic resonance imaging machine.

NCCN clinical guidelines on prostate cancer (v.4.2018) list MRS as an advanced imaging technique but make no recommendations for its use.⁴⁴

NCCN clinical guidelines on breast cancer (v.1.2018) do not mention MRS.⁴⁵

American Association of Neurological Surgeons et al

The American Association of Neurological Surgeons and Congress of Neurological Surgeons (2015) gave a level III recommendation (level C) for the addition of MRS to anatomic imaging for the management of diffuse low-grade glioma, because the diagnostic accuracy is not well-defined and the role in clinical practice is still being defined.⁴⁶

Congress of Neurological Surgeons

The Congress of Neurological Surgeons (2016) published an evidence-based guideline on preoperative imaging assessment of patients with suspected nonfunctioning pituitary adenomas.⁴⁷ The Congress found that although the results were promising, there was insufficient evidence to recommend the use of MRS formally.

American College of Radiology et al

The American College of Radiology, American Society of Neuroradiology, and Society for Pediatric Radiology (2013) updated their joint practice parameters on MRS of the central nervous system.⁴⁸ Most of the update addressed the actual performance of MRS, but it also listed 22 possible indications for MRS when magnetic resonance imaging or computed tomography is inadequate for answering specific clinical questions.

American College of Radiology appropriateness criteria for prostate cancer, last reviewed in 2016, stated that MRS cannot yet be considered to provide significant advantages in local staging before treatment.⁴⁹

American College of Radiology appropriateness criteria for imaging of dementia and movement disorders (updated in 2015) considered MRS to be usually inappropriate.⁵⁰

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT00067821	A Comparative Study of Pediatric CNS Tumor Activity as Assessed by [18]F-FDG PET Imaging and Proton Magnetic Resonance Spectroscopic Imaging([1]H-MRSI)	150	NR
NCT02731521	Clinical Development of MR Spectroscopy and Imaging in Brain Cancers	175	Dec 2019

NCT: national clinical trial; NR: not reported.

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

DIAGNOSES

Experimental / Investigational for all diagnoses related to this medical policy.

REVISIONS

06-16-2009	Added policy to bcbsks.com web site.
02-24-2012	Description updated.
	Rationale updated.
	References updated.
03-26-2013	Updated Description section.
	Updated Rationale section.
	Updated Reference section.
09-17-2014	Updated Rationale section.
	Updated Reference section.
06-23-2015	Updated Description section.
	Updated Rationale section.
	Updated references.
04-25-2016	Description section updated
	Rational section updated
	References updated
12-19-2018	Description section updated
	Rational section updated
	References updated

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