6.01.24	Magnetic Resonance Spectroscopy		
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Section:	6.0 Radiology	**Page:**	Page 1 of 29

Policy Statement

I. Magnetic resonance spectroscopy (MRS) is considered **investigational**.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Coding

See the Codes table for details.

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.

Related Policies

- Selected Positron Emission Tomography Technologies for Evaluation of Alzheimer Disease

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. 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.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

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

Rationale

Background

Magnetic resonance spectroscopy (MRS) is a noninvasive technique that can be used to measure the concentrations of 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 the emitted radiofrequency in MRI 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, 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 cm^3. 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, 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 (i.e., hydrogen 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. They include those:

- 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. NAA intensity is thought to be a marker of neuronal integrity and is the most important proton signal in studying central nervous system pathology. Decreases in the NAA signal are associated with neuronal loss, damage to neuronal structures, and/or reduced neural metabolism.
- Arising from choline-containing compounds (Cho), such as membrane phospholipids (e.g., phosphocholine, 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.
- 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 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.
- 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 these spectra and others (e.g., myo-inositol, glutamate/glutamine) in the healthy and diseased brain are the basis of clinical applications of MRS. MRS findings characteristically associated with non-necrotic brain tumors include elevated Cho levels and reduced NAA levels. The International Network for Pattern Recognition using Magnetic Resonance has developed a user-friendly computer program for spectral classification and a database of over 300 tumor spectra with histologically validated diagnoses to aid radiologists in MRS diagnosis.[1,2,]

One limitation of MRS is that it provides the metabolic composition of a given voxel, which may include more than 1 type of tissue. For some applications, the voxels are relatively large (e.g., >1 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.[3,] 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, e.g., close to the brain surface or in children with smaller brains because of the lipid signal from the skull. Some techniques are used

to deal with these issues; various MRS techniques continue to be explored as well. A combination of MRS is often used with other MRI techniques (e.g., diffusion-tensor imaging, susceptibility-weighted imaging) and other types of imaging such as positron emission tomography.

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.

All findings reported in this evidence review refer to proton MRS unless otherwise indicated.
Use of positron emission tomography (PET) in Alzheimer disease is addressed separately in Blue Shield of California Medical Policy: Selected Positron Emission Tomography Technologies for Evaluation of Alzheimer Disease.

Literature Review

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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Brain Tumors

Clinical Context and Test Purpose

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

The following PICO was used to select literature to inform this review.

Populations

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

Study Selection Criteria

For the evaluation of the clinical validity of the tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores);
- Included a suitable reference standard;
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described;
- Included a validation cohort separate from development cohort.

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).

Review of Evidence

Detection or Grading of Brain Tumors

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.[4,] 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.

Complementary Magnetic Resonance Spectroscopy

Hellstrom et al (2018) evaluated whether MRS adds to the diagnostic value of MRI in differentiating low-grade tumors, high-grade tumors, and non-neoplastic lesions through the retrospective analysis of data on 208 lesions from 186 individuals.[5,] Data are summarized in Table 1. No statistically significant difference was found between MRI and MRI + MRS (p=.055). Furthermore, additional data from MRS was found to be very beneficial, beneficial, inconsequential, or misleading in 3%, 12%, 68%, and 17% of cases, respectively. Therefore, in most cases, complementary MRS was not shown to add to the diagnostic value of MRI.

Table 1. Clinical Validity Results for MRI vs MRI+MRS

Confirmed Diagnosis	Actual Prevalence, N (%)	Diagnostic Accuracy	Modality	
			MRI, N (%)	*MRI+MRS, N (%)*
Any Diagnosis	Total, 208 (100%)	Correct	130 (62%)	134 (64%)
	Neoplastic, 138 (66%)	Indeterminate	39 (19%)	23 (11%)
	Non-neoplastic, 70 (33%)	Incorrect	39 (19%)	51 (25%)
		Total	208 (100%)	208 (100%)
High-grade Tumor	Total, 95 (46%)	Correct	40 (45%)	46 (52%)
		Indeterminate	23 (26%)	6 (7%)
		Incorrect	26 (29%)	37 (41%)
		Total	89 (100%)	89 (100%)
Low-grade Tumor	Total, 43 (21%)	Correct	30 (70%)	30 (70%)
		Indeterminate	5 (12%)	7 (16%)
		Incorrect	8 (18%)	6 (14%)
		Total	43 (100%)	43 (100%)
Diagnostic Agreement		Radiological Diagnostic Accuracy	MRI and MRI+MRS, N	
Matching Radiological Diagnosis		Correct	109	
		Indeterminate	12	
		Incorrect	30	

MRI: magnetic resonance imaging; MRS: magnetic resonance spectroscopy.
Data adapted from Hellstrom et al (2018).[5,]

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 (2019) prospectively evaluated children with brain lesions aged 16 years and under (N=51) between December 2015 and 2017 via MRI and single-voxel MRS, blinded to histopathology.[6,] MRS spectra were obtained in 47/51 eligible children, however, only 72% of tumors were considered analyzable via MRS. Proportions of correct diagnoses and interrater agreement at each stage were assessed. The diagnostic accuracy of the principal MRI diagnosis was 69%, improving to 77% with MRS. Together, MRI and MRS resulted in a significant increase in additionally correct diagnoses compared to MRI alone (p=.035) and a significant increase in interrater agreement (p=.046). Children were managed without conclusive histopathology in 25% of cases.

Manias et al (2018) reported on a multicenter U.K. study that retrospectively evaluated MRS for the noninvasive diagnosis of brain tumors.[7,] 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 the 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. A subsequent study by Manias et al (2018) assessed the diagnostic accuracy of MRS alone in diagnosing children (N=26) with pilocytic astrocytoma, ependydoma, and medulloblastoma, reporting modest correct classification rates of 60%, 50%, and 80%, respectively.[8,]

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 U.S.[9,] MRI and MRS were performed in 120 children as part of the usual presurgical workup, followed by biopsy or resection. For the first 60 children (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 children 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<.05). For the second group of 60 children who were diagnosed using MRI plus MRS, tumor type was correctly identified in 87% of patients (p<.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 children 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<.05).

Diagnosis of Isocitrate Dehydrogenase Mutant Glioma

A systematic review and meta-analysis of 460 individuals with stage II-IV glioma by Suh et al (2018) was conducted to assess 2-hydroxyglutarate (2HG) MRS as a noninvasive and accurate diagnostic alternative to confirmation via biopsy with immunohistochemistry and/or genomic sequencing analysis.[12,] According to the World Health Organization, isocitrate dehydrogenase (IDH) mutation status (*IDH1*/*IDH2*) is one of the most valuable prognostic biomarkers for appropriate clinical

management of gliomas. The pooled sensitivity and specificity was 95% (95% confidence interval [CI], 85 to 98%) and 91% (95% CI, 83 to 96%), respectively.

Andronesi et al (2018) reported on an open-label phase I clinical trial investigating the utility of 2HG MRS to assess the pharmacodynamics of an investigational mutant *IDH1* inhibitor drug (IDH305, Novartis Pharmaceuticals).[13,] Eight individuals were enrolled, and data from 5 patients were available for tumor 2HG level analysis at baseline and following 1 week of treatment with IDH305. Tumor 2HG levels were found to decrease during mutant *IDH1* inhibition, with statistically significant decreases in the ratios of 2HG to healthy creatinine (2HG/hCr), tumor creatinine (2HG/tCr), and glutamine plus glutamate (2HG/Glx). However, further study is required to validate whether these results can identify treatment response as clinical outcomes were not reported in the present study. Furthermore, the authors acknowledge that recent preclinical data have failed to show an effect on tumor growth with mutant *IDH1* inhibitors. Importantly, individuals with mutant *IDH1* have significantly longer survival compared to individuals with wild-type *IDH1*, therefore the value of mutant *IDH1* treatment and response monitoring is currently unclear.

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 (N=455).[14,] 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)/creatine (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).[15,] This study compared MRS with single-photon emission computed tomography (SPECT) in the identification of residual or recurrent glioma versus radiation necrosis in 24 patients treated with surgery and radiotherapy. MRS and SPECT results differed in 9 cases of recurrence and were more accurate with SPECT. The specificity and positive predictive value were 100% in both MRS and SPECT; however, the sensitivity was 61.1% versus 88.8%, and negative predictive value was 46.2% versus 75%, respectively. The use of a single-voxel rather than multiple voxels 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 (N=228) evaluating the diagnostic performance of MRS in differentiating high- from low-grade gliomas.[16,] 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. A recent study by Lin et al (2018) only noted a significant difference for the Cho/NAA ratio, with a sensitivity and specificity of 61.54% and 86.36%, respectively.[17,]

A systematic review conducted by Bhandari et al (2021) evaluated the diagnostic accuracy of 2HG MRS for determination of IDH status in differentiating low-grade glioma (WHO grade II or III) from glioblastoma (WHO grade IV).[18,] Although the systematic review conducted by Suh et al (2018)[12,] described above found 2HG MRS for prediction of gliomas with IDH mutations associated with high sensitivity and specificity, results were not stratified according to glioma grade. IDH mutations are found in about 80% of low-grade gliomas, but only about 5% of glioblastomas.

The Bhandari review included 9 studies of individuals with low-grade glioma (n=181) or glioblastoma (n=77) undergoing preoperative 2HG MRS using histopathological diagnosis as a reference standard. Pooled sensitivity and specificity was 93% (95% CI 58% to 99%; I^2=82%) and 84% (95% CI 51% to 96%; I^2=60%) for low-grade glioma; for glioblastoma, sensitivity was 84% (95% CI 25% to 99%; I^2=0%) and specificity was 97% (95% CI 43% to 100%; I^2=23%). There was no statistical difference between tumor type senstivities (p=.58) or specificities (p=.06). Positive and negative predictive values were 87% and 73% for low-grade glioma and 50% and 97% for glioblastoma. Study quality was assessed using the QUADAS-2 tool and studies were generally judged to be of low risk of bias and applicability concerns, although 2 studies were found to have high risk of patient selection bias. The included studies also used different MRS techniques and cut-off values, potentially affecting pooled measures of diagnostic accuracy.

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.[19,] 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.[20,21,]

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, more effective therapy, or avoid unnecessary therapy or 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.[7,] The prospective study by Manias et al (2019; discussed above) reported that 25% of patients were managed without a conclusive histopathological diagnosis.[6,]

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 non-randomized studies have assessed detection, characterization, grading, prognosis, and differentiation of tumor recurrence versus 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 better define 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 individuals with breast cancer is to improve the specificity of breast imaging, which has a high false-positive rate.

The following PICO was used to select literature to inform this review.

Populations

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

Study Selection Criteria

For the evaluation of the clinical validity of the tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores);
- Included a suitable reference standard;
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described;
- Included a validation cohort separate from development cohort.

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).

Review of Evidence

Diagnosis of Breast Cancer

Billy et al (2023) conducted a systematic review and meta-analysis on the diagnostic accuracy of diffusion weighted imaging (DWI) compared to MRS in differentiating between benign and malignant breast lesions.[22,] Eight studies with 632 individuals and 687 breast lesions were included. The sensitivity and specificity of DWI (8 studies, 627 breast lesions) were 92% (95% CI: 85% to 96 %) and 88% (95% CI: 75% to 94%), respectively. The sensitivity and specificity of MRS (8 studies, 685 breast lesions) were 85% (95% CI: 66% to 94 %) and 85% (95% CI: 77% to 91%), respectively. No significant difference was noted in the sensitivity or specificity between DWI and MRS. The authors noted there was a risk of bias due to insufficient methodological reporting and substantial heterogeneity.

Baltzer et al (2013) conducted a systematic review and meta-analysis of 19 studies on MRS for detecting benign versus malignant breast lesions.[23,] The studies included 1,183 individuals with 452 benign and 773 malignant lesions. In the pooled estimates, the sensitivity of MRS was 73% (556/761; 95% 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 versus benign lesions was 0.88. There was significant heterogeneity between studies and evidence of publication bias.

Treatment Response

Bayoumi et al (2019) conducted a prospective study evaluating the additive role of MRS and MRI in the confirmation of pathological complete response after neoadjuvant chemotherapy of breast cancer in 47 patients.[24,] Individuals were evaluated via MRI and MRS at baseline and following treatment with 4 cycles of anthracycline-based chemotherapy administered at 3 week intervals. Pathological response to neoadjuvant chemotherapy was confirmed via histopathological evaluation following surgical excision. A Cho peak at 3.2 ppm was considered positive. The mean tumor size before and after treatment was 4.21 ± 0.99 cm and 0.9 ± 0.44 cm, respectively, with corresponding mean Cho signal-to-noise ratios of 9.53 ± 1.7 ppm and 2.53 ± 1.3 ppm. MRI detected a complete response in 22/47 patients, corresponding to a sensitivity of 83.3%, specificity of 65.7%, positive predictive value (PPV) of 45.5%, negative predictive value (NPV) of 92%, and a diagnostic accuracy of 70.2%. In contrast, combined MRI and MRS demonstrated a sensitivity of 75%, specificity of 97.1%, PPV of 75%, NPV of 91.9%, and an improved diagnostic accuracy of 91.5%. The cut-off for differentiating between complete response and residual disease was 1.95 ppm with a corresponding diagnostic accuracy of 85.11%. Patient characteristics and eligibility criteria were not specified.

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, more effective therapy, or avoid unnecessary therapy or 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 individuals 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 following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals 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.

Study Selection Criteria
For the evaluation of the clinical validity of the tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores);
- Included a suitable reference standard;
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described;
- Included a validation cohort separate from development cohort.

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).

Review of Evidence
Systematic Reviews
A meta-analysis by Cai et al (2019) reviewed 19 studies utilizing MRS imaging for the diagnosis of prostate cancer.[25,] 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 (i.e., dynamic contrast-enhanced MRI, diffusion-weighted MRI) compared with T2-MRI and transrectal ultrasound.[26,] In these studies, the patients had a suspicion of prostate cancer due to elevated prostate-specific antigen levels, despite a previous negative biopsy. Characteristics and results of these reviews are summarized in Tables 2 and 3.

Table 2. SR & M-A Characteristics for Prostate Cancer

Study	Dates	Trials	Participants[1]	N (Range)	Design	Duration
Cai et al (2019)[25,]	2004-2017	19	Studies applying MRS for the diagnosis of PC. Individuals with clinical suspicion of PC and diagnosis confirmed with pathology. Studies with diagnostic accuracy data.	1406 (20 to 346)	Prospective cohort Retrospective cohort Cross-sectional	NR
Mowatt et al (2013)[26,]	NR	51	Individuals with suspected PC and elevated PSA but previously negative biopsy. Studies utilizing MRS, standard MRI, and other imaging modalities for PC diagnosis.	>10000 (NR)	NR	NR

M-A: meta-analysis; MRI: magnetic resonance imaging; MRS: magnetic resonance spectroscopy; NR: not reported; PC: prostate cancer; PSA: prostate-specific antigen; SR: systematic review.
[1] Key eligibility criteria.

Table 3. SR & M-A Results for Prostate Cancer

Study; Subgroup	Sensitivity	Specificity	PPV	NPV
Cai et al (2019)[25,]				
MRS				
Total N	NR	NR	777	581
Pooled effect (95% CI)	84% (75 to 91%)	79% (69 to 87%)	64% (NR)	88% (NR)
I^2 (95% CI)	85.77% (80.33 to 91.21%)	88.35% (84.15 to 92.56%)	NR	NR
Range of effect sizes	14 to 100%	29 to 100%	NR	NR
Mowatt et al (2013)[26,]				
MRS				
Total N	438	438	220	218
Pooled effect (95% CI)	92% (86 to 95%)	76% (61 to 87%)	66% (NR)	94% (NR)
I^2 (95% CI)	NR	NR	NR	NR
Range of effect sizes	71 to 100%	44 to 96%	NR	NR
Standard MRI				
Total N	620	620	356	264
Pooled effect (95% CI)	86% (74 to 93%)	55% (44 to 66%)	47% (NR)	85% (NR)
I^2 (95% CI)	NR	NR	NR	NR
Range of effect sizes	48 to 100%	17 to 86%	NR	NR

CI: confidence interval; M-A: meta-analysis; MRI: magnetic resonance imaging; MRS: magnetic resonance spectroscopy; NPV: negative predictive value; NR: not reported; PPV: positive predictive value; SR: systematic review.

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).[27,] Study inclusion criteria required 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 and 45.5% of group B. Fifty individuals 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. Given the concerns about potential overtreatment among individuals with early-stage prostate cancer, the benefits of detecting these additional cancers must be evaluated by examining clinical outcomes. In a similar report from the same institution and author group, 150 individuals 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 biopsy[28,] (see also Panebianco et al [2012][29,]). Characteristics, results, and limitations of these studies are summarized in Tables 4 to 7.

Table 4. Summary of Key Prostate Cancer Trial Characteristics

Study; Trial	Study Design	Countries	Sites	Dates	Participants[2]	Interventions[1]	
						Active	*Comparator*
Sciarra et al (2010)[27,]	RCT	EU	1	2007-NR	Individuals with initial negative prostate biopsy, elevated PSA, and negative initial transrectal ultrasound-guided biopsy.	MRS + DCE-MRI Targeted Biopsy: 90	Random Biopsy: 90

Study; Trial	Study Design	Countries	Sites	Dates	Participants[2]	Interventions[1]	
						Active	*Comparator*
Panebianco et al (2010)[28,]	Prospective	EU	1	2007-NR	Individuals with persistently high PSA levels and with a negative finding on initial transrectal ultrasound-guided biopsy.	MRS+DCE-MRI Targeted Biopsy: 150	Random Biopsy: 150

DCE-MRI: dynamic contrast-enhanced magnetic resonance imaging; MRS: magnetic resonance spectroscopy; NR: not reported; PSA; prostate-specific antigen; RCT: randomized controlled trial.
[1] Number randomized; intervention; mode of delivery; dose (frequency/duration).
[2] Key eligibility criteria

Table 5. Summary of Key Prostate Cancer Trial Results

Study; Subgroup	Sensitivity (95% CI)	Specificity (95% CI)
Sciarra et al (2010)[27,]		
MRS	92.3% (NR)	88.2%
MRS+DCE-MRI	92.6%	88.8%
Panebianco et al (2010)[28,]		
MRS	82.8% (NR)	91.8% (NR)
MRS+DCE-MRI	93.7% (NR)	90.7% (NR)

CI: confidence interval; DCE-MRI: dynamic contrast-enhanced magnetic resonance imaging; MRS: magnetic resonance spectroscopy; NR: not reported.

Table 6. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Sciarra et al (2010)[27,]			1-2. Not clearly defined; not standard or optimal (vs DRE).	1. Key health outcomes not addressed.	1-2. Not sufficient duration for benefit or harms.
Panebianco et al (2010)[28,]			1-2. Not clearly defined; not standard or optimal (vs DRE).	1. Key health outcomes not addressed.	1-2. Not sufficient duration for benefit or harms.

DRE: digital rectal examination.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 7. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Sciarra et al (2010)[27,]	3. Allocation concealment unclear.	1-2. Blinding unclear.	1. Not registered.	6. No intent to treat analysis.	1. Power calculations not reported.	3. Confidence intervals and/or p values not reported.
Panebianco et al (2010)[28,]	3. Allocation concealment unclear.	1-2. Blinding unclear.	1. Not registered.	6. No intent to treat analysis.	1. Power calculations not reported.	3. Confidence intervals and/or p values not reported.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. No intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

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, more effective therapy, or avoid unnecessary therapy or 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 individuals with prostate cancer, the cumulative evidence remains uncertain. Data comparing the diagnostic accuracy of MRS with alternative imaging strategies are limited. Additionally, the impact of MRS imaging compared with other imaging strategies on clinical management and health outcomes is unknown.

Dementia

Clinical Context and Test Purpose

The purpose of MRS in individuals with dementia is to improve the diagnosis and management of dementia.

The following PICO was used to select literature to inform this review.

Populations

The relevant populations of interest is individuals being evaluated for dementia.

Interventions

The intervention of interest is MRS. Use of positron emission tomography (PET) in Alzheimer disease is addressed separately in Blue Shield of California Medical Policy: Selected Positron Emission Tomography Technologies for Evaluation of Alzheimer Disease.

Comparators
The following practice is currently being used to make decisions about managing dementia: observation.

Outcomes
The outcomes of interest are sensitivity and specificity and the effect on health outcomes. The time of interest is at the initial evaluation or at clinical follow-up.

Study Selection Criteria
For the evaluation of the clinical validity of the tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores);
- Included a suitable reference standard;
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described;
- Included a validation cohort separate from development cohort.

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).

Review of Evidence
Systematic Reviews
Piersson et al (2020) conducted a systematic review of 24 studies to clarify the relationship between neurochemical changes and MRS metabolite levels against validated Alzheimer's disease (AD) biomarkers.[30,] Decreased levels of N-aspartylacetate (NAA), NAA/creatine (NAA/Cr), and NAA/myo-inositol (NAA/mI), and increased mI, mI/Cr, choline/Cr (Cho/Cr), and mI/NAA were detected in the posterior cingulate cortex and precuneus. Increased NAA/mI and decreased NAA/Cr was associated with increased tau levels. NAA and glutathione levels are reduced in apolipoprotein E (APOE) ε4 carriers. The authors concluded that large, longitudinal studies are necessary to elucidate the effect of APOE ε4 on brain metabolites.

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 individuals with AD, mild cognitive impairment (MCI), and healthy controls.[31,] 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 AD-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.[32,] 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 paratrigonal 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, more effective therapy, or avoid unnecessary therapy or 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
Clinical Context and Test Purpose
The purpose of MRS in individuals with liver disease is to improve the diagnosis and management of liver disease.

The following PICO was used to select literature to inform this review.

Populations
The relevant populations of interest is individuals being evaluated for liver disease.

Interventions
The intervention of interest is MRS.

Comparators
The following practice is currently being used to make decisions about managing liver disease: liver biopsy.

Outcomes
The outcomes of interest are sensitivity and specificity and the effect on health outcomes. The time of interest is at the initial evaluation or at clinical follow-up.

Study Selection Criteria
For the evaluation of the clinical validity of the tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores);
- Included a suitable reference standard;
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described;
- Included a validation cohort separate from development cohort.

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).

Review of Evidence
Diagnostic Accuracy Studies
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 with liver biopsy as the reference standard. 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, with a sensitivity and specificity of 90.9% and 94%, respectively[33,] (see also Taouli et al [2009][34,]).

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, more effective therapy, or avoid unnecessary therapy or 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 for assessment of hepatic steatosis.

Multiple Sclerosis
Clinical Context and Test Purpose
The purpose of MRS in individuals with multiple sclerosis (MS) is to improve the diagnosis and management of MS.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals being evaluated for MS.

Interventions
The intervention of interest is MRS.

Comparators
The following practice is currently being used to make decisions about managing MS: observation.

Outcomes
The outcomes of interest are sensitivity and specificity and the effect on health outcomes. The time of interest is at the initial evaluation or at clinical follow-up.

Study Selection Criteria
For the evaluation of the clinical validity of the tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores);
- Included a suitable reference standard;
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described;
- Included a validation cohort separate from development cohort.

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).

Review of Evidence
Non-Randomized Studies
MS is a chronic disease with variable prognosis and clinical course. Predictors of future disease course might help select individuals who would benefit most from disease-modifying treatments.[35,]

Solanky et al (2020) published a cross-sectional analysis of 119 individuals with secondary-progressive MS recruited from the MS-Secondary Progressive Multi-Arm Randomization Trial (MS-SMART).[36,] The relationship between neurometabolites and various clinical disability measures was examined via Spearman rank correlations. Significant associations were further analyzed via multiple regression models adjusted for age, sex, disease duration, T2 lesion load, normalized brain volume and history of recent relapse occurrence. Significant associations in normal-appearing white matter were found for N-acetyl-aspartate (tNAA) and Nine-Hole Peg Test (9HPT) (r = 0.23; 95% CI, 0.06 to 0.40), tNAA and Paced Auditory Serial Addition Test (PASAT) (r = 0.21; 95% CI, 0.03 to 0.38), tNAA/tCr and PASAT (r = 0.19; 95% CI, 0.01 to 0.36), and mIns/tCr and PASAT (r = -0.23; 95% CI, -0.39 to -0.05). No significant associations were found for any neurometabolite levels and the Expanded Disability Status Scale (EDSS) or Timed 25-Foot Walk (T25FW) tests following multiple regression analysis.

John et al (2023) published a longitudinal analysis of individuals with secondary-progressive MS (N=108) recruited from the MS-SMART trial.[37,] They found that in the placebo group, total choline (tCho) increased in gray matter (mean difference = -0.32 institutional units [IU]) but decreased in normal appearing white matter (NAWM) (mean difference = 0.13 IU) over 96 weeks. Fluoxetine was associated with lower myo-inositol/total creatine (mIns/tCr) (β = -0.21; 95% CI: -0.40 to -0.02) in NAWM, while riluzole reduced glutamate + glutamine (Glx) (β = -0.25; 95% CI: -0.47 to -0.04) and Glx/tCr (β = -0.29; 95% CI: -0.50 to -0.08) in gray matter. Baseline total tNAA (β = 0.22; 95% CI: 0.02 to 0.41) and tNAA/tCr (β = 0.23; 95% CI: 0.5 to 0.42) in NAWM were associated with better 9HPT scores at 96 weeks. The authors noted several methodological limitations of the study, and stated therefore the results are reported as estimates, not absolute concentrations.

Llufriu et al (2014) published a study assessing the use of MRS in a preliminary data set of 59 individuals with MS and 43 healthy controls, and in a confirmatory independent data set of 220 individuals.[38,] Change in brain volume and measures of disability were obtained annually. The myo-inositol to NAA ratio in the normal-appearing white matter was found to be a predictor of brain volume change over 4 years (p=.02) and of clinical disability (e.g., a decrease in the Multiple Sclerosis Functional Composite evolution scale of -0.23 points annually, p=.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, more effective therapy, or avoid unnecessary therapy or 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 MS, serial measurements of outcomes, and complementary measures of disease activity.[35,]

Psychiatric Disorders
Clinical Context and Test Purpose
The purpose of MRS in individuals with psychiatric disorders is to improve the diagnosis and management of psychiatric disorders.

The following PICO was used to select literature to inform this review.

Populations
The relevant populations of interest are individuals being evaluated for psychiatric disorders.

Interventions
The intervention of interest is MRS.

Comparators
The following practices are currently being used to make decisions about diagnosing and managing psychiatric disorders: standard care (e.g., unstructured clinical interview and observation) or structured clinical interviews (ice, application of Diagnostic and Statistical Manual of Mental Disorders, 5th Edition [DSM-5] criteria).

Outcomes
The outcomes of interest are sensitivity and specificity and the effect on health outcomes. The time of interest is at the initial evaluation or at clinical follow-up.

Study Selection Criteria
For the evaluation of the clinical validity of the tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores);

- Included a suitable reference standard;
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described;
- Included a validation cohort separate from development cohort.

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).

Review of Evidence
Research use of MRS continues to evolve and test correlations between brain biomarker levels and various psychiatric disorders (e.g., major depressive disorder, bipolar disorder, schizophrenia, post-traumatic stress disorder, psychosis risk, and others) to inform diagnosis or patient management.[39,-,51,]

Prospective Studies
Henigsberg et al (2019) evaluated 48 individuals with unipolar depression from recovery onset until recurrence of depression or until discontinuation of antidepressant maintenance therapy.[52,] Depressive symptom remission was confirmed with a Montgomery-Asberg rating Scale (MADRS) score ≤10. 1H MRS scans were performed at the onset of recovery and after 6 months. N-acetylaspartate, Cho, and glutamine/glutamate and GABA metabolic spectra were obtained from the left amygdala region. Individuals were evaluated with psychiatric interviews and MADRS assessments during the study period at regular intervals of 6 months or less, for up to 7 years. Twenty patients experienced recurrence, 23 individuals achieved antidepressant discontinuation, and follow-up data was missing for 5 individuals. Cho levels at the beginning of recovery and subsequent changes conveyed the highest risk for earlier recurrence. Individuals with higher amygdala Cho after recovery were found to be at significantly lower risk for depression recurrence (hazard ratio [HR] 0.32; 95% CI, 0.13 to 0.77). Study participants were managed on various antidepressant medications, and criteria for antidepressant discontinuation were unclear.

Godlewska et al (2019) published a study assessing the use of MRS to track and predict treatment response to lamotrigine in 21 individuals with bipolar depression.[53,] Before starting lamotrigine and after 10 to 12 weeks of treatment, patients underwent MRS scanning to determine levels of glutamate (Glx) in the anterior cingulate cortex. Baseline levels of Glx did not predict response to lamotrigine (p=.49). Responders to lamotrigine showed a significant increase in Glx levels from baseline (p=.012), however, the size of this increase was small (14.8 ± 1.3 to 14.3 ± 0.98 µmol/g). The significance between final Glx levels in responders and nonresponders was not reported.

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, more effective therapy, or avoid unnecessary therapy or 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: Psychiatric Disorders

Although a number of studies have examined the use of MRS for identifying and understanding psychiatric disorders, the present evidence does not support any role for MRS outside of the research setting. Numerous methodologies for the use of MRS in this setting have been described, with inconsistent diagnostic validity results. Additionally, preliminary studies have thus far failed to demonstrate the successful application of MRS for the prediction of treatment response. Furthermore, the impact of MRS on health outcomes for this indication is unknown.

Other Indications

MRS has also been evaluated for other uses, such as tracking disease changes among patients with systemic lupus erythematosus,[54,] assessing carotid plaque morphology,[55,] identifying biomarkers of traumatic brain injury,[56,57,] and predicting long-term neurodevelopmental outcome after neonatal encephalopathy.[58,59,60,61,62,] MRS has also been used to evaluate pediatric patients with seizures,[63,] and other applications in children.[64,] Additional evidence on these applications is needed.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Association of Neurological Surgeons and Congress of Neurological Surgeons

The American Association of Neurological Surgeons and Congress of Neurological Surgeons (2015) gave a level III recommendation (reflecting unclear clinical certainty) 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.[65,]

American College of Radiology et al

The American College of Radiology, American Society of Neuroradiology, and Society for Pediatric Radiology (2019) updated their joint practice parameters on MRS of the central nervous system.[66,] Most of the update addressed the actual performance of MRS, but it also listed 25 possible indications for MRS when magnetic resonance imaging or computed tomography is inadequate for answering specific clinical questions.

MRS of the head without IV contrast is considered "usually not appropriate" in dementia (including cognitive decline and suspected Alzheimer disease), head trauma in adults and children, movement disorders, and neurodegenerative diseases.[67,]

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.[68,] The Congress found that although the results were promising, there was insufficient evidence to recommend the use of MRS formally.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) clinical guidelines on central nervous system cancers (v.2.2024) identifies magnetic resonance spectroscopy (MRS) as 1 of several modalities that can be considered to rule out radiation necrosis, as compared with recurrence of brain tumors.[69,] 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. The NCCN clinical guidelines on prostate cancer (v.4.2024) list MRS as an advanced imaging technique but make no recommendations for its use.[70,]

The NCCN clinical guidelines on breast cancer (v.4.2024) do not mention MRS.[71,]

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (NICE) guidance on primary brain tumors and brain metastases in adults, updated in 2021, includes the following recommendations regarding the use of MRS:[72,]

- In patients undergoing imaging for suspected glioma, advanced magnetic resonance imaging (MRI) techniques, such as MR perfusion and MRS may be considered to assess the potential of a high-grade transformation in a tumor appearing to be low grade on standard structural MRI.
- In patients undergoing follow-up for glioma or brain metastases, advanced MRI techniques such as MR perfusion, diffusion tensor imaging and MRS may be considered if findings from standard imaging are unclear regarding whether there is recurrence and early identification is potentially clinically useful.

The NICE guidance on Parkinson's disease in adults, published in 2017, states that MRS should not be used in the differential diagnosis of parkinsonian syndromes.[73,]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 8.

Table 8. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05664464	A Phase Ib/II Randomized, Open Label Drug Repurposing Trial of Glutamate Signaling Inhibitors in Combination With Chemoradiotherapy in Patients With Newly Diagnosed Glioblastoma	120	Dec 2026
NCT03324360	Role of Hyperpolarized 13C-Pyruvate MR Spectroscopy in Patients with Intracranial Metastasis Treated with Stereotactic Radiosurgery	156	Jan 2025 (recruiting)
NCT00581906	Dynamic Contrast Enhanced MRI (DCE-MRI), Diffusion-Weighted MRI (DW-MRI), and Magnetic Resonance Spectroscopy (MRS) of Head and Neck Tumors	272	Feb 2025 (ongoing)
NCT02714894	Response to Clozapine in Treatment Resistant Schizophrenia: A Longitudinal Magnetic Resonance Spectroscopy Study	108	Jul 2022 (unknown status)

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT02137759[a]	Quantitative Magnetic Resonance Spectroscopic Imaging (MRSI) to Predict Early Response to Standard Radiation Therapy (RT)/Temozolomide (TMZ) ± Belinostat Therapy in Newly-Diagnosed Glioblastomas (GBM)	29	Aug 2024 (active, not recruiting)
NCT04540107[a]	Metabolic Imaging of Patients With Lower Grade Glioma Using Hyperpolarized 13C Pyruvate	300	Jan 2025 (recruiting)
NCT03952598	Studying the Biology of IDH-mutant Gliomas Via Longitudinal Observation of 2-Hydroxyglutarate (2-HG) Using MR Spectroscopy	270	Dec 2025 (recruiting)
NCT03677999	Spectroscopic Magnetic Resonance Imaging of Glioma (MEGA-PRESS)	304	Sep 2025 (recruiting)
NCT01653093	Imaging of the Prostate Gland Using High Field Strength 3T MRI	280	Dec 2024 (active, not recruiting)
Unpublished			
NCT02388659	Clinical Development of Cancer-Specific MRS Biomarkers in Malignant Gliomas	142	Dec 2021 (completed)
NCT02731521	Clinical Development of MR Spectroscopy and Imaging in Brain Cancers	112	Dec 2021 (completed)
NCT00474604	MRI Evaluation of Breast Tumor Growth and Treatment Response	209	Apr 2023 (completed)

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0609T	Magnetic resonance spectroscopy, determination and localization of discogenic pain (cervical, thoracic, or lumbar); acquisition of single voxel data, per disc, on biomarkers (i.e., lactic acid, carbohydrate, alanine, laal, propionic acid, proteoglycan, and collagen) in at least 3 discs

Type	Code	Description
	0610T	Magnetic resonance spectroscopy, determination and localization of discogenic pain (cervical, thoracic, or lumbar); transmission of biomarker data for software analysis
	0611T	Magnetic resonance spectroscopy, determination and localization of discogenic pain (cervical, thoracic, or lumbar); postprocessing for algorithmic analysis of biomarker data for determination of relative chemical differences between discs
	0612T	Magnetic resonance spectroscopy, determination and localization of discogenic pain (cervical, thoracic, or lumbar); interpretation and report
	76390	Magnetic resonance spectroscopy
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
09/01/2003	MPC adopted CTAF consent BCBSA TEC June Vol. 18, No. 1, June 2003.
03/01/2005	Statement unchanged, BCBSA MPP 6.01.24 3Q2004 review.
10/01/2010	Policy Revision
05/29/2015	Coding update
09/30/2015	Policy revision without position change
04/01/2016	Policy revision without position change
06/01/2017	Policy revision without position change
11/01/2017	Policy revision without position change
11/01/2018	Policy revision without position change
11/01/2019	Policy revision without position change
08/01/2020	Coding update
11/01/2020	Annual review. No change to policy statement. Literature review updated.
12/01/2021	Annual review. No change to policy statement. Literature review updated.
12/01/2022	Annual review. No change to policy statement. Literature review updated.
12/01/2023	Annual review. No change to policy statement. Literature review updated.
12/01/2024	Annual review. No change to policy statement. Policy guidelines and literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with

generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Magnetic Resonance Spectroscopy 6.01.24 **Policy Statement** I. Magnetic resonance spectroscopy (MRS) is considered **investigational**.	**Magnetic Resonance Spectroscopy 6.01.24** **Policy Statement:** I. Magnetic resonance spectroscopy (MRS) is considered **investigational**.