Magnetic Resonance Spectroscopy (MRS)

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

Aetna considers magnetic resonance spectroscopy (MRS) (also known as NMR spectroscopy) medically necessary for distinguishing recurrent brain tumor from radiation necrosis.

Aetna considers magnetic resonance spectroscopy (MRS) (also known as NMR spectroscopy) experimental and investigational for all other indications, including the following (not an all-inclusive list) because there is a lack of evidence of its efficacy in the medical literature.

- Breast cancer
- Dementia and movement disorders (e.g., Alzheimer's disease, dementia with Lewy bodies, frontotemporal dementia, Huntington disease, motor neuron disease, normal-pressure hydrocephalus, Parkinson disease/Parkinsonian syndromes, vascular dementia)
- Dermatomyositis
- Head trauma

Policy History

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Definitions

Additional Information

Clinical Policy Bulletin Notes
- Juvenile myoclonic epilepsy
- Low back pain
- Lyme neuroborreliosis
- Monitoring hepatocellular carcinoma and liver cirrhosis development
- Mucopolysaccharidosis
- Polymyositis
- Prostate cancer
- Psychiatric disorders (e.g., attention-deficit/hyperactivity disorder, autism spectrum disorders, bipolar disorder, depression, emotional dysregulation, obsessive-compulsive disorder, and schizophrenia)
- Radiation encephalopathy
- Sport-related concussion
- Substance use disorders

**Background**

Magnetic resonance spectroscopy (MRS), also known as nuclear magnetic resonance (NMR) spectroscopy, is a non-invasive analytical technique that has been used to study metabolic changes in brain tumors, strokes, seizure disorders, Alzheimer's disease, depression and other diseases affecting the brain. It has also been used to study the metabolism of other organs.

Magnetic resonance spectroscopy can be done as part of a routine magnetic resonance imaging (MRI) on commercially available MRI instruments. The probe accessory necessary to perform MRS was granted 510(k) clearance from the Food and Drug Administration (FDA). Magnetic resonance spectroscopy and MRI use different software to acquire and mathematically manipulate the signal. Whereas MRI creates an image, MRS creates a graph or "spectrum" arraying the types and quantity of chemicals in the brain or other organs.

The role of MRS in diagnosis and therapeutic planning has not been established by adequate clinical studies. Specifically, there have been no clinical trials demonstrating improved outcomes in patients evaluated with MRS compared to patients evaluated with conventional imaging modalities.
Guidelines on central nervous system cancers from the National Comprehensive Cancer Network (NCCN, 2016) state that magnetic resonance spectroscopy may be useful in anaplastic gliomas and glioblastoma to differentiate tumor from radiation necrosis ("pseudoprogression").

Zhang, et al. (2014) conducted a meta-analysis to evaluate the diagnostic quality of magnetic resonance spectroscopy (MRS) in differentiating glioma recurrence from radiation necrosis. Studies about evaluation of MRS for the differential diagnosis of glioma recurrence from radiation necrosis were systematically searched in PubMed, Embase and Chinese Biomedical databases up to May 4, 2014. The data were extracted to perform heterogeneity test, threshold effect test and to calculate sensitivity (SEN), specificity (SPE) and areas under summary receiver operating characteristic curve (SROC).

Eighteen articles comprising a total sample size of 455 patients (447 lesions) with suspected glioma recurrence after radiotherapy, met all inclusion and exclusion criteria, and were included in our meta-analysis. Quantitative synthesis of studies showed that the pooled SEN and SPE for Cho/Cr ratio were 0.83 (95% CI: 0.77, 0.89) and 0.83 (95% CI: 0.74, 0.90). The area under the curve (AUC) under the SROC was 0.9001. The pooled SEN and SPE for Cho/NAA ratio were 0.88 (95% CI: 0.81, 0.93) and 0.86 (95% CI: 0.76, 0.93). The AUC under the SROC was 0.9185. The authors concluded that this meta-analysis shows that MRS alone has moderate diagnostic performance in differentiating glioma recurrence from radiation necrosis using metabolite ratios like Cho/Cr and Cho/NAA ratio. The authors strongly recommended that MRS should combine other advanced imaging technologies to improve diagnostic accuracy. This authors states that this metaanalysis underlines the importance of implementing multimodal imaging trials and multicentre trials in the future.

Chuang, et al. (2016) conducted a metaanalysis examining the roles of several metabolites in differentiating recurrent tumor from necrosis in patients with brain tumors using MR perfusion and spectroscopy. Medline, Cochrane, EMBASE, and
Google Scholar were searched for studies using perfusion MRI and/or MR spectroscopy published up to March 4, 2015 which differentiated between recurrent tumor vs. necrosis in patients with primary brain tumors or brain metastasis. Only two-armed, prospective or retrospective studies were included. A meta-analysis was performed on the difference in relative cerebral blood volume (rCBV), ratios of choline/creatine (Cho/Cr) and/or choline/N-acetyl aspartate (Cho/NAA) between participants undergoing MRI evaluation. A $\chi^2$-based test of homogeneity was performed using Cochran's Q statistic and I². Of 397 patients in 13 studies who were analyzed, the majority had tumor recurrence. As there was evidence of heterogeneity among 10 of the studies which used rCBV for evaluation ($Q$ statistic = 31.634, $I^2 = 97.11\%$, $P < 0.0001$) an random-effects analysis was applied. The pooled difference in means (2.18, 95%CI = 0.85 to 3.50) indicated that the average rCBV in a contrast-enhancing lesion was significantly higher in tumor recurrence compared with radiation injury ($P = 0.001$). Based on a fixed-effect model of analysis encompassing the six studies which used Cho/Cr ratios for evaluation ($Q$ statistic = 8.388, $I^2 = 40.39\%$, $P = 0.137$), the pooled difference in means (0.77, 95%CI = 0.57 to 0.98) of the average Cho/Cr ratio was significantly higher in tumor recurrence than in tumor necrosis ($P = 0.001$). There was significant difference in ratios of Cho to NAA between recurrent tumor and necrosis (1.02, 95%CI = 0.03 to 2.00, $P = 0.044$). The authors concluded that MRS using Cho/NAA and Cho/Cr ratios and rCBV may increase the accuracy of differentiating necrosis from recurrent tumor in patients with primary brain tumors or metastases.

The consensus in the literature is that further studies are necessary to determine MRS' role in the diagnosing and planning treatment in neurological diseases.

Magnetic resonance spectroscopy (MRS) in the evaluation of brain tumors (either primary tumors or brain metastases) is considered investigational/experimental because there is inadequate evidence in the published peer-reviewed clinical
literature regarding its effectiveness.

An assessment of MRS prepared by the Tuft’s-New England Medical Center Evidence-Based Practice Center for the Agency for Healthcare Research and Quality (AHRQ) (Jordan et al, 2003) reached the following conclusions: “[h]uman studies conducted on the use of MRS for brain tumors demonstrate that this non-invasive method is technically feasible and suggest potential benefits for some of the proposed indications. However, there is a paucity of high quality direct evidence demonstrating the impact on diagnostic thinking and therapeutic decision-making. In addition, the techniques of acquiring the MRS spectra and interpreting the results are not well standardized. In summary, while there are a large number of studies that confirm MRS’ technical feasibility, there are very few published studies to evaluate its diagnostic accuracy and whether it can positively affect diagnostic thinking and therapeutic choice. Those studies that do address these areas often have significant design flaws including inadequate sample size, retrospective design and other limitations that could bias the results.”

A structured evidence review of MRS for evaluation of suspected brain tumor conducted by the BlueCross BlueShield Association Technology Evaluation Center (2003) concluded that “[t]he evidence is insufficient to permit conclusions concerning the effect of magnetic resonance spectroscopy on health outcomes.”

The Center for Medicare and Medicaid Services (CMS, 2004) has determined that there is insufficient evidence to deem MRS “reasonable and necessary” for brain tumor diagnosis. Due to “methodological shortcomings” in the 11 studies reviewed on the use of MRS for brain lesion detection and a lack of a controlled comparison of MRS and traditional diagnostic strategies, CMS has announced that it will continue its current national non-coverage determination.

Gluch (2005) stated that ex vivo and in vivo applications of MRS
have been developed, which aid in distinguishing malignant from normal tissues. Studies of breast, colon, cervix, esophageal, and prostate cancer reveal both the successes and failings of present technology. The author noted that verification that these non-invasive tests might supplant conventional histology in obtaining spatial diagnostic and chemical prognostic information remains for the time being illusive.

Willmann et al (2006) evaluated the additional pre-operative value of (1)H MRS in identifying the epileptogenic zone (EZ) for epilepsy surgery by performing a meta-analysis. The authors concluded that MRS still remains a research tool with clinical potential. Their findings indicated the connection of ipsilateral MRS abnormality to good outcome. The ability for prediction of post-operative outcome may depend on the assessed population. They noted that prospective studies limited to non-localized ictal scalp electroencephalography or MRI-negative patients are needed for validation of these data. Furthermore, Hollingworth et al (2006) stated that (1)H MRS is a potentially useful adjunct to anatomical MRI in the characterization of brain tumors. These investigators performed an updated systematic review of the evidence. They concluded that the current evidence on the accuracy of (1)H MRS in the characterization of brain tumors is promising. However, additional high-quality studies are needed to convince policy makers.

The clinical evidence is not sufficient to permit conclusions on the health outcome effects of magnetic resonance spectroscopy in the evaluation of prostate cancer. Magnetic resonance spectroscopy (MRS) provides metabolic information about the prostate gland by assessing the prostatic metabolites choline and citrate. Alterations in levels of these metabolites may provide prognostic information that may be useful for treatment planning.

According to Jung and Westphalen (2012) studies have demonstrated that the addition of proton magnetic resonance
spectroscopic imaging (1H-MRSI) to T2-weighted MR imaging improves tumor localization, volume estimation, staging, tissue characterization, and identification of recurrent disease after therapy. A recent multicenter study supported by the American College of Radiology Imaging Network, however, showed that the combination of 1H-MRSI and T2-weighted MR images does not improve tumor detection in patients with low-grade, low-volume disease selected to undergo radical prostatectomy. These results suggest that positive 1H-MRSI findings are more likely to reflect higher tumor grade and/or volume.

NCCN Clinical Practice Guidelines in Oncology for prostate cancer (2011) state: “A negative biopsy following post-radiation biochemical recurrence poses clinical uncertainties. Observation, androgen deprivation therapy (ADT), or enrolling in clinical trials are viable options. Alternatively, the patients may undergo more aggressive workup, such as repeat biopsy, MR spectroscopy, and/or endorectal MRI.”

According to the textbook Wein: Campbell-Walsh Urology (2011), in the initial evaluation of the patient with prostate cancer, tumor-selective imaging tests, such as monoclonal antibody scans, positron emission tomographic scans, magnetic resonance spectroscopy, and lymphotrophic magnetic resonance imaging (MRI) are not widely used, although they might prove more useful in the future. The use of MRI, alone or in combination with MRS for tumor staging remains controversial. Current research involves the use of magnetic resonance spectroscopy to guide radiation administration by directing higher doses to the metabolically active areas of the tumor. Magnetic resonance spectroscopy–optimized implants are also under study to give higher doses to metabolically active regions of the tumor.

The textbook Abeloff’s Clinical Oncology (2008) states that new imaging technologies, including MRS give great potential for improving the assessment of local and distant prostate cancer extent.
In a retrospective trial, Fradet et al (2010) studied the role that MRI and MRS findings obtained at the time of diagnosis play in the progression of disease in patients whose prostate cancer is being managed with active surveillance and compared the role of these findings with the role of transrectal ultrasonography (US) findings. The final cohort included 114 patients with a median follow-up of 59 months. Two urologists blinded to the clinical outcome in these patients independently reviewed and dichotomized the MRI report and the MRS imaging report as normal or suggestive of malignancy. One urologist performed all US examinations that were then dichotomized similarly. Patients with a lesion that was suggestive of cancer at MRI had a greater risk of the Gleason score being upgraded at subsequent biopsy (hazard ratio, 4.0; 95% confidence interval: 1.1, 14.9) than did patients without such a lesion. Neither MRS imaging nor transrectal US could be used to predict cancer progression.

Westphalen and colleagues (2010), in a retrospective single-institution study, compared resonance (MR) spectroscopic imaging with T2-weighted MR imaging alone in the detection of locally recurrent prostate cancer after definitive external beam radiation therapy. Sixty-four men who underwent endorectal MR imaging, MR spectroscopic imaging, and transrectal ultrasonographically guided biopsy for suspected local recurrence of prostate cancer after definitive external beam radiation therapy were retrospectively identified. Thirty-three patients had also received androgen therapy. Recurrent cancer was determined to be present or absent in the left and right sides of the prostate at T2-weighted MR imaging and MR spectroscopic imaging by a radiologist and a spectroscopist, respectively. Area under the receiver operating characteristic curve (A(Z)) was calculated for T2-weighted MR imaging alone and combined T2-weighted MR imaging and MR spectroscopic imaging by using generalized estimating equations and by using biopsy results as the reference standard. Recurrent prostate cancer was identified at biopsy in 37 (58%) of the 64 men. Recurrence was unilateral in 28 patients and bilateral in nine (total of 46 affected prostate sides). A(Z) analysis revealed that
use of combined T2-weighted MR imaging and MR spectroscopic imaging \( (A(Z) = 0.79) \), as compared with T2-weighted MR imaging alone \( (A(Z) = 0.67) \), significantly improved the detection of local recurrence \( (P = .001) \). The addition of MR spectroscopic imaging to T2-weighted MR imaging was found to significantly improve the diagnostic accuracy of endorectal MR imaging in the detection of locally recurrent prostate cancer after definitive external beam radiation therapy.

Zakian and colleagues (2005) evaluated whether hydrogen 1 MR spectroscopic imaging can be used to predict aggressiveness of prostate cancer. A total of 123 patients (median age, 58 years; age range, 40-74 years) who underwent endorectal MRI and MR spectroscopic imaging between January 2000 and December 2002 were included. MR imaging and spectroscopy were performed by using combined pelvic phased-array and endorectal probe. Data from 94 patients were included. Pathologic evaluation was used to identify 239 lesions. Overall sensitivity of MR spectroscopic imaging was 56% for tumor detection, increasing from 44% in lesions with Gleason score of 3 + 3 to 89% in lesions with Gleason score greater than or equal to 4 + 4. There was a trend toward increasing \( \frac{(\text{Cho} + \text{Cr})}{\text{Cit}} \) with increasing Gleason score in lesions identified correctly with MR spectroscopic imaging. Tumor volume assessed with MR spectroscopic imaging increased with increasing Gleason score.

Kline et al (2006) measured citrate in samples from 61 participants, of whom 16 without and 21 with cancer donated semen, and 17 without and 7 with cancer donated expressed prostatic secretions. Mean citrate +/- SE compared to that in controls was 2.7-fold lower in patients with cancer samples in semen \( (132.2 +/- 30.1 \text{ versus } 48.0 +/- 7.9 \text{ mM, } p < 0.05) \) and expressed prostatic secretions \( (221.4 +/- 55.4 \text{ versus } 81.5 +/- 36.0 \text{ mM, } p < 0.05) \). ROC curve analysis showed that measurements of citrate in semen performed as well as measurements of citrate in expressed prostatic secretion for detecting prostate cancer \( (AUC 0.81, 95 \% \text{ confidence interval} \)
[CI]: 0.60 to 0.92 and AUC 0.73, 95 % CI: 0.38 to 0.90, respectively, p > 0.05). ROC curve analysis also showed that the measurement of citrate in either fluid outperformed prostate specific antigen measurement for detecting prostate cancer in these subjects (AUC 0.61, 95 % CI: 0.44 to 0.74). The authors concluded that in vitro nuclear MRS measurement of the citrate concentration in semen or expressed prostatic secretions outperforms prostate specific antigen testing for detecting prostate cancer.

Wetter et al (2006) examined fifty patients with biopsy-proven prostate carcinoma. For spectroscopy, a 3D chemical shift imaging (CSI) spin-echo sequence was used. Image interpretation was performed by 2 radiologists. The total number of tumor voxels and tumor voxels per slice were counted to estimate the tumor volume in every patient. The potential of MR spectroscopy to differentiate between T2 and T3 tumors, based on the estimated tumor volumes, was compared with the staging performance of MRI. The MR measurement time was 19.01 minutes, and the total procedure time averaged 35 minutes. Seventy-six percent of the spectroscopic examinations were successful. Statistically significant differences in the number of tumor voxels per slice and tumor volumes were found between T2 and T3 tumors. The descriptive parameters of MRI and MR spectroscopy did not differ significantly; sensitivity and specificity were 75 % and 87 %, respectively, for MRI and 88 % and 70 %, respectively, for MR spectroscopy. The combination of both methods resulted in only a slight improvement in staging performance and was not statistically significant. The authors concluded that combined MRI and MRS of the prostate has no diagnostic advantage in staging performance over MRI alone.

According to Shah et al (2006), “although MRS has mainly been used in diagnostics and tumor evaluation for brain cancer, it is becoming an increasingly important adjunct to conventional diagnostic and monitoring procedures for cancer of the prostate, colon, breast, cervix, pancreas, and esophagus. The clinical usefulness of MRS has yet to be fully substantiated”. 
Rajesh et al (2007) noted that 3D MRS is emerging as a new and sensitive tool in the metabolic evaluation of prostate cancer. Zapotoczna et al (2007) stated that the increasing sensitivity and specificity of MRS to the prostate is causing new interest in its potential role in the definition of target subvolumes at higher risk of failure following radical radiotherapy. Prostate MRS might also play a role as a non-invasive predictive factor for tumor response and treatment outcome. However, guidelines on the pre-treatment staging of prostate cancer by the American College of Radiology (ACR)'s expert panel on urologic imaging and radiation oncology (Israel et al, 2007) stated that one group of investigators have demonstrated that prostate cancers have a characteristic loss of the citrate peak and gain in the choline/creatinine peak on MRS imaging. Moreover, the ratio of choline to citrate is related to the Gleason score, suggesting that MRS imaging may provide information about tumor aggressiveness. Improvements in diagnostic accuracy and staging have been reported. However, MRS imaging is technically demanding and time consuming. It has not been proven in multi-institutional trials, although a clinical trial under the auspices of the American College of Radiology Imaging Network (ACRIN) is currently underway. Thus, MRS imaging can not yet be considered a routine diagnostic tool.

In a meta-analysis of the accuracy of prostate cancer studies which use MRS as a diagnostic tool, Wang et al (2008) concluded that as a new method in the diagnosis of prostate cancer, MRS has a better applied value compared to other common modalities. Ultimately, large scale randomized controlled trial studies are needed to evaluate its clinical value.

The clinical evidence is not sufficient to support the use of magnetic resonance spectroscopy in the evaluation of mucopolysaccharidosis. Vedolin and colleagues (2007) examined the influence of aging on conventional MRI and MRS findings of patients with mucopolysaccharidosis (MPS), and tested the correlation of enzyme levels, urinary glycosaminoglycans (GAG), and neuroimaging findings. A total
of 60 patients with MPS types I (n = 8), II (n = 31), IV-A (n = 4), and VI (n = 17) underwent T2, fluid-attenuated inversion recovery (FLAIR), and MRS of the brain. For analysis of MRI variables, the researchers measured the normalized cerebral volume (NCV), CSF volume (NCSFV), ventricular volume (NVV), and lesion load (NLL) on FLAIR using semi-automated and automated segmentation techniques. For MRS, a point-resolved spectroscopy technique was used. Voxels were positioned at the white and gray matter. Statistical analysis involved Pearson or Spearman tests for correlation between neuroimaging, age, enzyme levels, and urinary GAG. The median age at onset of the disease was 20 months. Patients with longer disease duration had more NLL in the white matter \( r = 0.28, p = 0.03 \), and this difference was more pronounced in MPS II patients \( r = 0.44, p = 0.02 \). Metabolites ratios in MRS, NCV, NCSFV, and NVV did not correlate with disease duration or age of the patients \( p > 0.05 \). Magnetic resonance imaging and MRS variables in either the white or the gray matter did not correlate with enzymatic activity or GAG levels. Patients with MPS II had a lower mean NCV \( p < 0.001 \). The authors concluded that these findings showed that white matter lesion is more extensive as disease duration increases, especially in mucopolysaccharidosis type II patients. Magnetic resonance imaging and MRS findings did not correlate with either enzymatic or glycosaminoglycan levels.

Boesch et al (2007) evaluated and compared biochemical and volumetric features of the cerebellum in patients with spinocerebellar ataxia type 2 (SCA2) and patients with the cerebellar variant of multiple system atrophy (MSA-C). Nine genetically assigned SCA2 patients and 6 MSA-C patients who met the clinical criteria of MSA-C underwent a clinical and neuro-radiological work-up with respect to cerebellar features. The MR protocol consisted of a sagittal T1-weighted 3-dimensional fast low-angle shot (3D FLASH) sequence and a transversal T2- and spin-density-weighted turbo spin-echo sequence. The proton magnetic resonance spectroscopic imaging \((1)\text{H-MRSI}\) protocol consisted of 2 chemical shift imaging (CSI) sequences (echo time (TE) = 20 and 135 msec). Both short- and long-TE
MRS images showed significant decreases in values for N-acetylaspartate to creatine (NAA/Cr), and choline to creatine (Cho/Cr) ratios in MSA-C and SCA2 compared to normal controls, though there was no difference between the 2 patient groups. In contrast, distinct cerebellar lactate (Lac) peaks were detected in 7 SCA2 patients, and small peaks were detected in 2. However, these investigators did not detect any definite Lac peak in MSA-C or control subjects. The authors concluded that MRSI revealed Lac pathology in SCA2 but not in MSA-C. Whether this indicates distinct pathogenetic mechanisms of cerebellar degeneration remains to be established.

Dyke et al (2007) explored (1)H MRSI as a means to assess peri-tumoral tissue response post-resection and Gliadel((R)) implantation in patients with high-grade gliomas. Pilot (1)H MRSI data are presented that demonstrate non-invasive, serial monitoring of metabolic changes at the tumor site following Gliadel implantation. Three patients with newly diagnosed glioblastoma multiforme (GBM) underwent MRI and (1)H MRSI at 3.0 Tesla prior to resection and at 3 to 5 and greater than or equal to 12 weeks post-operatively. Baseline MRS spectra of tumor tissue from all patients were characterized by marked increases of choline (CHO) and lactate (LAC), and a decrease of N-acetylaspartate (NAA), typical of GBM compared with normal contra-lateral brain tissue. Post-operatively, spectra were analyzed from the resection cavity and peri-tumoral regions and compared with normal tissue from the contra-lateral brain at baseline. In 2 of 3 patients, peri-tumoral NAA/CRE increased and CHO/NAA decreased compared to contra-lateral brain at 3 to 5 weeks compared with baseline following Gliadel therapy and surgery but prior to radiotherapy. This study indicated that (1)H MRSI has the ability to localize regions of heterogeneous response following Gliadel treatment. Although data are limited, these results suggested that metabolic indicators of outcome can be successfully monitored pre- and post-surgical resection and Gliadel implantation with (1)H MRSI. Additional study of patients receiving Gliadel Wafers using (1)H MRSI may serve to aid clinicians in assessing tumor regression and gauging efficacy of this chemotherapy treatment.
De Stefano et al (2007) reviewed current MRS clinical applications in multiple sclerosis (MS), and discussed the potential and limitations of the technique, and suggested recommendations for the application of MRS to clinical trials. The authors concluded that despite some important limitations, proton MRS has the potential to be implemented in large, multi-centered clinical trials of MS. The usefulness of MRS-derived outcome measures in MS clinical trial has yet to be proven. Future studies and the few clinical trials that are currently incorporating MRS into their imaging protocols will reveal if MRS has a role in quantifying the impact of therapeutic intervention on tissue damage in MS and will help to determine if MRS can become a standard and accepted part of the assessment of MS treatment in the near future. European Federation of Neurological Societies guidelines on the use of neuroimaging in the management of MS (Filippi et al, 2006) noted that the performance and contribution of diffusion tensor MRI (DT-MRI) and MRS) in multi-center studies still have to be evaluated.

Biomarkers of disc degeneration have been previously described using NMR spectroscopy, but the link between discogenic back pain and biomarkers has not been completely understood. Keshari et al (2008) used quantitative ex vivo proton high resolution magic angle spinning (HR-MAS) NMR spectroscopy to identify biochemical markers associated with discogenic back pain. HR-MAS NMR spectroscopy was performed on snap frozen samples taken from 9 patients who underwent discectomies for painful disc degeneration. The resulting proton NMR spectrums were compared with those from discs harvested from a reference population consisting of 9 scoliosis patients. Spectral analyses demonstrated significantly lower proteoglycan (PG)/collagen (0.31 +/- 0.22 versus 0.77 +/- 0.48) and PG/lactate (0.46 +/- 0.24 versus 2.24 +/- 1.11) ratios, and a higher lactate/collagen (0.77 +/- 0.49 versus 0.40 +/- 0.21) ratio in specimens obtained from discogenic pain patients when compared with scoliosis patients. The authors concluded that these findings suggested that spectroscopic markers of proteoglycan, collagen, and
lactate may serve as metabolic markers of discogenic back pain. These results provided a further basis of the potential to develop in vivo MRS for the investigation of discogenic back pain.

Guidelines on bone tumors by ACR's expert panel on musculoskeletal imaging (Morrison et al, 2005) noted that MRS has potential to differentiate benign from malignant lesions, however, more research is needed.

In a review on MRS as an imaging tool for cancer, Shah et al (2006) stated that the clinical usefulness of MRS has yet to be fully substantiated. As MRS availability and access increases, appropriate evaluations of its strengths and weaknesses will be made. The authors concluded that research to date and primary observation indicated that MRS is a promising clinical tool for oncologic management of patients.

Magnetic resonance spectroscopy in the evaluation of suspected breast cancer is considered experimental and investigational because there is inadequate evidence in the peer-reviewed clinical literature regarding its effectiveness.

Bartella and Huang (2007) stated that proton (hydrogen 1) [1H]) MRS provides biochemical information about the tissue under investigation. Its diagnostic value in cancer is typically based on the detection of elevated levels of choline compounds, choline being a marker of active tumor. The 2 main potential clinical applications of 1H MRS are (i) as an adjunct to breast MRI to improve specificity in differentiating benign from malignant lesions, and (ii) for monitoring or even predicting response to treatment in patients undergoing neoadjuvant chemotherapy. Preliminary data are promising, with study results suggesting that 1H MRS may decrease the number of benign biopsies recommended on the basis of MRI findings and may help predict response as early as 24 hours after the first dose of neoadjuvant chemotherapy. Although several limitations currently exist that make the technique premature for clinical use, further evaluation with larger, preferably multi-center trials
is certainly warranted.

Tse et al (2007) noted that in vivo proton (1)H-MRS has been demonstrated to be successful in the differentiation of benign and malignant breast lesions in a non-invasive manner by detecting increased levels of composite choline (Cho) compounds. Currently there is molecular evidence of increased Cho metabolism in breast cancer cells. In breast malignancies, (1)H-MRS achieved a high-overall sensitivity (82 %). Most test cases were infiltrating duct carcinoma, but infiltrating lobular, medullary, mucinous and adenoid cystic carcinomas were also positive by (1)H-MRS. Large lesional size is a pre-requisite for (1)H-MRS testing, and technical problems account for some of the false negative results. Another potential of (1)H-MRS is to assess patients' response to neoadjuvant chemotherapy. In ductal carcinoma in situ, the results of (1)H-MRS on the limited number of cases were negative. Most of the assessed benign breast lesions including fibroadenoma, fibrocystic changes, cysts and galactoceles, papilloma, tubular adenoma and phyllodes tumors and were mostly negative by (1)H-MRS, with an overall false-positive rate was about 8 %. Normal breast tissue was almost always negative by (1)H-MRS, whereas, lactating breast tissue showed positivity with a slightly different spectrum on further analysis. With the clinical use of stronger field MR scanners and better coils, the sensitivity of (1)H-MRS may be further improved. With these improvements, (1)H-MRS may potentially be useful in detection of smaller malignant lesions, characterization of malignant lesions into non-invasive or invasive, and as an invaluable tool in disease progression monitoring.

Kesler et al (2009) stated that males with fragile X syndrome (FRAX) are at risk for significant cognitive and behavioral deficits, particularly those involving executive prefrontal systems. Disruption of the cholinergic system secondary to fragile X mental retardation protein deficiency may contribute to the cognitive-behavioral impairments associated with fragile X. These investigators measured choline in the dorso-lateral prefrontal cortex of 9 males with FRAX and 9 age-matched
typically developing controls using (1)H MRS. Right choline/creatine was significantly reduced in the fragile X group compared to controls. In controls, both left and right choline was significantly positively correlated with intelligence and age was significantly negatively correlated with left choline. There were no correlations in the fragile X group. Subjects with FRAX participating in a pilot open-label trial of donepezil demonstrated significantly improved cognitive-behavioral function. The authors concluded that studies utilizing biochemical neuroimaging techniques such as these have the potential to significantly impact the design of treatment strategies for FRAX and other genetic disorders by helping identify neurochemical targets for intervention as well as serving as metrics for treatment efficacy.

Umbehr et al (2009) meta-analyzed the diagnostic accuracy of combined MRI/MRS in prostate cancer and explored risk profiles with highest benefit. The authors searched the MEDLINE and EMBASE databases and the Cochrane Library, and screened reference lists and contacted experts. There were no language restrictions. They identified 31 test-accuracy studies (1,765 patients); 16 studies (17 populations) with a total of 581 patients were suitable for meta-analysis. Nine combined MRI/MRS studies (10 populations) examining men with pathologically confirmed prostate cancer (297 patients; 1,518 specimens) had a pooled sensitivity and specificity on prostate subpart level of 68 % (95 % confidence interval [CI]: 56 to 78 %) and 85 % (95 % CI: 78 to 90 %), respectively. Compared with patients at high-risk for clinically relevant cancer (6 studies), sensitivity was lower in low-risk patients (4 studies) (58 % [46 to 69 %] versus 74 % [58 to 85 %]; p > 0.05) but higher for specificity (91 % [86 to 94 %] versus 78 % [70 to 84 %]; p < 0.01). Seven studies examining patients with suspected prostate cancer at combined MRI/MRS (284 patients) had an overall pooled sensitivity and specificity on patients level of 82 % (59 to 94 %) and 88 % (80 to 95%). In the low-risk group (5 studies), these values were 75 % (39 to 93 %) and 91 % (77 to 97 %), respectively. The authors concluded that a limited number of small studies suggested that MRI combined with
MRS could be a rule-in test for low-risk patients. Moreover, they stated that these findings need further confirmation in larger studies and cost-effectiveness needs to be established.

In a prospective, multi-center study, Weinreb et al (2009) determined the incremental benefit of combined endorectal MRI and MRS, as compared with endorectal MRI alone, for sextant localization of peripheral zone (PZ) prostate cancer. A total of 134 patients with biopsy-proved prostate adenocarcinoma and scheduled to undergo radical prostatectomy were recruited at 7 institutions. T1-weighted, T2-weighted, and spectroscopic MR sequences were performed at 1.5 T by using a pelvic phased-array coil in combination with an endorectal coil. Eight readers independently rated the likelihood of the presence of PZ cancer in each sextant by using a 5-point scale -- first on MR images alone and later on combined MR-MRS images. Areas under the receiver operating characteristic curve (AUCs) were calculated with sextant as the unit of analysis. The presence or absence of cancer at centralized histopathologic evaluation of prostate specimens was the reference standard. Reader-specific receiver operating characteristic curves for values obtained with MRI alone and with combined MRI-MRS imaging were developed. The AUCs were estimated by using Mann-Whitney statistics and appropriate 95% CI. Complete data were available for 110 patients (mean age of 58 years; range of 45 to 72 years).

Magnetic resonance imaging alone and combined MRI-MRS imaging had similar accuracy in PZ cancer localization (AUC, 0.60 versus 0.58, respectively; p > 0.05). AUCs for individual readers were 0.57 to 0.63 for MRI alone and 0.54 to 0.61 for combined MRI-MRS imaging. The authors concluded that in patients who undergo radical prostatectomy, the accuracy of combined 1.5-T endorectal MRI-MRS imaging for sextant localization of PZ prostate cancer is equal to that of MRI alone.

In a phase I study, Lee et al (2009) examined the use of SR4554, a fluorine-containing 2-nitroimidazole, as a hypoxia marker detectable with 19F MRS. These researchers investigated higher doses of SR4554 and intra-tumoral localization of the
19F MRS signal. Patients who had tumors greater than or equal to 3 cm in diameter and less than or equal to 4 cm deep were included in this study. Measurements were performed using 1H/19F surface coils and localized 19F MRS acquisition. SR4554 was administered at 1,400 mg m(-2), with subsequent increase to 2,600 mg m(-2) using prophylactic metoclopramide. Spectra were obtained immediately post-infusion (MRS no. 1), at 16 hrs (MRS no. 2) and 20 hrs (MRS no. 3), based on the SR4554 half-life of 3.5 hrs determined from a previous study.

19F fluorine retention index (%) was defined as (MRS no. 2/MRS no. 1) * 100. A total of 26 patients enrolled at: 1,400 (n = 16), 1,800 (n = 1), 2,200 (n = 1) and 2,600 mg m(-2) (n = 8). SR4554 was well-tolerated and toxicities were all less than or equal to grade 1; mean plasma elimination half-life was 3.7 +/- 0.9 hrs. SR4554 signal was seen on both unlocalized and localized MRS no. 1 in all patients. Localized 19F signals were detected at MRS no. 2 in 5 out of 9 patients and 4 out of 5 patients at MRS no. 3. The mean retention index in tumor was 13.6 (range of 1.6 to 43.7) compared with 4.1 (range of 0.6 to 7.3) for plasma samples taken at the same times (p = 0.001) suggesting (19)F retention in tumor and, therefore, the presence of hypoxia. The authors concluded that they have demonstrated the feasibility of using 19F MRS with SR4554 as a potential method of detecting hypoxia. Certain patients showed evidence of 19F retention in tumor, supporting further development of this technique for detection of tumor hypoxia.

Sturrock et al (2010) evaluated in vivo brain metabolite differences in control subjects, individuals with pre-manifest Huntington disease (pre-HD), and individuals with early HD using 1H MRS and assessed their relationship with motor performance. A total of 85 subjects (30 controls, 25 pre-HD, and 30 early HD) were recruited as part of the TRACK-HD study; 84 were scanned at 3 T with single-voxel spectroscopy in the left putamen. Disease burden score was greater than 220 among pre-HD individuals. Subjects underwent TRACK-HD motor assessment including Unified Huntington's Disease Rating Scale (UHDRS) motor scoring and a novel quantitative motor battery. Statistical analyses included linear regression
and 1-way analysis of variance. Total N-acetylaspartate (tNAA), a neuronal integrity marker, was lower in early HD (about 15 \%) versus controls (p < 0.001). N-acetylaspartate (NAA), a constituent of tNAA, was lower in pre-HD (about 8 \%) and early HD (about 17 \%) versus controls (p < 0.05). The glial cell marker, myo-inositol (mI), was 50 \% higher in early HD versus pre-HD (p < 0.01). In early HD, mI correlated with UHDRS motor score (R^2 = 0.23, p < 0.05). Across pre-HD and early HD, tNAA correlated with performance on a tongue pressure task (R^2 = 0.30, p < 0.0001) and with disease burden score (R^2 = 0.17, p < 0.005). This study demonstrated lower putaminal tNAA in early HD compared to controls in a cross-section of subjects. A novel biomarker role for mI in early HD was also identified. These findings resolve disagreement in the literature about the role of MRS as an HD biomarker. The authors concluded that putaminal MRS measurements of NAA and mI are promising potential biomarkers of HD onset and progression. Moreover, they stated that the longitudinal assessment of their cohort, and replication of this study in a second large pre-manifest and early HD cohort, ideally in the setting of a therapeutic trial, will be necessary to fully validate these findings.

Beadle and Frenneaux (2010) noted that 31-phosphorous (31P) MRS is a technique that allows the non-invasive characterization of the biochemical and metabolic state of the myocardium in vivo. Magnetic resonance spectroscopy is a pure form of molecular imaging using magnetic resonance signals from nuclei with nuclear spin to assess cardiac metabolism without the need for external radioactive tracers. (31P) MRS provides information on the underlying metabolic abnormalities that are fundamental to common conditions including ischemic heart disease, cardiomyopathy, hypertrophy and valvular disease. (31P) MRS could potentially also have a role to play in assessing response to therapy as well as the effectiveness of metabolic modulating agents. However, the use of MRS is currently limited to research due to its poor reproducibility, low spatial and temporal resolution, and long acquisition times. With technical advances in both the spectrometers and post-processing, MRS is likely to play a role
in the future of multi-modal non-invasive cardiac assessment.

Horska and Barker (2010) noted that the utility of MRS in diagnosis and evaluation of treatment response to human brain tumors has been widely documented. These researchers discussed the role of MRS in tumor classification, tumors versus non-neoplastic lesions, prediction of survival, treatment planning, monitoring of therapy, and post-therapy evaluation. They concluded that there is a need for standardization and further study in order for MRS to become widely used as a routine clinical tool.

The clinical evidence is not sufficient to permit conclusions on the health outcome effects of magnetic resonance spectroscopy in the evaluation of leukoencephalopathy. In a 2008 article, Bizzi et al reported that childhood white matter disorders often show similar MR imaging signal-intensity changes, despite different underlying pathophysiologies. The purpose of this study was to determine if proton MR spectroscopic imaging (1H-MRSI) may help identify tissue pathophysiology in patients with leukoencephalopathies. Seventy patients (mean age of 6; range, of 0.66 to 17 years) were prospectively examined by 1H-MRSI; a diagnosis of leukoencephalopathy due to known genetic defects leading to lack of formation, breakdown of myelin, or loss of white matter tissue attenuation (rarefaction) was made in 47 patients. The diagnosis remained undefined (UL) in 23 patients. Patients with definite diagnoses were assigned (on the basis of known pathophysiology) to 3 groups corresponding to hypomyelination, white matter rarefaction, and demyelination. Choline (Cho), creatine (Cr), and N-acetylaspartate (NAA) signals from 6 white matter regions and their intra- and intervoxel (relative to gray matter) ratios were measured. Analysis of variance was performed by diagnosis and by pathophysiology group. Stepwise linear discriminant analysis was performed to construct a model to predict pathophysiology on the basis of 1H-MRSI, and was applied to the UL group. Analysis of variance by diagnosis showed 3 main metabolic patterns. Analysis of variance by pathophysiology showed
significant differences for Cho/NAA (\( p < 0.001 \)), Cho/Cr (\( p < 0.004 \)), and NAA/Cr (\( p < 0.002 \)). Accuracy of the linear discriminant analysis model was 75 %, with Cho/Cr and NAA/Cr being the best parameters for classification. On the basis of the linear discriminant analysis model, 61 % of the subjects in the UL group were classified as hypomyelinating.

Baltzer and Dietzel (2013) performed a systematic review and meta-analysis to estimate the diagnostic performance of breast proton MRS in differentiating benign from malignant lesions and to identify variables that influence the accuracy of MRS. A comprehensive search of the PubMed database was performed on articles listed until January 6, 2012. The Medical Subject Headings and text words for the terms "breast," "spectroscopy," and "magnetic resonance" were used. Investigations including more than 10 patients at 1.5 T or 3.0 T applying 1D single-voxel MRS or spatially resolved MRS for differentiation between benign and malignant breast lesions were eligible. A reference standard had to be established either by means of histopathologic examination or imaging follow-up of 12 or more months. Statistical analysis included pooling of diagnostic accuracy, control for data inhomogeneity, and identification of publication bias. A total of 19 studies were used for general data pooling. The studies included a total of 1,183 patients and 1,198 lesions (773 malignant, 452 benign). Pooled sensitivity and specificity were 73 % (556 of 761; 95 % CI: 64 % to 82 %) and 88 % (386 of 439; 95 % CI: 85 % to 91 %), respectively. The pooled diagnostic odds ratio (DOR) was 34.30 (95 % CI: 16.71 to 70.43). For breast cancers versus benign lesions, the area under the symmetric summary receiver operating characteristic curve of MRS was 0.88; and the Q* index was 0.81. There was evidence of between-studies heterogeneity regarding sensitivity and DOR (\( p < 0.0001 \)). No significant influences of higher field strength, post-contrast acquisition, or qualitative versus quantitative MRS measurements were identified. Egger testing confirmed significant publication bias in studies including small numbers of patients (\( p < 0.0001 \)). The authors concluded that breast MRS showed variable sensitivity and high specificity in the
diagnosis of breast lesions, independent from the technical MRS approach. Moreover, they stated that because of significant publication bias, pooled diagnostic measures might be over-estimated.

Furthermore, an UpToDate review on “MRI of the breast and emerging technologies” (Slanetz, 2013) states that “MR spectroscopy may provide an adjunct to conventional breast MRI, with the potential to increase specificity and avoid benign biopsies in a substantial number of women. MR spectroscopy is also promising for the evaluation of non-mass like suspicious findings on breast MRI. However, MR spectroscopy misses some breast cancers, because not all express choline. In a study of 16 invasive ductal tumors; 88 percent had detectable choline peaks. MR spectroscopy remains investigational, but it may have a future role in predicting outcome and monitoring response of therapy”.

Mowatt et al (2013) evaluated the diagnostic accuracy of MRS and enhanced MRI techniques [dynamic contrast-enhanced MRI (DCE-MRI), diffusion-weighted MRI (DW-MRI)] and the clinical effectiveness and cost-effectiveness of strategies involving their use in aiding the localization of prostate abnormalities for biopsy in patients with prior negative biopsy who remain clinically suspicious for harboring malignancy. The following databases were searched -- MEDLINE (1946 to March 2012), MEDLINE In-Process & Other Non-Indexed Citations (March 2012), EMBASE (1980 to March 2012), Bioscience Information Service (BIOSIS; 1995 to March 2012), Science Citation Index (SCI; 1995 to March 2012), the Cochrane Library (Issue 3 2012), Database of Abstracts of Reviews of Effects (DARE; March 2012), Medion (March 2012) and Health Technology Assessment database (March 2012). Direct studies/randomized controlled trials reporting diagnostic outcomes. Index tests included MRS, DCE-MRI and DW-MRI. Comparators were T2-weighted MRI (T2-MRI), transrectal ultrasound-guided biopsy (TRUS/Bx). Reference standard was histopathological assessment of biopsied tissue. A Markov model was developed to assess the cost-effectiveness of
alternative MRS/MRI sequences to direct TRUS-guided biopsies compared with systematic extended-cores TRUS-guided biopsies. A health service provider perspective was adopted and the recommended 3.5 % discount rate was applied to costs and outcomes. A total of 51 studies were included. In pooled estimates, sensitivity [95 % CI] was highest for MRS (92 %; 95 % CI: 86 % to 95 %). Specificity was highest for TRUS (imaging test) (81 %; 95 % CI: 77 % to 85 %). Life-time costs ranged from £3,895 using systematic TRUS-guided biopsies to £4,056 using findings on T2-MRI or DCE-MRI to direct biopsies (60-year old cohort, cancer prevalence 24 %). The base-case incremental cost-effectiveness ratio for T2-MRI was less than £30,000 per QALY (all cohorts). Probabilistic sensitivity analysis showed high uncertainty surrounding the incremental cost-effectiveness of T2-MRI in moderate prevalence cohorts. The cost-effectiveness of MRS compared with T2-MRI and TRUS was sensitive to several key parameters. The authors concluded that MRS had higher sensitivity and specificity than T2-MRI. Relative cost-effectiveness of alternative strategies was sensitive to key parameters/assumptions. Under certain circumstances T2-MRI may be cost-effective compared with systematic TRUS. If MRS and DW-MRI can be shown to have high sensitivity for detecting moderate/high-risk cancer, while negating patients with no cancer/low-risk disease to undergo biopsy, their use could represent a cost-effective approach to diagnosis. However, owing to the relative paucity of reliable data, further studies are required. In particular, prospective studies are needed in men with suspected PC and elevated PSA levels but previously negative biopsy comparing the utility of the individual and combined components of a multi-parametric magnetic resonance (MR) approach (MRS, DCE-MRI and DW-MRI) with both a MR-guided/-directed biopsy session and an extended 14-core TRUS-guided biopsy scheme against a reference standard of histopathological assessment of biopsied tissue obtained via saturation biopsy, template biopsy or prostatectomy specimens. Non-English-language studies were excluded. Few studies reported DCE-MRI/DW-MRI. The modelling was hampered by limited data on the relative diagnostic accuracy of alternative strategies, the natural history
of cancer detected at repeat biopsy, and the impact of diagnosis and treatment on disease progression and health-related quality of life.

An UpToDate review on “Diagnosis and differential diagnosis of dermatomyositis and polymyositis in adults” (Miller, 2013) did not mention the use of MRS as a management tool.

Gardner et al (2014) stated that traditional structural neuroimaging techniques are normal in athletes who sustain sport-related concussions and are only considered to be clinically helpful in ruling out a more serious brain injury. There is a clinical need for more sophisticated, non-invasive imaging techniques capable of detecting changes in neurophysiology after injury. Concussion is associated with neuro-metabolic changes including neuronal depolarization, release of excitatory neurotransmitters, ionic shifts, changes in glucose metabolism, altered cerebral blood flow, and impaired axonal function. Proton magnetic resonance spectroscopy (1H-MRS, or simply MRS) is capable of measuring brain biochemistry and has the potential to identify and quantify physiologic changes after concussion. These investigators provided an overview of research findings using MRS in sport-related concussion. A systematic review of articles published in the English language, up to February 2013, was conducted. Articles were retrieved via the databases: PsychINFO, Medline, Embase, SportDiscus, Scopus, Web of Science, and Informit using key terms: magnetic resonance spectroscopy, nuclear magnetic resonance spectroscopy, neurospectroscopy, spectroscopy, two-dimensional nuclear magnetic resonance spectroscopy, correlation spectroscopy, J-spectroscopy, exchange spectroscopy, nuclear overhauser effect spectroscopy, NMR, MRS, COSY, EXSY, NOESY, 2D NMR, cranio-cerebral trauma, mild traumatic brain injury, mTBI, traumatic brain injury, brain concussion, concussion, brain damage, sport, athletic, and athlete. Observational, cohort, correlational, cross-sectional, and longitudinal studies were all included in the current review. The review identified 11 publications that met criteria for inclusion, comprised of data on 200 athletes and 116 controls; 9
of 11 studies reported a MRS abnormality consistent with an alteration in neurochemistry. The authors concluded that these findings support the use of MRS as a research tool for identifying altered neurophysiology and monitoring recovery in adult athletes, even beyond the resolution of post-concussive symptoms and other investigation techniques returning to normative levels. Moreover, they stated that larger cross-sectional, prospective, and longitudinal studies are needed to understand the sensitivity and prognostic value of MRS within the field of sport-related concussion.

Furthermore, the American Medical Society for Sports Medicine’s position statement on “Concussion in sport” (Harmon et al, 2013) did not mention the use of MRS as a management tool.

Ustymowicz et al (2004) reported results of a MRS study in 12 patients with neuroborreliosis. These researchers used a PRESS sequence, placing an 8 cm³ voxel in normal-appearing white matter of the frontal lobe. Peaks indicating N-acetylaspartate (NAA), choline (Cho), creatine (Cr), myo-inositol (ml), lipids (Lip) and lactate (Lac) were identified and ratios of NAA/Cr, Cho/Cr, ml/Cr, Lip/Cr, Lac/Cr calculated. Significant increases in Cho/Cr and Lip/Cr were noted. No abnormality was found in mean NAA/Cr and Lac/Cr, but in 4 patients there was a decreased NAA peak; ml/Cr ratio was slightly increased. The authors concluded that although the spectroscopic profile in patients with neuroborreliosis seems to be non-specific, MRS might be useful for assessing tissue damage of the central nervous system.

Current Lyme disease guidelines have no recommendations for use of magnetic resonance spectroscopy (Wormser, et al., 2007; Mygland, et al., 2010). UpToDate reviews on “Nervous system Lyme disease” (Halperin, 2015) and “Clinical manifestations of Lyme disease in adults” (Hu, 2015) do not mention magnetic resonance spectroscopy as a management tool.

Wang et al (2014) determined the suitability of MRS for
screening brain tumors, based on a systematic review and meta-analysis of published data on the diagnostic performance of MRS. The PubMed and PHMC databases were systematically searched for relevant studies up to December 2013. The sensitivities and specificities of MRS in individual studies were calculated and the pooled diagnostic accuracies, with 95 % CI, were assessed under a fixed-effects model. A total of 24 studies were included, comprising a total of 1,013 participants. Overall, no heterogeneity of diagnostic effects was observed between studies. The pooled sensitivity and specificity of MRS were 80.05 % (95 % CI: 75.97 % to 83.59 %) and 78.46 % (95 % CI: 73.40 % to 82.78 %), respectively. The area under the summary receiver operating characteristic curve was 0.78. Stratified meta-analysis showed higher sensitivity and specificity in child than adult; CSI had higher sensitivity and SV had higher specificity. Higher sensitivity and specificity were obtained in short TE value. The authors concluded that although the qualities of the studies included in the meta-analysis were moderate, current evidence suggests that MRS may be a valuable adjunct to MRI for diagnosing brain tumors; but requires selection of suitable technique and TE value.

The American College of Radiology’s Appropriateness Criteria® on “Dementia and movement disorders” (Wippold et al, 2014) stated that “Advanced imaging techniques such as fMRI and MRS hold exciting investigative potential for better understanding of neurodegenerative disorders, but they are not considered routine clinical practice at this time”.

The American College of Radiology’s Appropriateness Criteria® on “Head trauma” (Ryan et al, 2014) stated that “There has been increasing interest in using higher order imaging techniques, such as positron emission tomography (PET), single-photon emission computed tomography (SPECT) perfusion, functional MRI (fMRI), diffusion tensor imaging (DTI), and proton magnetic resonance spectroscopy (MRS), to assess the functional and microstructural consequences of head trauma .... Advanced imaging techniques may visualize injury
occult by standard imaging but remain relatively untested in the pediatric population with few data to support routine clinical use at this time”.

Spencer et al (2014) noted that the major excitatory neurotransmitter in the brain, glutamate plays a critical role in normal brain function; thus, its dysregulation could lead to psychopathology in youth. A growing body of literature has investigated the role of glutamate in the pathophysiology of childhood psychiatric disorders through MRS. These researchers reviewed the existing literature to gauge the specificity of such findings. PubMed was searched for all scientific, peer-reviewed articles published in English that included MRS measurements of glutamatergic metabolites in pediatric psychiatric populations through August 14, 2013. A total of 50 articles were included in this review. These studies included measurements of glutamate or related metabolites with MRS in children with psychiatric disorders. All relevant data (e.g., population; number, sex, and age of subjects; method of comparison; treatment history; MRS Tesla; brain regions of interest; glutamatergic findings; other findings; and co-morbidities) were extracted from the included articles. The direction and significance of glutamate dysregulation and brain region(s) examined were used to compare the studies. Most consistently, increases in glutamatergic metabolites were found in the anterior cingulate cortex (ACC) and other regions in youth with attention-deficit/hyperactivity disorder (ADHD). Limited data suggested increases in glutamatergic metabolites in youth with autism spectrum disorders, emotional dysregulation, and high risk for schizophrenia and decreases in youth with major depression, bipolar disorder, and obsessive-compulsive disorder. There was limited but consistent evidence for normalization of glutamatergic levels with treatment, particularly in bipolar disorder and ADHD. The authors concluded that a relatively small number of studies have examined the role of glutamatergic dysregulation in pediatric psychiatric disorders. Some consistencies can be found, but interpretation of the data is limited by differences in methodology, including age of subjects, severity of current
symptoms, treatment, and scanning parameters.

Wang et al (2015) examined the patterns of cerebral metabolite changes in several cerebral regions that are strongly associated with cognitive decline in Alzheimer's disease patients. Using Hedges' g effect size, a systematic search was performed in PubMed, Cochrane Library, Ovid, Embase, and EBSCO, and 38 studies were integrated into the final meta-analysis. According to the observational studies, N-acetyl aspartate (NAA) in Alzheimer's disease patients was significantly reduced in the posterior cingulate (PC) (effect size (ES) = -0.924, p < 0.005) and bilateral hippocampus (left hippocampus: ES = -1.329, p < 0.005; right hippocampus: ES = -1.287, p < 0.005). NAA/Cr (creatinine) ratio decreased markedly in the PC (ES = -1.052, p < 0.005). Simultaneously, significant elevated myo-inositol (mI)/Cr ratio was found not only in the PC but also in the parietal gray matter. For lack of sufficient data, these researchers failed to elucidate the effectiveness of pharmacological interventions with the metabolites changes. The authors concluded that available data indicated that NAA, mI, and the NAA/Cr ratio might be potential biomarkers of brain dysfunction in Alzheimer's disease subjects. Choline (Cho)/Cr and mI/NAA changes might also contribute toward the diagnostic process. They stated that large, well-designed studies correlated with cerebral metabolism are needed to better estimate the cerebral extent of alterations in brain metabolite levels in Alzheimer's disease patients.

**Monitoring Hepatocellular Carcinoma and Liver Cirrhosis Development:**

In a randomized trial, Wang and Li (2015) examined the utility of H-MRS to quantify the differences in liver metabolites. Magnetic resonance spectroscopy was used as a means of predicting the probability of developing hepatocellular carcinoma (HCC) in patients with liver cirrhosis secondary to chronic hepatitis B. This study included 20 healthy volunteers, 20 patients with liver cirrhosis secondary to chronic hepatitis B (cirrhosis group), and 20 patients with small HCC secondary to
cirrhosis liver parenchyma (HCC group). All patients underwent routine MRI and H-MRS scanning. LCModel software was used to quantify Cho (Choline), Lip (lipid), and Cho/Lip in the 3 groups, and a 1-way ANOVA was used to compare the differences in these metabolites between groups. Choline levels were significantly different between the control and HCC group and between the cirrhosis group and the HCC group (all p < 0.001). There was also a significant difference in Lip levels between the control and cirrhosis group and the control and HCC groups (all p < 0.001). There were also differences in Cho/Lip between the control and cirrhosis groups, the control and HCC groups, and the cirrhosis and HCC groups (all p < 0.001). The authors concluded that H-MRS followed by the analysis with LCModel can be used to measure changes in hepatic metabolite levels in patients with liver cirrhosis secondary to chronic hepatitis B and HCC. They stated that H-MRS may be helpful in monitoring HCC and liver cirrhosis development. These preliminary findings need to be validated by well-designed studies.

**Substance Use Disorders:**

Hellem et al (2015) presented a systematic review of MRS studies of substance use disorders. As a non-invasive and non-ionizing imaging technique, MRS is being widely used in substance abuse research to evaluate the effects substances of abuse have on brain chemistry. Nearly 40 peer-reviewed research articles that focused on the utility of MRS in alcohol, methamphetamine, 3,4-methylenedioxymethamphetamine, cocaine, opiates, opioids, marijuana, and nicotine use disorders were reviewed. Findings indicated inconsistencies with respect to alterations in brain chemistry within each substance of abuse, and the most consistent finding across substances was decreased N-acetylaspartate and choline levels with chronic alcohol, methamphetamine, and nicotine use. The authors concluded that variation in the brain regions studied, imaging technique, as well as small sample sizes might explain the discrepancies in findings within each substance. They stated that future well-designed MRS studies offer promise in
examining novel treatment approaches in substance use disorders.

Finnell (2015) provided clinical translation of the aforementioned systematic review by Hellem et al (2015). These investigators provided an overview of the MRS technique and neuro metabolites that are commonly studied with MRS in the human brain. The methods and results are presented for the systemic review of MRS studies among adults and focus on alcohol, methamphetamine, MDMA, cocaine, opiates/opioids, marijuana, and nicotine. A total of 36 studies were included in the review of literature. Substance-specific studies indicated inconsistencies with respect to alterations in brain chemistry. A consistent finding across substances (alcohol, methamphetamine, and nicotine) was the decrease of 2metabolites (N-acetylaspartate and choline). The authors concluded that MRS offers the possibility of identifying brain biomarkers for disease and evaluating treatment response; studies employing standardized protocols for data acquisition and reporting are needed.

Low Back Pain:

Zhao and colleagues (2016) stated that low back pain (LBP) is a highly prevalent health problem around the world, affecting 50 % to 85 % of people at some point in life. These investigators summarized the previous proton MRS studies on brain chemical changes in patients with chronic LBP (CLBP). They identified relevant studies from a literature search of PubMed and Embase from 1980 to March 2016. Data extraction was performed on the subjects' characteristics, MRS methods, spectral analyses, cerebral metabolites and perceptual measurements. The review identified 9 studies that met the inclusion criteria, comprised of data on 135 CLBP subjects and 137 healthy controls; 7 of these studies reported statistically different neurochemical alterations in patients with CLBP. The results showed that compared to controls, CLBP patients showed reductions of (i) N-acetyl-aspartate (NAA) in the dorsolateral prefrontal cortex (DLPFC), right primary motor
cortex, left somatosensory cortex (SSC), left anterior insula and anterior cingulate cortex (ACC), (ii) glutamate in the ACC, (iii) myo-inositol in the ACC and thalamus, (iv) choline in the right SSC, and (v) glucose in the DLPFC. The authors concluded that the findings of this review provided evidence for alterations in the biochemical profile of the brain in patients with CLBP, which suggests that biochemical changes may play a significant role in the development and pathophysiology of CLBP and shed light on the development of new treatments for CLBP. They stated that future studies need to emphasize therapeutic response and the relationships between brain metabolites and functions.

This study had several drawbacks: (i) there are relatively few subjects in each cohort, and confounding factors, such as anxiety and depression, made it difficult to identify specific biochemical markers of CLBP, (ii) in 8 studies, almost 50 % of the patients had received prior treatment for CLBP. Although some of the patients refrained from medications for at least 24 hours before the study, it was unclear if this eliminated the influence caused by long-term medication use, and (iii) although these MRS studies have detected neurochemical alterations in these brain regions, the underlying causes of these metabolic changes are not fully understood. Therefore, further investigation is needed to explore the pathophysiological relationship between the neurochemical alterations and CLBP.

**Juvenile Myoclonic Epilepsy:**

Zhang and co-workers (2016) performed a meta-analysis of the MRS findings regarding juvenile myoclonic epilepsy (JME). These investigators searched for studies in the PubMed, Web of Science, and Embase electronic databases; 2 authors collected articles and extracted data independently. A meta-analysis was performed for diverse metabolites in different brain areas. The mean difference (MD) and 95 % CI were used to compare continuous variables. A decreased NAA/Cr was observed in the motor cortex (MD = 0.14, 95 % CI: 0.09 to 0.20), and the NAA was reduced in the thalamus (MD = 0.74, 95 % CI: 0.37 to 1.10)
and the frontal lobe (MD = 0.87, 95 % CI: 0.45 to 1.28); the GLX/Cr was increased in the insula (MD = -0.10, 95 % CI: -0.14 to -0.06) and the striatum (MD = -0.11, 95 % CI: -0.17 to -0.05). The authors concluded that JME may be a multi-regional, thalamo-frontal network epilepsy rather than an idiopathic generalized epilepsy syndrome.

Cevik and colleagues (2016) investigated the hypothesis of biochemical changes in frontal cortex and thalamo-cortical pathways in JME and the interaction between the biochemical changes and cortical functions; MRS was applied to 20 JME patients and 20 controls for measuring NAA, N-NAA to creatine ratio (NAA/Cr), glutamine and glutamate (GLX), glutamine-glutamate to Cr (GLX/Cr), choline (Cho) containing compounds and Cho/Cr levels. Neuropsychological cognitive tests for linguistic and visual attention, linguistic and visual memory, visuospatial and executive functions were applied to all participants; NAA and NAA/Cr concentrations were found lower in bilateral frontal and thalamic regions in JME group as compared with the control group (p < 0.05). There was no difference in frontal and thalamic GLX, GLX/Cr, Cho, Cho/Cr levels in between JME patients and controls (p > 0.05). Patients with JME were found more unsuccessful than the controls in attention, memory, visuospatial function, verbal fluency, Trail B test and executive functions, Stroop test, clock drawing test and Trail A test (p < 0.05). Prefrontal NAA/Cr level was positively related to visual attention, memory, Stroop test and thalamic NAA/Cr level was positively related to linguistic memory and Wisconsin card sorting test in JME patients. The authors concluded that this research highlighted regional brain changes and cognitive decline in JME patients and suggested that MRS may be a sensitive technique for showing subclinical cognitive changes. These preliminary findings need to be validated by well-designed studies.

Radiation Encephalopathy:

In a meta-analysis, Chen and associates (2016) noted that articles in English and Chinese were selected from available
electronic databases prior to September 2014. The metabolic concentrations and patterns of NAA, Cho, Cr, NAA/Cr, NAA/Cho, and Cho/Cr ratios in radiotherapy-induced radiation encephalopathy by proton MRS were extracted. A meta-analysis was performed to quantitatively synthesize findings of these studies. Weighted mean difference (WMD) and 95 % CIs were calculated using random or fixed effective models. Heterogeneity between studies was assessed using the Cochrane Q test and I (2) statistics. The results indicated that a total of 4 researches involving 214 patients met inclusion criteria. Depending on methodologies of selected studies, control groups were referred to as healthy subjects. The combined analysis revealed that there was no significant difference in value of Cr between radiotherapy group and healthy control group (WMD = -1.483, 95 % CI: -67.185 to 64.219, p = 0.965). However, there were significant difference in values of NAA (WMD = -18.227, 95 % CI: -36.317 to -0.137, p = 0.048), Cho (WMD = 38.003, 95 % CI: 5.155 to 70.851, p = 0.023), NAA/Cr (WMD = -1.175, 95 % CI: -1.563 to -0.787, p = 0.000), NAA/Cho (WMD = -1.108, 95 % CI: -2.003 to 0.213, p = 0.015), and Cho/Cr (WMD = -0.773, 95 % CI: 0.239 to 1.307, p = 0.005). The authors concluded that MRS can be regarded as an effective and feasible imaging test for radiotherapy-induced radiation encephalopathy in patients with nasopharyngeal carcinoma. They stated that more future large-scaled studies are needed to confirm these results.

This meta-analysis had several drawbacks: (i) there was no available detailed individual data and a more precise subgroup analysis should be performed on other variables such as age, sex, and stage of the disease, (ii) the sample sizes of the 4 included studies were rather small and not adequate enough to confirmedly assess the utilities of MRS in the detection of radiation-induced brain injury at an early stage, (iii) these authors included only published studies in this study; the unpublished data or clinical trials have not been included in this analysis, (iv) due to the number limitation of the included studies, there was existence of publication bias in some comparisons, which could potentially influence the results of
this meta-analysis, and (v) there was high heterogeneity in this study.

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<th>CPT Codes / HCPCS Codes / ICD-10 Codes</th>
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**Informa'tion in the [brackets] below has been added for clari fica'tion purposes. Codes requiring a 7th character are represented by "+":**

**CPT codes not covered for indications listed in the CPB:**

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**ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):**

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<td>C79.81</td>
<td>Secondary malignant neoplasm of breast</td>
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<td>C79.82</td>
<td>Secondary malignant neoplasm of genital organs [prostate]</td>
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<td>D07.5</td>
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<td>D24.1</td>
<td>Benign neoplasm of breast</td>
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<tr>
<td>Code</td>
<td>Description</td>
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<tr>
<td>D33.0-D33.2</td>
<td>Benign neoplasm of brain</td>
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<tr>
<td>D40.0</td>
<td>Neoplasm of uncertain behavior of prostate</td>
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<td>D43.0-D43.2</td>
<td>Neoplasm of uncertain behavior of brain and spinal cord</td>
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<td>D48.60-D48.62</td>
<td>Neoplasm of uncertain behavior of breast</td>
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<td>D49.3</td>
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<td>Neoplasm of unspecified behavior of other genitourinary organs</td>
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<td>E75.00-E75.19, E75.23, E75.25, E75.29, E75.4</td>
<td>Disorders of sphingolipid metabolism and other lipid storage disorders</td>
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<td>E76.01-E76.3</td>
<td>Mucopolysaccharidosis</td>
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<tr>
<td>F01.50-F03.91</td>
<td>Dementia</td>
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<tr>
<td>F02.80-F02.81</td>
<td>Dementia in other diseases classified elsewhere with or without behavioral disturbance</td>
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<tr>
<td>F03.90-F03.91</td>
<td>Unspecified dementia, with our without behavioral disturbance</td>
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<tr>
<td>F05</td>
<td>Delirium due to known physiological condition</td>
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<tr>
<td>F10.27</td>
<td>Alcohol dependence with alcohol-induced persisting dementia</td>
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<tr>
<td>F10.97</td>
<td>Alcohol use, unspecified with alcohol-induced persisting dementia</td>
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<tr>
<td>F11.10-F16.99</td>
<td>Substance abuse disorders</td>
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<td>Codes</td>
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<td>F18.17, F18.27, F18.97, F19.17, F19.27, F19.97</td>
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<td>F20.0 - F20.9</td>
<td>Schizophrenia</td>
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<td>F30.10 - F39</td>
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<td>G13.2 - G13.8</td>
<td>Systemic atrophy primarily affecting central nervous system in diseases classified elsewhere</td>
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<td>G20 - G21.9</td>
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<td>Extrapyramidal and movement disorders</td>
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<tr>
<td>G30.0 - G31.1</td>
<td>Alzheimer's disease and other degenerative diseases of nervous system, not elsewhere classified</td>
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<td>G31.81 - G31.9</td>
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<td>Epilepsy and recurrent seizures</td>
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<td>Transient cerebral ischemic attacks and related syndromes, and cerebral artery syndrome</td>
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<td>G93.89 - G94</td>
<td>Other and unspecified disorders of the brain</td>
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<td>Cerebral infarction, occlusion and stenosis of cerebral and precerebral arteries not resulting in cerebral infarction</td>
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<td>I67.1 - I67.2</td>
<td>Cerebrovascular diseases and disorders</td>
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<td>I67.4 - I67.9</td>
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<td>K74.0 - K74.69</td>
<td>Fibrosis and cirrhosis of liver</td>
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<td>M33.00 - M33.99</td>
<td>Dermatopolymyositis</td>
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<td>S02.0xx+ - S02.92x+</td>
<td>Fracture of skull and facial bones</td>
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<td>S06.0X0+ - S06.0X9+</td>
<td>Concussion</td>
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<td>S09.8xx+ - S09.90x+</td>
<td>Specified and unspecified head injury</td>
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</table>

The above policy is based on the following references:


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Amendment to
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There are no amendments for Medicaid.