MAGNETIC RESONANCE SPECTROSCOPY (MRS)

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INSTRUCTIONS FOR USE

This protocol provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificate of Coverage (COC) or Evidence of Coverage (EOC)) may differ greatly. In the event of a conflict, the enrollee's specific benefit document supersedes this protocol. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Protocol. Other Protocols, Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Protocols, Policies and Guidelines as necessary. This protocol is provided for informational purposes. It does not constitute medical advice. This policy does not govern Medicare Group Retiree members.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

COMMERCIAL & MEDICAID COVERAGE RATIONALE

Magnetic resonance spectroscopy (MRS) is not medically necessary.

There is a lack of evidence demonstrating that the use of MRS improves health outcomes such as increasing diagnosis rates, reducing the number of unnecessary biopsies, and improving care or treatment planning accuracy in patients with conditions such as psychiatric or neurological disorders, and prostate cancer. In addition, the techniques of acquiring the MRS spectra and interpreting the results are not well standardized. Further clinical trials that include well conducted randomized controlled trials and cohort studies are necessary to demonstrate the clinical usefulness of this procedure.
MEDICARE COVERAGE RATIONALE

Medicare does not cover magnetic resonance spectroscopy (MRS); it is considered an investigational procedure. Refer to the National Coverage Determination (NCD) for Magnetic Resonance Spectroscopy (220.2.1) (accessed August 2016).

Magnetic Resonance Spectroscopy (220.2.1)
General
MRS is an application of magnetic resonance imaging (MRI). It is a non-invasive diagnostic test that uses strong magnetic fields to measure and analyze the chemical composition of human tissues. On March 22, 1994, Centers for Medicare and Medicaid Services considered MRS an investigational procedure and issued a national non-coverage determination for all indications of MRS.

Indications and Limitations of Coverage
Nationally Non-covered Indications

After thorough review and reconsideration of the existing national non-coverage determination for MRS, as well as the available evidence for the use of MRS as a diagnostic tool for distinguishing indeterminate brain lesions, and/or as an aid in conducting brain biopsies, CMS has determined that the evidence is not adequate to conclude that MRS is reasonable and necessary within the meaning of section 1862(a) (1) (A) of the Social Security Act, for use in the diagnosis of brain tumors. Therefore, CMS reaffirms its current national non-coverage determination for all indications of MRS.

For Medicare and Medicaid Determinations Related to States Outside of Nevada:
Please review Local Coverage Determinations that apply to other states outside of Nevada. http://www.cms.hhs.gov/mcd/search

Important Note: Please also review local carrier Web sites in addition to the Medicare Coverage database on the Centers for Medicare and Medicaid Services’ Website.

DESCRIPTION OF SERVICES

Magnetic resonance spectroscopy (MRS) is a noninvasive technique that is used to measure the concentrations of different metabolites within body tissue. The basic scientific principle of MRS is identical to that of magnetic resonance imaging (MRI), except that, instead of anatomical images, radiofrequency waves are translated into biochemical composition of the scanned tissue. The metabolic profile that emerges is a reflection of underlying cellular integrity, proliferation, metabolism, and indicative of pathological status. Therefore, it is thought that MRS may be useful in identifying brain tumors; specifically in differentiating neoplastic from non-neoplastic, malignant from benign, primary from metastatic, and radiation injury from recurrence, as well as locating epileptic foci and/or brain lesions and ischemic stroke. MRS may also potentially be useful in grading tumors and in guiding the biopsy to the region of greatest malignancy.

A conventional MRI is typically performed with a magnet of 1.5 tesla (T) strength. MRS is performed with a magnet of 3.0 T strength or higher. An MRI magnet with 3.0 T field strength may allow for shorter imaging times and higher signal-to-noise ratios (SNRs). The SNR is used to measure the
quality of images and evaluate the effectiveness of image enhancement and signal processing techniques.

**CLINICAL EVIDENCE**

Evidence reviewed for this policy focuses on the most commonly reported clinical applications of magnetic resonance spectroscopy (MRS). These include brain tumors, epilepsy, ischemic stroke, and prostate cancer. Almost all of the reviewed studies involved small, often heterogeneous study populations. The imaging technique varied among the studies. Most studies evaluated proton MRS (1H MRS or (1)H-MRS), as only a small number of patients have been studied using other spectroscopy modalities.

**Brain Tumors**

**MRS for Classifying Brain Tumors**

Usinskiene et al. (2016) performed a meta-analysis of advanced magnetic resonance imaging (MRI) metrics, including relative cerebral blood volume (rCBV), normalized apparent diffusion coefficient (nADC), and spectroscopy ratios choline/creatine (Cho/Cr) and choline/N-acetyl aspartate (Cho/NAA), for the differentiation of high- and low-grade gliomas (HGG, LGG) and metastases (MTS). For systematic review, 83 articles (dated 2000-2013) were selected from the NCBI database. Twenty-four, twenty-two, and eight articles were included respectively for spectroscopy, rCBV, and nADC meta-analysis. In the meta-analysis, the authors calculated overall means for rCBV, nADC, Cho/Cr (short TE-from 20 to 35 ms, medium-from 135 to 144 ms), and Cho/NAA for the HGG, LGG, and MTS groups. The authors used a random effects model to obtain weighted averages and select thresholds. LGG had significantly lower rCBV, Cho/Cr, and Cho/NAA values than HGG or MTS. No significant differences were found for nADC. The authors concluded that best differentiation between HGG and LGG is obtained from rCBV, Cho/Cr, and Cho/NAA metrics. MTS could not be reliably distinguished from HGG by the methods investigated.

Wang Q. et al. (2015) performed a meta-analysis to evaluate the diagnostic performance of magnetic resonance spectroscopy (MRS) in differentiating high-grade gliomas (HGGs) from low-grade gliomas (LGGs) preoperatively. PubMed and Embase databases were systematically searched for relevant studies of glioma grading assessed by MRS through 27 March 2015. Based on the data from eligible studies, pooled sensitivity, specificity, diagnostic odds ratio and areas under summary receiver operating characteristic curve (SROC) of different metabolite ratios were obtained. Thirty articles comprising a total sample size of 1228 patients were included in our meta-analysis. Quantitative synthesis of studies showed that the pooled sensitivity/specificity of Cho/Cr, Cho/NAA and NAA/Cr ratios was 0.75/0.60, 0.80/0.76 and 0.71/0.70, respectively. The area under the curve (AUC) of the SROC was 0.83, 0.87 and 0.78, respectively. The authors concluded that MRS demonstrated moderate diagnostic performance in distinguishing HGGs from LGGs using metabolite ratios including Cho/Cr, Cho/NAA and NAA/Cr. Although there was no significant difference in AUC between Cho/Cr and Cho/NAA groups, Cho/NAA ratio showed higher sensitivity and specificity than Cho/Cr ratio and NAA/Cr ratio. The authors suggested that MRS should combine other advanced imaging techniques to improve diagnostic accuracy in differentiating HGGs from LGGs.

Abdelaziz et al. (2016) compared the diagnostic yields of MRS and stereotactic biopsy in the characterization of brain lesions. A prospective study was conducted on 27 consecutive patients.
presenting with multifocal, diffuse, as well as deeply seated intra-axial brain lesions. All patients had both brain MRI and MRS prior to stereotactic biopsy. Histopathologic examinations of the obtained tissue specimens, using appropriate stains including immunostains, were performed. MRS diagnosed neoplastic brain lesions in 15 cases (56%) and nonneoplastic brain lesions in 12 (44%). Correlation between the preoperative diagnosis by MRS and the histopathologic diagnosis following stereotactic biopsy of either a neoplastic or nonneoplastic lesion revealed matching in 25 of 27 cases (sensitivity 88%; specificity 100%). Within the group of cases (n = 15) diagnosed preoperatively by MRS as neoplastic, 12 patients were diagnosed with brain gliomas of different grades. The MRS grading of gliomas exactly matched the histopathologic grading following stereotactic biopsy in 10 of the 12 cases (sensitivity 89%; specificity 67%). The authors concluded that MRS is a useful addition to the management armamentarium, providing molecular information that assists in the characterization of various brain lesions. According to the authors, multivoxel MRS may increase the diagnostic yield of stereotactic biopsy by guidance to target the higher choline and lower N-acetylaspartate areas, expected to have greater tumor activity. This is an uncontrolled study with a small sample size.

Guzmán-De-Villoria et al. (2014) evaluated if advanced magnetic resonance (MR) techniques, such as perfusion-weighted imaging (PWI), diffusion-weighted imaging (DWI), and magnetic resonance spectroscopy (MRS), could provide additional information to conventional MRI. The authors prospectively analyzed 129 patients diagnosed with primary brain tumors (118 gliomas) classified as low-grade in 30 cases and high-grade in 99 cases. Significant differences were obtained in high-grade tumors for conventional MRI variables such as necrosis, enhancement, edema, hemorrhage, and neovascularization. Among conventional MRI variables, the presence of enhancement and necrosis were demonstrated to be the best predictors of high grade in primary brain tumors (sensitivity 95.9%; specificity 70%). The authors concluded that MRI is highly accurate in the assessment of tumor grade. Only a slight improvement was obtained with respect to conventional MRI criteria combined with the only advanced MRI variable considered as predictive. No advanced MR variables seem to add value to conventional MRI alone in the determination of grade in gliomas.

**MRS for Discriminating Tumor Recurrence from Treatment-Related Changes**

**Systematic Reviews**

Wang X. et al. (2015) conducted a meta-analysis of 23 studies that compared the diagnostic values of fluorine-18- fluorodeoxyglucose ((18)F-FDG) and (11)C-methionine ((11)C-MET) PET (positron emission tomography) or PET/CT (computed tomography) and magnetic resonance spectroscopy (MRS) in predicting tumor recurrence of gliomas. The pooled estimated sensitivity, specificity, positive likelihood ratios, negative likelihood ratios and summary receiver operating characteristic curves of (18)F-FDG and (11)C-MET PET or PET/CT and MRS in detecting tumor recurrence were calculated. According to the authors, the meta-analysis has several potential limitations: 1) The included studies were mostly retrospective with small samples, 2) Clinical characteristics were heterogeneous among the studies, 3) Various types and grades of glioma were included in the metaanalysis, 4) The gold standard for diagnosis tumor recurrence was histopathology or radiological follow-up. Histopathological results were not obtained for all patients in some included studies, 5) The image equipment used in the included studies varied because of the extended span of time. For example, only three studies used PET/CT. Different MRS methods were also applied (three-dimensional MRS or two dimensional MRS) in the studies, and 6) Publication, selection and language biases possibly exist in this meta-analysis. Based on the current results, the authors tentatively conclude that MRS is a suitable imaging method in the detection of tumor recurrence in glioma.
because of high sensitivity. 18F-FDG PET (PET/CT) is highly specific but has low sensitivity in recurrence diagnosis. 11C-MET does not have a noticeable advantage over 18F-FDG. However, the results of the meta-analysis were drawn from studies with small samples. Future studies of other PET tracers may provide new and promising results. Using prospective designs and large-sample randomized controlled trials that study PET/CT versus MR imaging techniques to detect glioma recurrence would draw more accurate conclusions.

Chuang et al. (2016) conducted a meta-analysis that examined roles of several metabolites in differentiating recurrent tumor from necrosis in patients with brain tumors using MR perfusion and spectroscopy. Databases were searched for studies using perfusion MRI and/or MR spectroscopy 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. 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, a random-effects analysis was applied. The pooled difference in means indicated that the average rCBV in a contrast-enhancing lesion was significantly higher in tumor recurrence compared with radiation injury. Based on a fixed-effect model of analysis encompassing the six studies which used Cho/Cr ratios for evaluation, the pooled difference in means of the average Cho/Cr ratio was significantly higher in tumor recurrence than in tumor necrosis. There was significant difference in ratios of Cho to NAA between recurrent tumor and necrosis. The authors concluded that MR spectroscopy and MR perfusion 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. According to the authors, this meta-analysis had the following limitations: a limited number of studies were available for the meta-analysis, the operators/observers who evaluated rCBV and other MR spectroscopy data might not be blinded to other clinical data, the MR spectroscopy parameters used across different studies were not consistent, different studies used different cut-off values of metabolites for comparison, and delayed radiation effects can have a long latency period and may skew MR spectroscopy results.

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. Eighteen articles comprising a total sample size of 455 patients (447 lesions) with suspected glioma recurrence after radiotherapy were included in the meta-analysis. The meta-analysis indicated that using 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 state that it is strongly recommended that MRS be combined with other advanced imaging technologies to improve diagnostic accuracy. According to the authors, there are still some problems unsolved if multimodal imaging is adopted (i.e., how the relative value of each technique is determined; how the techniques are selected; and how the sequence is planned in the follow-up). The authors recommend that multimodal imaging trials and multicentre trials should be implemented in the future.

Wang et al. (2014) evaluated the suitability of magnetic resonance spectroscopy (MRS) for screening brain tumors, based on a systematic review and meta-analysis of published data on the diagnostic performance of MRS. Twenty-four studies were included in the review, comprising a total of 1013
participants. Overall, no heterogeneity of diagnostic effects was observed between studies. The pooled sensitivity and specificity of MRS were 80.05% and 78.46%, 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. Chemical shift imaging (CSI) had higher sensitivity and single voxel (SV) had higher specificity. 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 magnetic resonance imaging for diagnosing brain tumors, but requires selection of suitable technique and TE value. According to the authors, the present meta-analysis had several limitations. First, no large-scale prospective validation studies have been carried out by stereotactic biopsy. Second, the included studies did not provide sufficient information to assess the diagnostic values of other imaging techniques for comparison with multimodal imaging studies. Third, the included studies used a combination of different controls (normal, necrosis, and low-grade, respectively) as reference standards for determining diagnostic accuracy. Fourth, although the diagnostic accuracy of MRS for brain tumors was evaluated in the meta-analysis, more gliomas were included.

**Primary Studies**

This section discusses studies identified during an independent literature search that were not included the systematic reviews.

Anbarloui et al. (2015) developed an algorithm for analyzing magnetic resonance spectroscopy (MRS) findings and studied its accuracy in differentiation between radiation necrosis and tumor recurrence. Thirty-three patients with a history of intraparenchymal brain tumor resection and radiotherapy, which had developed new enhancing lesion were evaluated by MRS and subsequently underwent reoperation. Lesions with Choline (Cho)/N-acetyl aspartate (NAA) > 1.8 or Cho/Lipid > 1 were considered as tumor recurrence and the remaining as radiation necrosis. Finally, pre-operative MRS diagnoses were compared with histopathological report. The histological diagnosis was recurrence in 25 patients and necrosis in 8 patients. Mean Cho/NAA in recurrent tumors was 2.72, but it was 1.46 in radiation necrosis. Furthermore, Cho/Lipid was significantly higher in recurrent tumors with the mean of 2.78 in recurrent tumors and 0.6 in radiation necrosis. Sensitivity, specificity, and diagnostic accuracy of the algorithm for detecting tumor recurrence were 84%, 75% and 81%, respectively. The authors concluded that MRS is a safe and informative tool for differentiating between tumor recurrence and radiation necrosis. This is an uncontrolled study with a small sample size.

Lotumolo et al. (2016) compared magnetic resonance spectroscopy (MRS) and diffusion weighted imaging (DWI) in the assessment of progression and regression of brain tumors in order to assess whether there was a correlation between MRS and DWI in the monitoring of patients with primary tumors after therapy. Magnetic resonance imaging (MRI) was performed in 80 patients, 48 affected by high grade gliomas (HGG) and 32 affected by low grade gliomas (LGG). The variation of apparent diffusion coefficient (ADC) value and metabolite ratios before and after treatment was used to test DWI sequences and MRS as predictor to response to therapy. Comparison between post contrast-enhancement sequences, MRS and DWI was done in terms of accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). In the case of HGG, MRS showed better sensitivity, specificity, PPV, NPV and accuracy compared to DWI, especially when considering the Choline/N-acetylaspartate (Cho/NAA) ratio.
Regarding the LGG, the technique that better evaluates the response to treatment appears to be the DWI. A moderate correlation between ADC deviations and Cho, Lipide (Lip) and Lactate (Lac) was found in LGG; while NAA revealed to be weakly correlated to ADC variation. Considering HGG, a weak correlation was found between ADC deviations and MRS metabolites. The authors concluded that a combination of DWI and MRS can help to characterize different changes related to treatment and to evaluate brain tumor response to treatment. According to the authors, a limitation of MRS is that voxel sizes are most often restricted to at least 0.5 cm³ making the assessment of smaller lesions unreliable. The authors indicated that larger study populations are needed to further validate the study results and to define cutoff values and the optimum time for assessment of metabolic and physiological MRI variables in relation to treatment effects in gliomas.

Rao et al. (2013) evaluated the usefulness of preoperative magnetic resonance spectroscopy (MRS) in neurosurgical patients with diagnostically challenging intracranial lesions. The study included 23 consecutive patients presenting to the neurosurgery service with diagnostically challenging intracranial lesions who were investigated by conventional MR imaging and proton ((1)H) MRS, followed by surgery with subsequent histopathological diagnosis. An experienced neuroradiologist (RJ) blinded to the final histopathology evaluated the imaging studies retrospectively. Provisional diagnoses based on preoperative clinical and conventional MR data versus preoperative MRS data were compared with definitive histopathological diagnoses. Compared with preoperative clinical and conventional MR data, (1)H MRS improved the accuracy of MR imaging from 60.9% to 83%. MRS reliably distinguished between abscess and high-grade tumour, and between high-grade glioma and low-grade glioma, but was not able to reliably distinguish between recurrent glioma and radiation necrosis. In 12/23 cases (52%) the (1)H MRS findings positively altered our clinical management. The authors conclude that this study supports a beneficial role for (1)H MRS in certain diagnostic intracranial dilemmas presenting to neurosurgeons. The authors state that the information gleaned from preoperative (1)H MRS can be a useful adjunct to clinical and conventional MR imaging data in guiding the management of patients with intracranial pathologies, particularly high-grade tumour versus abscess, and high-grade versus low-grade glioma. According to the authors, further larger prospective studies are needed to clearly define the utility of (1)H MRS in diagnostically challenging intracranial lesions in neurosurgery. Study limitations include a small study population.

The goal in the study by Lin et al. (1999) was to determine if proton MRS could be incorporated into the clinical management of patients with known or suspected brain tumors, in situations in which stereotactic biopsy might otherwise be employed. Prior to each MRS examination, one of the clinical investigators would define a treatment plan that would be carried out in the absence of a diagnostic MRS study, to determine if MRS directly impacted upon and altered clinical decision-making. Proton MRS accurately predicted the pathological nature and clinical outcome of lesions in 15 of 16 regions of interest (ROIs). Interpretations directly influenced clinical decision-making in 12 patients, and altered surgery planning in 7 patients. This study was limited by the small number of patients and the vague description of controls. However, it is a pivotal study in that it clearly showed the positive impact on clinical decision-making in this patient population.

**Epilepsy**

A meta-analysis performed by Willmann et al. (2006) included 22 studies evaluating proton MRS for use in the preoperative assessment of epilepsy surgery. Only patients with intractable temporal lobe epilepsy were included in the meta-analysis. Sixty-four percent of all patients and 72% of patients with
good outcome had an ipsilateral MRS abnormality concordant with the epileptogenic zone. The positive predictive value of patients with ipsilateral MRS abnormality for good outcome was 82%. The authors concluded that MRS still remains a research tool with clinical potential. Prospective studies limited to non-localized ictal scalp EEG or MRI-negative patients are required for validation of these data.

In a case-control study, Azab et al. (2015) assessed the ability of magnetic resonance spectroscopy (MRS) to detect the lateralization side in patients with temporal lobe epilepsy (TLE) in correlation with electroencephalography (EEG) and magnetic resonance imaging (MRI) findings. The study included 40 patients diagnosed (clinically and by EEG) as having temporal lobe epilepsy (aged 8 to 14 years) and 20 healthy children with comparable age and gender as the control group. All patients were subjected to clinical examination, interictal EEG, MRI, and proton MRS. According to the findings of EEG, the patients were classified to three groups: Group 1 included 20 patients with unitemporal (lateralized) epileptic focus, group 2 included 12 patients with bitemporal (non-lateralized) epileptic focus and group 3 included 8 patients with normal EEG. MRS could lateralize the epileptic focus in 19 patients in group 1, nine patients in group 2 and five patients in group 3 with overall lateralization of (82.5%), while EEG was able to lateralize the focus in (50%) of patients and MRI detected lateralization of mesial temporal sclerosis in (57.5%) of patients. The authors concluded that MRS is a promising tool in evaluating patients with epilepsy and offers increased sensitivity to detect temporal pathology that is not obvious on structural MRI imaging. The small study population limits the validity of this conclusion.

**Stroke and Carotic Artery Occlusion**

For stroke, MRS may identify biochemical signals of ischemia such as lactate (Dani et al. 2012), but the impact of MRS on patient management has not yet been adequately examined.

Zhang et al. (2011) evaluated the value of proton MRS in patients with stenosis or occlusion of the internal carotid artery (ICA) or middle cerebral artery (MCA). Fifty noninfarcted patients with stenosis or occlusion of unilateral ICA/MCA were included in the study. Twenty-five patients with cerebral infarction and 25 healthy control subjects were also enrolled. All patients and healthy control subjects underwent proton MRS. Cerebral metabolic changes were studied in the noninfarcted patients and compared with the infarcted patients as well as healthy control subjects. In 50 noninfarcted patients N-acetylaspartate (NAA) decreased and choline increased in the ischemic hemisphere compared with the contralateral side and control subjects. The authors concluded that proton MRS can demonstrate abnormal metabolic changes in cerebral tissues with no infarction, while with ICA/MCA may show stenosis or occlusion at an early stage, which may help guide treatment decisions and preoperative evaluation. However, further research is needed to confirm how this information would be used in physician decision-making.

**Traumatic and Hypoxic Brain Injury**

For traumatic brain injury, MRS studies have detected neurochemical changes that appear to extend beyond the area of focal anatomic lesions seen on standard MRI (Johnson et al. 2012, Vagnozzi et al. 2010, Chen et al. 2012; Gardner et al. 2014; Chen et al. 2014); however, there is no conclusive data regarding its ability to improve treatment outcome.
The Department of Defense (DoD) prepared a congressional report summarizing the effectiveness of seven neuroimaging modalities (computed tomography [CT], magnetic resonance imaging [MRI], transcranial Doppler [TCD], positron emission tomography, single photon emission computed tomography, electrophysiologic techniques [magnetoencephalography and electroencephalography], and functional near-infrared spectroscopy) to assess the spectrum of traumatic brain injury (TBI) from concussion to coma. For this report, neuroimaging experts identified the most relevant peer-reviewed publications and assessed the quality of the literature for each of these imaging techniques in the clinical and research settings. Although CT, MRI, and TCD were determined to be the most useful modalities in the clinical setting, no single imaging modality proved sufficient for all patients due to the heterogeneity of TBI. All imaging modalities reviewed demonstrated the potential to emerge as part of future clinical care (Amyot et al. 2015).

Demyelination or Dysmyelination Disorder
While MRS may provide some information about the pathological changes of multiple sclerosis (Anik, 2011; Rahimian, 2013; Llufriu, 2014), there is no published research data indicating how MRS affects patient management compared to standard clinical assessment, including use of magnetic resonance imaging.

Dementia and Alzheimer’s Disease
For dementia and Alzheimer’s disease, MRS may identify biochemical signals of dementia (Warsi et al. 2012, Jessen, 2009; Garcia Santos, 2008; Tumati, 2013; Murray, 2014), but the impact of MRS on patient management has not yet been adequately examined.

Psychiatric Disorders
MRS has been used in clinical trials to examine the neurochemistry of patients with psychiatric disorders (Tibbo, 2013; Chen, 2009; Yoon, 2010; Bustillo, 2008; Chitty, 2013; Schwerk, 2014; Tükel, 2014). These studies do not address the impact of MRS on diagnostic accuracy and therapeutic decision making and often have significant design flaws including small sample sizes and retrospective design. Further clinical trials demonstrating the clinical usefulness of MRS are necessary before it can be considered proven for these conditions.

Inborn Errors of Metabolism
Although MRS has been used to characterize a variety of inborn errors of metabolism including mitochondrial, peroxisomal, lysosomal, and amino and organic acid disorders, (Scarabino et al. 2009, Tarnacka et al. 2009, Pulai et al., 2014), no studies have validated MRS findings with improved treatment outcomes. Further clinical trials demonstrating the clinical benefits of MRS are necessary before it can be considered proven for these conditions.

Prostate Cancer
In a randomized single center study, Sciarra et al. (2010) prospectively analyzed the role of magnetic resonance spectroscopy imaging (MRSI) and dynamic-contrast enhancement magnetic resonance (DCEMR) in the detection of prostate tumor foci. One hundred and eighty patients with persistently elevated prostate-specific antigen levels and prior negative random trans-rectal ultrasound (TRUS)-guided biopsy were included in the study. Patients in group A were submitted to a second random prostate biopsy; whereas patients in group B were submitted to a (1) HMRSI- DCEMR examination and samples targeted on suspicious areas were associated to the random biopsy. At the second biopsy,
a prostate adenocarcinoma histologic diagnosis was found in 22 of 90 cases (24.4%) in group A and in 41 of 90 cases (45.5%) in group B. On a patient by patient basis, MRSI had 92.3% sensitivity, 88.2% specificity, 85.7% positive predictive value (PPV), 93.7% negative predictive value (NPV), and 90% accuracy; DCEMR had 84.6% sensitivity, 82.3% specificity, 78.5% PPV, 87.5% NPV, and 83.3% accuracy; and the association MRSI plus DCEMR had 92.6% sensitivity, 88.8% specificity, 87.7% PPV, 92.7% NPV, and 90.7% accuracy, for predicting prostate cancer detection. The investigators concluded that the combination of MRSI and DCEMR showed the potential to guide biopsy to cancer foci in patients with previously negative TRUS biopsy. To avoid a potential bias, represented from having taken more samples in group B (mean of cores, 12.17) than in group A (10 cores), in the future a MRSI/DCEMR directed biopsy could be prospectively compared with a saturation biopsy procedure. This analysis was limited to the peripheral zone of the prostate as MR and MRSI evaluation are both inadequate in the differential diagnosis between adenoma (benign) and adenocarcinoma (cancer) arising from the transition region of the prostate.

In a meta-analysis, Zhang et al. (2014) assessed the diagnostic performance of magnetic resonance imaging (MRI) for targeting prostate cancer in patients with previous negative biopsies and elevated prostate-specific antigen (PSA) levels. Fourteen studies involving 698 patients met the inclusion criteria. The mean prostate cancer detection rate was 37.5%. Twelve studies had a pooled sensitivity, specificity, and diagnostic odds ratio (DOR) of 88%, 69%, and 16.84 by patient analysis, respectively. In the subgroup analysis, magnetic resonance spectroscopy imaging (MRSI) provided higher pooled sensitivity (91%) and specificity (69%) compared with T2-weighted imaging (T2WI). MRSI combined with MRI had the highest pooled specificity (73%). By site analysis, the pooled sensitivity, specificity, and DOR in nine studies were 57%, 90%, and 1.34, respectively. In the subgroup analysis, MRSI combined with MRI showed higher pooled sensitivity (58%) and specificity (93%) compared with T2WI. Diffusion-weighted MRI (DWI) showed the highest pooled specificity: 95% but the lowest pooled sensitivity: 38%. According to the authors, a limited number of studies suggest that the value of MRI to target prostate cancer in patients with previous negative biopsies and elevated PSA levels may be significant.

Umbehr et al. (2009) conducted a meta-analysis to evaluate the diagnostic accuracy of combined MRI/MRSI in prostate cancer and to explore risk profiles with highest benefit. A total of 31 test-accuracy studies (1765 patients) were identified; 16 studies (17 populations) with a total of 581 patients were suitable for meta-analysis. Nine combined MRI/MRSI studies (10 populations) examining men with pathologically confirmed prostate cancer (297 patients; 1518 specimens) had a pooled sensitivity and specificity on prostate subpart level of 68% and 85%, respectively. Compared with patients at high risk for clinically relevant cancer (six studies), sensitivity was lower in low-risk patients (four studies) (58% vs 74%); but higher for specificity (91% vs 78%). Seven studies examining patients with suspected prostate cancer at combined MRI/MRSI (284 patients) had an overall pooled sensitivity and specificity on patients level of 82% (59-94%) and 88% (80-95%). In the low-risk group (five studies) these values were 75% (39-93%) and 91% (77-97%), respectively. The investigators concluded that a limited number of small studies suggest that MRI combined with MRSI could be a rule-in test for low-risk patients. However, this finding needs further confirmation in larger studies.

In a prospective multicenter study conducted by the American College of Radiology Imaging Network (ACRIN), the incremental benefit of combined endorectal magnetic resonance (MR) imaging and MR
spectroscopic imaging, as compared with endorectal MR imaging alone was evaluated for sextant localization of peripheral zone (PZ) prostate cancer. One hundred thirty-four patients with biopsy-proved prostate adenocarcinoma and scheduled to undergo radical prostatectomy were recruited at seven institutions. Complete data were available for 110 patients. MR imaging alone and combined MR imaging-MR spectroscopic imaging had similar accuracy in PZ cancer localization. AUCs for individual readers were 0.57-0.63 for MR imaging alone and 0.54-0.61 for combined MR imaging-MR spectroscopic imaging. The investigators concluded that in patients who undergo radical prostatectomy, the accuracy of combined 1.5-T endorectal MR imaging-MR spectroscopic imaging for sextant localization of PZ prostate cancer is equal to that of MR imaging alone. The study did not confirm that the addition of MR spectroscopic imaging to MR imaging would improve tumor localization (Weinreb et al. 2009).

In a systematic review, Mowatt et al. (2013) assessed the diagnostic accuracy of magnetic resonance spectroscopy (MRS) and enhanced magnetic resonance imaging (MRI) techniques [dynamic contrast-enhanced MRI (DCE-MRI), diffusion-weighted MRI (DW-MRI)] and the clinical 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. A total of 51 studies were included in the review. In pooled estimates, sensitivity [95% confidence interval (CI)] was highest for MRS (92%; 95% CI 86% to 95%). Specificity was highest for TRUS (imaging test) (81%; 95% CI 77% to 85%). The authors concluded that MRS had higher sensitivity and specificity than T2-weighted magnetic resonance imaging (T2-MRI). The authors indicated that 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 an effective approach to diagnosis. According to the authors, further studies are required due to limited reliable data.

Lawrentschuk and Fleshner (2008) published a systematic review of prospective studies of MRS for prostate cancer. They identified 6 studies of 215 men who had MRI/MRS after a negative biopsy conducted due to elevated PSA levels. For MRI or combined MRI/MRS, the sensitivity of predicting a positive repeat biopsy was 57% to 100% and the specificity was 44% to 96%.

Umbeher et al. (2008) also published a systematic review of the accuracy of the combination of MRI/MRS in diagnosing prostate cancer. The authors identified 9 case studies of 297 men with biopsy-confirmed prostate cancer and calculated for MRI/MRS a sensitivity of 68% (95% confidence interval [CI]: 56% to 78%) and a specificity of 85% (95% CI: 78 to 90%). The authors also identified 7 diagnostic cohort studies of 284 men suspected of having prostate cancer and calculated for combined MRI/MRS a sensitivity of 82% (95% CI: 59% to 94%) and a specificity of 88% (95% CI: 80% to 95%).

Razi et al. (2015) evaluated the efficacy of magnetic resonance spectroscopy imaging (MRSI) for predicting locally advanced prostate cancer (PC). Between April 2009 and July 2012, 80 consecutive patients with clinically localized PC had undergone endorectal MRSI before radical retropubic prostatectomy. Clinicopathological parameters, including age, preoperative prostate-specific antigen (PSA), Gleason score (GS) at biopsy, perinural invasion at biopsy, prostate weight at surgery, GS of surgical specimen, and pathological staging were recorded. The MRSI findings were compared with the histopathological findings of the radical prostatectomy. The diagnostic accuracy measures
consisting of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of MRSI, and other variables in the diagnosis of locally advanced PC (Pathology Stages pT3a, pT3b, or pT4) were evaluated. Sensitivity, specificity, PPV, and NPV of MRSI in detecting locally advanced PC is 42.4%, 93.6%, 82.3%, and 69.8%. MRSI, cancer-positive core percentage at biopsy, and GS at biopsy are more accurate factors among all the predictive variables in predicting locally advanced PC. The authors concluded that MRSI may be considered as a complementary diagnostic modality with high specificity and moderate sensitivity in predicting locally advanced PC. The authors indicated that combination of this modality with other predictive factors helps the surgeon and patient to select an appropriate treatment strategy. According to the authors, this study was limited because they evaluated predicting values of the combination of conventional MRI and MRSI in detecting PC extracapsular extension (ECE), and consequently, accuracy of conventional MRI only in diagnosing ECE and the usefulness or uselessness of adding MRSI is not assessed in this study.

Villeirs et al. (2008) investigated the feasibility and diagnostic value of a whole prostate qualitative approach to combined magnetic resonance imaging and spectroscopy (MRI+MRS) in the detection of prostate cancer in patients with elevated PSA. Three hundred and fifty six subjects were examined with fast-T2-weighted images (MRI) and 3D-magnetic resonance spectroscopy (MRS). Prostate cancer was histopathologically proven in 220 patients and non-evidence of cancer was determined after at least 12 months clinical follow-up in 136 subjects. Receiver operating curve analysis revealed a significantly better diagnostic performance of MRI+MRS (A(z)=0.857) than MRI alone (A(z)=0.801) and MRS alone (A(z)=0.810). The sensitivity, specificity and accuracy of MRI+MRS for detection of prostate cancer were 72.3%, 92.6%, and 80.1%, respectively. The investigators concluded that spectral evaluation with a whole prostate qualitative approach is feasible in routine clinical practice. The combination of MRI and MRS yields superior diagnostic results than either modality alone. Further research is needed to confirm this conclusion.

According to a National Institute for Health and Care Excellence (NICE) guideline for prostate cancer, multiparametric MRI, or CT can be considered if MRI is contraindicated, for men with histologically proven prostate cancer if knowledge of the T or N stage could affect management. Multiparametric MRI can also be considered if not previously performed at enrolment for men in active surveillance. If there is concern about clinical or prostate specific antigen (PSA) changes at any time during active surveillance, reassessment with multiparametric MRI and/or rebiopsy can be considered. According to the NICE guideline, multiparametric MRI (using T2- and diffusion-weighted imaging) can be considered for men with a negative transrectal ultrasound 10─12 core biopsy to determine whether another biopsy is needed. NICE defines a multiparametric magnetic resonance imaging study as one or more sequences based on diffusion weighted imaging, dynamic contrast enhanced imaging or magnetic resonance spectroscopy.(NICE 2014).

**Other Conditions**

Chen et al. (2016) conducted a meta-analysis to evaluate the diagnostic value of magnetic resonance spectroscopy in radiation encephalopathy induced by radiotherapy for patients with nasopharyngeal carcinoma. In this study, articles in English and Chinese were selected from available electronic databases prior to September 2014. The metabolic concentrations and patterns of N-acetylaspartic acid (NAA), Choline (Cho), Creatine (Cr), NAA/Cho, NAA/Cr, and Cho/Cr ratios in radiotherapy-induced radiation encephalopathy by proton magnetic resonance spectroscopy were extracted. A meta-analysis was performed to quantitatively synthesize findings of these studies. The results indicated that a total
of 4 studies 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. The authors concluded that this meta-analysis suggests that MRS could be an effective way in detecting the radiation encephalopathy by monitoring the changes of the metabolic parameters. According to the authors, future large-scaled studies are needed to confirm these results.

Using meta-analysis, Wang H. et al. (2015) investigated the patterns of cerebral metabolite changes in several cerebral regions that are strongly associated with cognitive decline in Alzheimer's disease (AD) patients to determine if the application of non-invasive proton magnetic resonance spectroscopy (1H-MRS) could potentially identify changes. 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 AD patients was significantly reduced in the posterior cingulate (PC) (effect size (ES) and bilateral hippocampus. NAA/Cr (creatine) ratio decreased markedly in the PC. Simultaneously, significant elevated myo-inositol (mI)/Cr ratio was found not only in the PC but also in the parietal gray matter. The authors concluded that the available data indicates that NAA, mI, and the NAA/Cr ratio might be potential biomarkers of brain dysfunction in AD subjects. Choline (Cho)/Cr and mI/NAA changes might also contribute toward the diagnostic process. Thus, large, well-designed studies correlated with cerebral metabolism are needed to better estimate the cerebral extent of alterations in brain metabolite levels in AD patients.

Hellem et al. (2015) conducted a systematic review of magnetic resonance spectroscopy (MRS) studies of substance use disorders. As a noninvasive and nonionizing 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 indicate 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. Variation in the brain regions studied, imaging technique, as well as small sample sizes might explain the discrepancies in findings within each substance. According to the authors, future well-designed MRS studies offer promise in examining novel treatment approaches in substance use disorders.

MRS-detected biochemical abnormalities have been characterized for other diseases such as Parkinson’s disease (Zanigni et al., 2015; Zhou, 2014), spinocerebellar ataxia (Boesch, 2007), brain abscess (Dev et al. 1998), heart disease (Schmidt, 2006), motor neuron disease (van der Graaff et al. 2010) liver disease (Friedrich-Rush et al. 2010; Orlacchio, 2008; Hajek, 2011; Noureddin et al. 2013; Awai et al. 2014), and breast cancer (Ramazan et al., 2016; Tan et al., 2015; Cen and Xu, 2014; Baltzer et al. 2012). However, these MRS findings have not been translated into proven clinical practice demonstrating improved patient outcomes.

Wardlaw et al. (2013) systematically reviewed studies comparing diagnostic accuracy of MRI at 3 Tesla with 1.5 Tesla for brain imaging. Among 150 studies identified (4,500 subjects), most were small, compared old 1.5 T with new 3 T technology, and only 22 (15 %) described diagnostic
accuracy. Ten studies concerned tumors, 14 multiple sclerosis (MS), 4 stroke, 13 aneurysm/arteriovenous malformation (AVM)/other vascular conditions, 9 epilepsy and the rest various miscellaneous conditions. Sixty-four studies concerned structural sequences, 16 diffusion tensor MRI, 27 fMRI, 13 spectroscopy, 5 perfusion imaging, 14 MRA and 24 concerned some other form of imaging. The 3 T images were often described as "crisper", but little evidence was found of improved diagnosis. Improvements were limited to research applications [functional MRI (fMRI), spectroscopy, automated lesion detection]. For spectroscopy, signal-to-noise ratio (SNR) was clearly increased, although the 100% theoretical increase was not achieved, even in phantoms. The documented increases ranged from 23-50%. Most gain in SNR was with short echo time spectroscopy with little improvement at long echo times. Artefacts were worse and acquisitions took slightly longer at 3 T. The authors concluded that objective evidence to guide routine diagnostic use of 3 T technology is lacking.

The Canadian Agency of Drugs and Technologies in Health (CADTH) published a systematic review for 1.5 tesla magnetic resonance imaging scanners compared with 3.0 tesla magnetic resonance imaging scanners. Twenty-five studies met the inclusion criteria for the systematic review. The six neurology studies, four cerebrovascular studies, three cardiac studies, one renal study, three musculoskeletal studies, and eight oncology studies were assessed. All studies were prospective and observational, assessing between 20 patients and 65 patients who received repeat testing with 1.5 T MRI and with 3.0 T MRI within one week for acute conditions and one month for chronic conditions. None of the identified evidence assessed differences in diagnoses, patient management, and clinical outcomes between the two technologies. According to the CADTH, all of the included studies were of low quality; that is, they were highly susceptible to bias and should be interpreted cautiously. The report concluded that the evidence on clinical test parameters (for example, number of lesions) shows that 3.0 T MRI, in general, performs as well as or better than 1.5 T MRI for the studies included in the review. The CADTH states that the evidence on diagnostic and technical test parameters does not indicate whether patients will receive different clinical management or experience different health outcomes. That is, the relative clinical effectiveness of 3.0 T MRI compared with 1.5 T MRI cannot be determined (Wood, 2011).

Professional Societies
American College of Radiology (ACR)

In a practice parameter for the Performance and Interpretation of Magnetic Resonance Spectroscopy of the Central Nervous System, the ACR in collaboration with the American Society of Neuroradiology (ASNR) and the Society for Pediatric Radiology (SPR) recommends MRS as a proven and useful method for the evaluation, assessment of severity, and follow-up of diseases of the brain and other regions of the body. The guidelines, however, caution that MRS findings may be misleading and, therefore, should be interpreted by taking into consideration the results from other diagnostic studies, physical examination, clinical history, and laboratory results. According to the ACR – ASNR – SPR practice guideline (developed through consensus; not evidence-based), when conventional imaging by magnetic resonance imaging (MRI) or computed tomography (CT) is inadequate to answer specific clinical questions, indications for MRS in adults and children include, but are not limited to, the following (ACR, 2014):

1. Evidence or suspicion of primary or secondary neoplasm (pretreatment and post treatment).
2. Grading of primary glial neoplasm, particularly high grade versus low grade glioma.
3. Evidence or suspicion of brain infection, especially cerebral abscess (pretreatment and post-treatment) and HIV-related infections.
4. Seizures, especially temporal lobe epilepsy.
5. Evidence or suspicion of neurodegenerative disease, especially Alzheimer’s disease, Parkinson’s disease, and Huntington’s disease.
6. Evidence or suspicion of subclinical or clinical hepatic encephalopathy.
7. Evidence or suspicion of an inherited metabolic disorder such as Canavan’s disease, mitochondrial encephalopathies, and other leukodystrophies.
8. Suspicion of acute brain ischemia or infarction.
9. Evidence or suspicion of a demyelination or dysmyelination disorder.
10. Evidence or suspicion of traumatic brain injury.
11. Evidence or suspicion of brain developmental abnormality and cerebral palsy.
12. Evidence or suspicion of other neurodegenerative diseases such as amyotrophic lateral sclerosis.
13. Evidence or suspicion of chronic pain syndromes.
14. Evidence or suspicion of chromosomal and inherited neurocutaneous disorders such as neurofibromatosis and tuberous sclerosis.
15. Evidence or suspicion of neurotoxicity disorders.
16. Evidence or suspicion of hypoxic ischemic encephalopathy.
17. Evidence or suspicion of spinal cord disorders such as tumors, demyelination, infection, and trauma.
18. Evidence of neuropsychiatric disorders such as depression, post-traumatic stress syndrome, and schizophrenia.
19. Differentiation between recurrent tumor and treatment related changes or radiation injury.
20. Differentiation of cystic lesions, e.g., abscess versus cystic metastasis or cystic primary neoplasm.
21. Evidence or suspicion of cerebral vasculitis, systemic lupus erythematosus (SLE), and neuropsychiatric systemic lupus erythematosus (NPSLE).

According to the ACR Appropriateness Criteria for Pretreatment Detection, Staging, and Surveillance for prostate cancer, improvements in diagnostic accuracy and staging have been reported with magnetic resonance spectroscopy imaging (MRSI) for prostate cancer. However, a recent clinical trial under the auspices of the American College of Radiology Imaging Network® (ACRIN®) showed no benefit of MR spectroscopy for localizing prostate cancer over standard MRI alone (Weinreb 2009). Thus, MRSI cannot yet be considered to provide significant advantages in local staging prior to treatment (ACR, 2012).

The ACR Appropriateness Criteria for Neurology indicates the following ratings for MRS (ACR Expert Panel on Neurologic Imaging):
- The criteria for dementia and movement disorders (last review date 2015) state that advanced imaging techniques such as MRS hold exciting investigative potential for better understanding of neurodegenerative disorders, but they are not considered routine clinical practice at this time.
- The criteria for dementia and movement disorders indicate ratings of 3 or less for MRS except for suspected prion disease (Creutzfeld-Jakob, iatrogenic, or variant) which is assigned a rating of 5 for MRS.
The criteria for focal neurological deficits (last review date 2012) indicate ratings of 4 or less for MRS.

The criteria for cerebrovascular disease (last review date 2011) indicate a rating of 1 for all criteria.

The criteria for ataxia (last review date 2012) indicate ratings of 2 or less for MRS except for acute or subacute ataxia as a manifestation of suspected infection (adult or child) which is assigned a rating of 6 for MRS.

The ACR Rating Scale is as follows: 1, 2, 3 - Usually not appropriate; 4, 5, 6 - May be appropriate; 7, 8, 9 - Usually appropriate (ACR Appropriateness Criteria Rating Round Information 2015).

**American Academy of Neurology (AAN)**

The AAN guideline for Utility of MRI in Suspected Multiple Sclerosis states that new imaging technologies, such as magnetization transfer ratios (MTR), MRS, diffusion tensor imaging, tractography, and brain atrophy measurements will undoubtedly facilitate a better understanding of the extent and dynamic aspects of disease pathology in MS. Each of these new MRI techniques will need to be evaluated for sensitivity and specificity in detecting tissue injury in MS and for predicting the development of MS in the future (Frohman, 2003; reaffirmed on October 23, 2005, November 15, 2008, and July 13, 2013).

The AAN guideline Neuroimaging of the Neonate states that for diagnostic assessment, MRI should include MRS if single-voxel proton MRS is available for infants with neonatal encephalopathy (Ment, 2002).

**American Urological Association (AUA)**

In a best practice statement, the AUA states that endorectal coil MRI together with magnetic resonance spectroscopy (MRS) for characterization of cancer stage and volume is still considered an investigational procedure, but has shown promise in preliminary studies. The AUA also states that MRS allows MRI technology to identify functional and metabolic abnormality. However, imaging modalities of various types are being refined and will likely play a greater role in the routine diagnosis, staging, treatment and post-treatment evaluation of prostate cancer in the future (American Urological Association, 2013).

In 2013, the American Urological Association (AUA) and the American Society for Radiation Oncology (ASTRO) released a guideline for adjuvant and salvage radiotherapy after prostatectomy. A systematic review of the literature was conducted to identify peer-reviewed publications relevant to the use of radiotherapy after prostatectomy. The guideline did not make any recommendations regarding imaging but the authors noted that specificities for proton magnetic resonance spectroscopic imaging (1H-MRSI) were above 80% for detection of local recurrence. According to the authors, the decision regarding which imaging modality to use to determine the presence or absence of local recurrence will depend on the availability of specific modalities and on the clinician’s goals for imaging (Thompson, 2013).

**American Association of Neurological Surgeons (AANS)**

The AANS and the Congress of Neurological Surgeons released guidelines to indicate which imaging techniques (primarily magnetic imaging based and radiotracer techniques) most accurately differentiate true tumor progression from pseudo-progression or treatment related changes in patients with
previously diagnosed glioblastoma. According to the guidelines, magnetic resonance spectroscopy (MRS) is recommended as a diagnostic method to differentiate true tumor progression from treatment-related imaging changes or pseudo-progression in patients with suspected progressive glioblastoma (Level II – moderate degree of clinical certainty). According to the guidelines, the current data on the role of imaging in progressive or recurrent glioblastoma available is lacking in high levels of evidence due primarily to poor study design, heterogeneity of the patient population, and variability in practices at the time of progression and general lack of prospectively collected data with comparable groups in this challenging patient population. The authors state that a series of well-designed studies would greatly clarify the issue of the diagnostic accuracy of current and future imaging techniques in identifying progressive tumor (Ryken et al. 2014).

**National Comprehensive Cancer Network (NCCN)**

NCCN practice guidelines (2015) for central nervous system cancers states that MR spectroscopy is used to assess metabolites within brain tumors and normal tissue and may be useful in differentiating tumor from radiation necrosis in recurrent disease for anaplastic oligodendroglioma, anaplastic oligoastrocytoma, anaplastic astrocytoma, anaplastic glioma, and glioblastoma. The NCCN practice guidelines also state the MR spectroscopy may be helpful in grading brain tumors or assessing response. If clinically indicated, MR spectroscopy may also be considered when pseudo-progression of a brain tumor is suspected. The NCCN guidelines indicate that the use of MRI spectroscopy may be limited when tumors are near vessels, air spaces, or bone.

The above NCCN recommendations are based on category 2A level of evidence (lower-level evidence and NCCN consensus).

The NCCN practice guideline for prostate cancer indicates that functional imaging techniques include advanced MRI techniques such as MR spectroscopy but does not make specific recommendations regarding when MR spectroscopy should be performed (NCCN, 2016).

**U.S. FOOD AND DRUG ADMINISTRATION (FDA)**

Magnetic resonance spectroscopy (MRS) devices are regulated by the FDA as Class II devices. MRS manufacturers have gained marketing clearance for their systems under the 510(k) substantial equivalence process. The FDA has granted 510(k) marketing clearance for several 3.0 Tesla MRI scanners. However, the FDA has not yet granted marketing clearance for a system with a stronger magnet.


Use the following product codes:
- Product code LNI (system, nuclear magnetic resonance spectroscopic)
- Product code LNH (system, nuclear magnetic resonance imaging)
- Product code MOS (coil, magnetic resonance specialty)

The FDA cautions that magnetic resonance examination is contraindicated for patients who have metallic implants or electrically, magnetically or mechanically activated implants (e.g., cardiac pacemakers) because the magnetic and electromagnetic fields may produce strong attraction and/or
torque to the implant or may interfere with the operation of these devices. This applies also to patients who rely on electrically, magnetically or mechanically activated life support systems. Scanning patients with intracranial aneurysm clips is contraindicated unless the physician is certain that the clip is not magnetically active. Scanning patients with intracranial aneurysm clips is contraindicated unless the physician is certain that the clip is not magnetically active. See the following Web site for more information: [http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm135362.htm](http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm135362.htm). (Accessed August 2016)

**Additional Products**

Elscint 2T Prestige; 1.5T Infinion, 1.5T Intera; 1.5T Signa MR/i; Proton Spectroscopy Package for use with EXCELART™ with Pianissimo; Signa VH/i Magnetic Resonance System with SW version VH2; Picker MR Spectroscopy Package. Manufacturers of 3.0 T MRI scanner systems include the following: GE Healthcare, Siemens Medical Solutions USA, Inc. (Malvern, PA, USA), Philips Healthcare (Andover, MA, USA); ACS NT; Magnetom Symphony; Magnetom Vision; ProBE (Proton Brain Exam); Signa Advantage; and Signa Excite.

**APPLICABLE CODES**

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

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**REFERENCES**


Lawrentschuk, N, Fleshner, N. The role of magnetic resonance imaging in targeting prostate cancer in patients with previous negative biopsies and elevated prostate-specific antigen levels. BJU Int. 2009. Jan 14.


PROTOCOL HISTORY/REVISION INFORMATION

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The foregoing Health Plan of Nevada/Sierra Health & Life Health Operations protocol has been adopted from an existing UnitedHealthcare coverage determination guideline that was researched, developed and approved by the UnitedHealthcare Coverage Determination Committee.