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MAGNETIC RESONANCE SPECTROSCOPY (MRS)

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Instructions for Use ⓘ

Community Plan Policy
- Magnetic Resonance Spectroscopy (MRS)

COVERAGE RATIONALE

Magnetic resonance spectroscopy (MRS) is unproven and not medically necessary due to insufficient evidence of efficacy.

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.

CPT Code	Description
76390	Magnetic resonance spectroscopy

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DESCRIPTION OF SERVICES

Magnetic resonance spectroscopy (MRS), also known as nuclear magnetic resonance spectroscopy (NMRS), 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 (^{1}H MRS or (1) H-MRS), as only a small number of patients have been studied using other spectroscopy modalities.

Brain Tumors
MRS for Diagnosing and Classifying Brain Tumors

In a systematic review and meta-analysis, Wang et al. (2017) measured the diagnostic examination quality of magnetic resonance spectroscopy in differentiating high-grade gliomas from metastases. Seven studies with a total of 261 patients were included. Quantitative synthesis of studies showed that pooled sensitivity/specificity of Cho/NAA and Cho/Cr ratio in peritumoral region was 0.85/0.93 and 0.86/0.86. The area under the curve of the summary receiver-operating characteristic curve was 0.95 and 0.90. Pooled sensitivity, specificity, and area under the curve of magnetic resonance spectroscopy to identify high-grade gliomas from metastases were 0.85, 0.84, and 0.90, respectively. The authors concluded that magnetic resonance spectroscopy demonstrated moderate diagnostic performance in distinguishing high-grade gliomas from metastases. According to the authors, the conclusion is valuable only as a general guide and multicentric trials with large samples are needed to confirm the results of this study.

In a meta-analysis, Verburg et al. (2017) addressed the diagnostic accuracy of imaging to delineate diffuse glioma. The authors systematically searched studies of adults with diffuse gliomas and correlation of imaging with histopathology. Low- and high-grade gliomas were analyzed in subgroups. Sixty-one studies describing 3532 samples in 1309 patients were included. The mean Standard for Reporting of Diagnostic Accuracy score (13/25) indicated suboptimal reporting quality. For diffuse gliomas as a whole, the diagnostic accuracy was best with T2-weighted imaging, measured as area under the curve, false-positive rate, true-positive rate, and diagnostic odds ratio of 95.6%, 3.3%, 82%, and 152. For low-grade gliomas, the diagnostic accuracy of T2-weighted imaging as a reference was 89.0%, 0.4%, 44.7%, and 205; and for high-grade gliomas, with T1-weighted gadolinium-enhanced MR imaging as a reference, it was 80.7%, 16.8%, 73.3%, and 14.8. In high-grade gliomas, MR spectroscopy (85.7%, 35.0%, 85.7%, and 12.4) and 11C methionine-PET (85.1%, 38.7%, 93.7%, and 26.6) performed better than the reference imaging. According to the authors, this study was limited by the following: true-negative samples were underrepresented in the data, so false-positive rates are probably less reliable than true-positive rates; and multimodality imaging data were unavailable. The authors concluded that the diagnostic accuracy of commonly used imaging is better for delineation of low-grade gliomas than high-grade gliomas on the basis of limited evidence. The authors stated that improvement is indicated from advanced techniques, such as MR spectroscopy and PET.

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. (2016) 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.

Yang et al. (2017) performed a systematic review and meta-analysis to assess the roles of positron emission tomography (PET), magnetic resonance spectroscopy (MRS), and single photon emission computed tomography (SPECT) in distinguishing primary central nervous system lymphoma (PCNSL) from other focal brain lesions (FBLs) in human immunodeficiency virus (HIV)-infected patients. PubMed, Scopus, and Medline were systematically searched for eligible studies from 1980 to 2016. Two authors extracted characteristics of patients and their lesions using

predefined criteria. Eighteen studies on SPECT containing 667 patients, 6 studies on PET containing 108 patients, and 3 studies on MRS containing 96 patients were included. The authors concluded that SPECT has good diagnostic accuracy for discriminating PCNSL from other FBL-causing disorders in HIV patients. Of the 3 studies on MRS which contained extractable data, 2 reported only modest sensitivity and specificity in differentiating of lymphoma from other FBLs in HIV patients.

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.

Wang H. 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.

MRS for Assessing Treatment Response and Discriminating Tumor Recurrence from Treatment-Related Changes
Systematic Reviews
van Dijken et al. (2017) performed a systematic meta-analysis to assess the diagnostic accuracy of anatomical and advanced MRI for treatment response in high-grade gliomas. Databases were searched systematically. Study selection and data extraction were done by two authors independently. Meta-analysis was performed using a bivariate random effects model when ≥5 studies were included. Anatomical MRI (five studies, 166 patients) showed a pooled sensitivity and specificity of 68% and 77%, respectively. Pooled apparent diffusion coefficients (seven studies, 204 patients) demonstrated a sensitivity of 71% and specificity of 87%. DSC-perfusion (18 studies, 708 patients) sensitivity was 87% with a specificity of 86%. Dynamic contrast enhanced (DCE)-perfusion (five studies, 207 patients) sensitivity was 92% and specificity was 85%. The sensitivity of spectroscopy (nine studies, 203 patients) was 91% and specificity was 95%. The authors concluded that advanced techniques showed higher diagnostic accuracy than anatomical MRI, the highest for spectroscopy, supporting the use in treatment response assessment in high-grade gliomas. According to the authors, large multicentre longitudinal prospective trials are needed to define the optimum time for assessment

of metabolic and physiological MRI parameters using advanced techniques. These should be in relation to histopathological changes in high-grade glioma, treatment effects, and patient outcomes.

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. Several of the studies included in this meta-analysis evaluated the capacity of MRS to distinguish between glioma recurrence and radiation necrosis. 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.

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

Zhou et al. (2018) examined the diagnostic accuracy of 2HG single-voxel spectroscopy (SVS) and chemical shift imaging (CSI) in both newly-diagnosed and post-treatment settings. Long-TE (97 ms) SVS and CSI were acquired in 85 subjects, including a discovery cohort of 39 patients who had postoperative residual or recurrent glioma with

confirmed isocitrate dehydrogenase (IDH)-mutation status and 6 normal volunteers, a prospective preoperative validation cohort of 24 patients with newly-diagnosed brain mass, and a prospective recurrent-lesion validation cohort of 16 previously-treated IDH-mutant glioma patients with suspected tumor recurrence. The optimal thresholds for both methods in diagnosing IDH status were determined by receiver operating characteristic analysis in the discovery cohort, and then applied to the two validation cohorts to assess the diagnostic performance. The optimal 2HG/Cr thresholds of SVS and 75th percentile CSI for IDH mutations were 0.11 and 0.23, respectively. When applied to the validation sets, the sensitivity, specificity and accuracy in distinguishing IDH-mutant gliomas in the preoperative cohort were 85.71%, 100.00% and 94.12% for SVS, and 100.00%, 69.23% and 81.82% for CSI, respectively. In the recurrent-lesion cohort, the sensitivity, specificity and accuracy for discriminating IDH-positive recurrent gliomas were 40.00%, 62.50% and 53.85% for SVS, and 66.67%, 100.00% and 86.67% for CSI, respectively. The authors concluded that 2-hydroxyglutarate (2HG) magnetic resonance spectroscopy provides diagnostic utility for IDH-mutant gliomas both preoperatively and at time of suspected tumor recurrence. SVS has a better diagnostic performance for untreated IDH-mutant gliomas, whereas CSI demonstrates greater performance in identifying recurrent tumors. This is an uncontrolled study with a small sample size.

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 mostoften restricted to at least 0.5 cm^{3}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.

The National Comprehensive Cancer Network (NCCN) Practice Guidelines (2018) 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. This guideline also indicates that magnetic resonance imaging (MRI) is the gold standard imaging modality to make treatment decisions.

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

Epilepsy

Aitouche et al. (2017) examined the value of proton magnetic resonance spectroscopy (H-MRS) in identifying patients with insular cortex epilepsy. Patients with possible nonlesional drug-refractory insular epilepsy underwent a voxel-

based H-MRS study prior to an intracranial electroencephalographic (EEG) study. Patients were then divided into two groups based on invasive EEG findings: the insular group with evidence of insular seizures and the non-insular group with no evidence of insular seizures. Sixteen age-matched healthy controls were also scanned for normative data. Twenty-two epileptic patients were recruited, 12 with insular seizures and 10 with extra-insular seizures. Ipsilateral and contralateral insular N-acetyl-aspartate concentrations ([NAA]) and NAA/Cr ratios were found to be similar in both patient groups. No significant differences in [NAA] or NAA/Cr ratios were found between the insular group, non-insular group, and healthy controls. [NAA] and NAA/Cr asymmetry indices correctly lateralized the seizure focus in only 16.7% and 0% of patients, respectively. The authors concluded that preliminary findings suggest that H-MRS fares poorly in identifying patients with nonlesional insular epilepsy.

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
For stroke, MRS has been used as a diagnostic biomarker to identify mild cognitive impairment following stroke (Meng et al., 2016) or to identify biochemical signals of ischemia such as lactate (Xiao et al., 2016; Wang et al., 2017), but the impact of MRS on patient management has not yet been adequately examined.

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 (Studerus-Germann et al., 2016; Gardner et al., 2014; Chen et al., 2014); however, there is no conclusive data regarding its ability to improve treatment outcome.

In a systematic review and meta-analysis, Brown et al. (2018) evaluated the association between traumatic brain injury (TBI) and magnetic resonance spectroscopy (MRS) metabolite changes. Included studies reported values for both adult TBI and control subjects. Cumulative and subgroup meta-analyses were performed using a random effects model. The literature search returned an initial 898 manuscripts, of which 36 (which included 748 unique subjects) met study criteria. Cumulatively, NAA/Cr ratios in TBI patients showed a significant decrease as compared to controls. When broken into subgroups by severity, the severe and mixed TBI subgroups showed decreases, but the mild TBI (mTBI) subgroup did not. When stratified by time, a significant decrease was seen in the subacute and chronic phases but not the acute phase. Cumulative post-TBI Cho/Cr levels were increased compared to controls. Significant changes were seen in all subgroups except the mild and mixed mTBI subgroups and the acute phase subgroup. The authors concluded that current evidence shows that MRS is able to detect changes to metabolites following TBI, but not in patients with mTBI or in the acute stage. Trials with larger samples are needed to confirm the results of this study.

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 (Kauv et al., 2017; Schneider et al., 2017; Sun et al., 2017), 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 (Mullins et al., 2018; Fayed et al., 2017; Su et al., 2016; Wang H et al., 2015), 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 (Egerton et al., 2017; Reid et al., 2018; Frydman et al., 2016; Shur et al., 2016; Tükel et al., 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, (Lunsing et al., 2017; 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 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 14.34, 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 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.

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Prostate Cancer outlines different functional imaging techniques including MR spectroscopy but does not make specific recommendations regarding when it should be performed (NCCN, 2018).

Other Conditions

Parikh (2016) conducted a systematic search and review that identified 47 published studies of advanced MRI (brain morphometry, diffusion MRI, magnetic resonance spectroscopy, and functional MRI) to predict neurodevelopmental impairments (NDI). Diffusion MRI and morphometry studies were the most commonly studied modalities. Although MRS has been around the longest, only five studies investigated brain metabolites in very preterm infants. The authors concluded that despite several limitations, studies clearly showed that brain structural and metabolite biomarkers are promising independent predictors of NDI. According to the authors, large representative multicenter studies are needed to validate these studies.

Yao et al. (2017) performed a systematic review of the PubMed database for imaging studies of pituitary adenomas (PAs) since its inception. Data concerning study characteristics, clinical symptoms, imaging modalities, and diagnostic accuracy were collected. After applying exclusion criteria, 25 studies of imaging pituitary adenomas using positron emission tomography (PET), magnetic resonance spectroscopy (MRS), and single photon emission computed tomography (SPECT) were reviewed. PET reliably detects PAs, particularly where MRI is equivocal, though its efficacy is limited by high cost and low availability. SPECT possesses good sensitivity for neuroendocrine tumors but its use with PAs is poorly documented. MRS consistently detects cellular proliferation and hormonal activity but warrants further study at higher magnetic field strength. The authors concluded that PET and MRS appear to have the strongest predictive value in detecting PAs. According to the authors, MRS has the advantage of low cost, but the literature is lacking in specific studies of the pituitary. Due to high recurrence rates of functional PAs and low sensitivity of existing diagnostic workups, further investigation of metabolic imaging is necessary.

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/Cr, NAA/Cho, 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.

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.

Wardlaw et al. (2012) 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 et al., 2012).

In a clinical trial, sponsored by the American College of Radiology Imaging Network, in collaboration with the National Cancer Institute (NCI), Bolan et al. (2017) estimated the accuracy of predicting response to neoadjuvant chemotherapy (NACT) in patients with locally advanced breast cancer using MR spectroscopy (MRS) measurements made very early in treatment. This prospective Health Insurance Portability and Accountability Act (HIPAA)-compliant protocol was approved by the American College of Radiology and local-site institutional review boards. One hundred nineteen women with invasive breast cancer of ≥3 cm undergoing NACT were enrolled between September 2007 and April 2010. MRS measurements of the concentration of choline-containing compounds ([tCho]) were performed before the first chemotherapy regimen (time point 1, TP1) and 20-96 hours after the first cycle of treatment (TP2). The change in [tCho] was assessed for its ability to predict pathologic complete response (pCR) and radiologic response using the area under the receiver operating characteristic curve (AUC) and logistic regression models. Of the 119 subjects enrolled, only 29 cases (24%) with eight pCRs provided usable data for the primary analysis. Technical challenges in acquiring quantitative MRS data in a multi-site trial setting limited the capture of usable data. In this limited data set, the decrease in tCho from TP1 to TP2 had poor ability to predict either pCR or radiologic response. According to the authors, the end results showed that the technical difficulty of acquiring quantitative MRS data in a multi-site clinical trial setting led to a low yield of analyzable data, which was insufficient to accurately measure the ability of early MRS measurements to predict response to NACT.

MRS-detected biochemical abnormalities have been characterized for other diseases such as Parkinson's disease (Guan et al., 2017; Zanigni et al., 2015), liver disease (Noureddin et al., 2013; Awai et al., 2014), and breast cancer (Ramazan et al., 2016; Tan et al., 2015; Cen and Xu, 2014). However, these MRS findings have not been translated into proven clinical practice demonstrating improved patient outcomes.

According to a National Institute for Health and Care Excellence (NICE) guideline for Parkinson's disease in adults, magnetic resonance spectroscopy should not be used in the differential diagnosis of parkinsonian syndromes (NICE 2017).

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) states that MRS is 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, revised 2013, amended 2014):
- Evidence or suspicion of primary or secondary neoplasm (pretreatment and post-treatment).
- Grading of primary glial neoplasm, particularly high grade versus low grade glioma.
- Evidence or suspicion of brain infection, especially cerebral abscess (pretreatment and post-treatment) and HIV-related infections.
- Seizures, especially temporal lobe epilepsy.
- Evidence or suspicion of neurodegenerative disease, especially Alzheimer's disease, Parkinson's disease, and Huntington's disease.
- Evidence or suspicion of subclinical or clinical hepatic encephalopathy.
- Evidence or suspicion of an inherited metabolic disorder such as Canavan's disease, mitochondrial encephalopathies, and other leukodystrophies.
- Suspicion of acute brain ischemia or infarction.
- Evidence or suspicion of a demyelination or dysmyelination disorder.
- Evidence or suspicion of traumatic brain injury.
- Evidence or suspicion of brain developmental abnormality and cerebral palsy.
- Evidence or suspicion of other neurodegenerative diseases such as amyotropic lateral sclerosis.
- Evidence or suspicion of chronic pain syndromes.

- Evidence or suspicion of chromosomal and inherited neurocutaneous disorders such as neurofibromatosis and tuberous sclerosis.
- Evidence or suspicion of neurotoxicity disorders.
- Evidence or suspicion of hypoxic ischemic encephalopathy.
- Evidence or suspicion of spinal cord disorders such as tumors, demyelination, infection, and trauma.
- Evidence of neuropsychiatric disorders such as depression, post-traumatic stress syndrome, and schizophrenia.
- Differentiation between recurrent tumor and treatment related changes or radiation injury.
- Differentiation of cystic lesions, e.g., abscess versus cystic metastasis or cystic primary neoplasm.
- Evidence or suspicion of cerebral vasculitis, systemic lupus erythematosus (SLE), and neuropsychiatric systemic lupus erythematosus (NPSLE).
- Evaluation of response to treatment of neurological disorders, e.g., tumor evaluation.

The ACR Appropriateness Criteria for Neurology indicates the following ratings for MRS:
- The criteria for focal neurological deficits (last review date 2012) indicate ratings of 4 or less for MRS.
- 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, 2017).

The ACR Appropriateness Criteria for pre-irradiation evaluation and management of brain metastases (last review date 2014) does not have a rating for MRS. The summary of literature review section of the document states that small studies have suggested that other tests such as dynamic contrast-enhanced MRI, perfusion imaging, and MR spectroscopy may help differentiate between brain metastases and high-grade gliomas.

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, 2009, amended 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 et. al., 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).

Congress of Neurological Surgeons
In an evidence based guideline on preoperative imaging assessment of patients with suspected nonfunctioning pituitary adenomas, The Congress of Neurological Surgeons states that although there are promising results suggesting the utility of magnetic resonance spectroscopy, magnetic resonance perfusion, positron emission tomography, and single-photon emission computed tomography, there is insufficient evidence to make formal recommendations pertaining to their clinical applications (Chen et al., 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. Additional information is available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm.
(Accessed April 10, 2018)

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)

MRS Devices
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.

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not cover magnetic resonance spectroscopy (MRS). Refer to the National Coverage Determination (NCD) for Magnetic Resonance Spectroscopy (MRS) (220.2.1). Local Coverage Determinations (LCDs) do not exist at this time.
(Accessed April 21, 2018)

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
01/01/2019	• Simplified coverage rationale (no change to guidelines) • Archived previous policy version 2018T0063P

INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Medical Policies 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.