Cerebral Perfusion Studies

Number: 0663

Policy

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

Aetna considers cerebral computed tomography (CT) perfusion studies medically necessary as a supplement to non-contrast head CT or when magnetic resonance imaging (MRI) is unavailable or contraindicated for the emergent evaluation of acute cerebral ischemia (acute stroke) when thrombolytic therapy is being considered.

Aetna considers cerebral CT perfusion studies experimental and investigational for the following indications because there is inadequate scientific evidence to support its use for these indications (not an all-inclusive list):

- Confirmation of brain death
- Evaluation of vasospasm and delayed cerebral ischemia following aneurysmal subarachnoid hemorrhage
- Evaluation of cerebral gliomas
- Evaluation of cerebral vasospasm
- Evaluation of chronic cerebral ischemia
- Evaluation of head trauma
- Evaluation of herpes simplex virus encephalitis
- Monitoring of Moyamoya disease

Policy History

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Review History

Definitions

Additional Information

Clinical Policy Bulletin Notes
- Triaging persons with stroke for thrombolytic therapy
- Use in the balloon occlusion test
- Use in vascular neurosurgery.

Aetna considers cerebral MRI perfusion studies (diffusion-weighted or perfusion-weighted) medically necessary for the evaluation of acute cerebral ischemia.

Aetna considers cerebral MRI perfusion studies experimental and investigational for the following indications (not an all-inclusive list) because its effectiveness for these indications has not been established:

- Assessment of response to angiogenesis inhibitors in persons with glioblastomas
- Evaluation of brain arterio-venous malformations
- Evaluation of head and neck cancers
- Evaluation of gliomas/glioblastomas
- Evaluation of idiopathic normal pressure hydrocephalus
- Evaluation of persistent pain
- Evaluation of traumatic brain injury
- Differentiation of radiation-induced necrosis from recurrent brain tumor
- Prognostication of obstructive sleep apnea
- Use as a putative biomarker of Parkinson’s disease

**Background**

**Computed Tomography Perfusion Studies:**

A computed tomography (CT) scan produces cross-sectional images from X-rays processed by a computer. Each image slice corresponds to a thin section of the body that can be examined to reveal internal structures in detail. Such precision is particularly important when considering conditions involving internal tissues and organs. CT scans are useful in detecting disease in symptomatic individuals.

Computed tomography (CT) perfusion imaging provides a quantitative measurement of regional cerebral blood flow.
Cerebral perfusion analysis is used in neuroradiology to assess tissue level perfusion and delivery of blood to the brain and/or tissues of the head. A perfusion CT study involves sequential acquisition of CT sections during intravenous administration of an iodinated contrast agent. The procedure involves injecting a contrast agent into the individual. The blood carries the contrast agent to the brain and the rate at which it accumulates in the brain is detected by a CT scanner. Analysis of the results allows the physician to calculate the regional cerebral blood volume, the blood mean transit time through the cerebral capillaries, and the regional cerebral blood flow.

Currently, non-contrast computed tomography is used to detect intracerebral hemorrhage in stroke patients who are being considered for thrombolytic therapy.

Computed tomography perfusion imaging has been proposed to be used primarily as a method of evaluating patients suspected of having an acute stroke whenever thrombolysis is considered. Computed tomography perfusion imaging may provide information about the presence and site of vascular occlusion, the presence and extent of ischemia, and about tissue viability. This information may help the clinician determine whether thrombolysis is appropriate.

Potential advantages of CT perfusion imaging are that it can be performed using standard CT scanners, which are more widely available and less expensive than magnetic resonance imaging (MRI), and it is less invasive than CT angiography. Computed tomography perfusion imaging can be performed rapidly, and involves injection of a relatively small amount of contrast agent.

Current literature on CT perfusion imaging has focused on its feasibility and technical capabilities. Prospective clinical studies are needed to determine the clinical value of CT perfusion imaging over standard non-contrast computed tomography in the assessment of patients with symptoms suggestive of acute stroke, and in the triage of patients in whom thrombolytic therapy is contemplated.
The Council on Cardiovascular Radiology of the American Heart Association provided guidelines and recommendations for perfusion imaging in cerebral ischemia (Latchaw et al, 2003). It stated that quantitative CT perfusion may possibly be useful to differentiate between reversibly and irreversibly ischemic tissues in patients with acute stroke. However, large prospective and appropriately blinded studies are needed to ascertain the value of this technique. There are no data regarding the ability of this technique to predict the potential for hemorrhage following thrombolysis, as there is for the diffusible tracer techniques. Furthermore, no recommendation can be made for the use of CT perfusion in patients with chronic ischemia, vasospasm, head trauma, or as part of the balloon occlusion test, the traditional method for identifying patients at risk for stroke.

In a review on imaging viable brain tissue with CT scan during acute stroke, Meuli (2004) stated that perfusion CT is now ready to be used in clinical trials as a decision-making tool to tailor more precisely the thrombolytic therapy to the individual patient.

Ding et al (2006) simultaneously examined regional cerebral blood volume (rCBV) and permeability surfaces (rPS) in glioma patients to determine their correlation with histological grade using CT perfusion imaging. A total of 22 patients with gliomas underwent multi-slice CT perfusion imaging pre-operatively. Low-grade and high-grade groups were categorized corresponding to World Health Organization (WHO) grade II gliomas and WHO grade III or IV gliomas, respectively, as determined by histopathological examination. Regional cerebral blood volume and rPSs were obtained from regions of maximal abnormality in tumor parenchyma on CBV and PS color perfusion maps. Perfusion parameters were compared using the Kruskal-Wallis test in order to evaluate the differences in relation to tumor grade. The Pearson coefficients of rCBV and rPS for each tumor grade were assessed using SPSS 13.0 software. Regional cerebral blood volume and rPS provided significant P-value in differentiating glioma grade (low-grade
gliomas 3.28 +/- 2.01 versus 2.12 +/- 3.19 ml/100 g/min, high-grade gliomas 8.87 +/- 4.63 versus 12.11 +/- 3.18 ml/100 g/min, p < 0.05). Receiver operating characteristic (ROC) curves revealed better specificity and sensitivity in PS than in CBV for glioma grade. A significant correlation between rCBV and rPS was observed in high-grade gliomas (r = 0.684). Regional cerebral blood volume in oligodendrogliomas were higher than in other low-grade gliomas, whereas their rPS values did not show a parallel difference. The authors concluded that perfusion CT provides useful information for glioma grading and might have the potential to significantly impact clinical management and follow-up of cerebral gliomas.

Marco de Lucas et al (2006) noted that an early diagnosis is crucial in herpes simplex virus encephalitis patients in order to institute acyclovir therapy and reduce mortality rates. Magnetic resonance imaging is considered the gold standard for evaluation of these patients, but is frequently not available in the emergency setting. These investigators reported the first case of a CT perfusion study that helped to establish a prompt diagnosis revealing abnormal increase of blood flow in the affected temporo-parietal cortex at an early stage.

Sajjad (2008) noted that cerebral perfusion imaging allows blood flow to the cerebral tissue to be imaged. It has been used in the management of acute ischemic stroke. Using either CT or MRI techniques, perfusion maps can be created in a short enough time to allow their routine use in clinical practice. Perfusion imaging enables physicians to directly estimate the tissue at risk, which can be salvaged with reperfusion, enabling appropriate patient selection. However, perfusion imaging has its limitations that need to be kept in mind when these studies are interpreted. Although perfusion imaging is widely used, the evidence to support its routine use in acute stroke is somewhat sparse and therefore there are no clear cut guidelines as to its role in this context.

Parsons (2008) stated that combining perfusion CT with CT angiography (CTA) and non-contrast CT (NCCT) provides much
more information about acute stroke pathophysiology than NCCT alone. This multi-modal CT approach adds only a few minutes to the standard NCCT and is more accessible and rapidly available in most centers than MRI. Perfusion CT can distinguish between infarct core and penumbra, which is not possible with NCCT alone. A small infarct core and large penumbra, plus the presence of vessel occlusion on CTA may be an ideal imaging "target" for thrombolysis. To date, multi-modal CT has predominantly been assessed in hemispheric stroke due to its limited spatial coverage. This will become less of an issue as slice coverage continues to improve with new generation CT scanners. Apart from the concepts above, more specific perfusion CT and CTA criteria that increase (or decrease) probability of response to thrombolytic treatment are yet to be determined. Nonetheless, perfusion CT thus has the potential to improve patient selection for thrombolysis.

Provenzale et al (2008) performed a meta-analysis on perfusion imaging to determine its role in clinical decision making for patients with acute cerebral ischemia. These investigators searched Medline by using a strategy that combined terms related to perfusion imaging with terms related to acute cerebral ischemia and brain tumors. They identified 658 perfusion imaging articles and classified them according to the clinical usefulness criteria of Thornbury and Fryback; and found 59 articles with promise of indicating usefulness in clinical decision making. These researchers devised and implemented a clinical decision-making scoring scale more appropriate to the topic of acute cerebral ischemia. Several articles provided important insights into the physiological processes underlying acute cerebral ischemia by correlation of initial perfusion imaging deficits with clinical outcome or ultimate size of the infarct. However, most articles showed relatively low relevance to influencing decisions in implementing treatment. The authors concluded that most perfusion imaging articles were oriented toward important topics such as optimization of imaging parameters, determination of ischemia penumbra, and prediction of outcome. However, information as to the role of perfusion
imaging in clinical decision-making is lacking. They stated that studies are needed to demonstrate that use of perfusion imaging changes outcome of patients with acute cerebral ischemia.

Wang et al (2010) noted that CT perfusion (CTP) mapping has been reported to be useful in the differentiation of the infarct core and ischemic penumbra. However, the value of the CTP source imaging (CTP-SI) during the arterial and venous phases has not been fully investigated. These researchers developed a CTP-SI methodology for acute ischemic stroke and compared its effectiveness with cerebral blood flow (CBF) and cerebral blood volume (CBV) in predicting infarct core and penumbra. Computed tomographic examinations, including NCCT, CTP, and CTA, were performed in 42 patients with symptoms of stroke for less than 9 hours. The Alberta Stroke Program Early CT Score (ASPECTS) was analyzed on the arterial phase CTP-SI and venous phase CTP-SI and then compared with the ASPECTS on CBF and CBV for effectiveness assessment. The ASPECTS on the arterial phase CTP-SI was closely correlated with the ASPECTS on CBF, the Pearson correlation coefficient was 0.88 (p < 0.001), and the concordance correlation coefficient was 0.7603 (95 % confidence interval [CI]: 0.6331 to 0.8476). The ASPECTS on the venous phase CTP-SI revealed a significant correlation with the ASPECTS on CBV, the Pearson correlation coefficient was 0.92 (p < 0.001), and the concordance correlation coefficient was 0.8880 (95 % CI: 0.8148 to 0.9334). Significant differences were shown between the arterial phase CTP-SI/ venous phase CTP-SI (p < 0.001) and CBF/CBV (p < 0.001). The authors concluded that this study provides preliminary evidence that the arterial phase and venous phase CTP-SI mis-match model could possibly be applied to ischemic regions in the acute stage of stroke to determine penumbra and infarct core.

In a prospective, pilot series, Schichor et al (2010) analyzed the feasibility of intra-operative CTA and brain perfusion mapping using an up-to-date multi-slice CT scanner. A total of 10 patients with unruptured aneurysms underwent intra-operative scanning with a 40-slice sliding-gantry CT scanner. Multi-modal
CT acquisition was obtained in 8 patients consisting of dynamic CTP scanning followed by intra-cranial CTA. Two of these patients underwent CTA and CTP 2 times in 1 session as a control after re-positioning cerebral aneurysm clips. In another 2 patients, CTA was performed alone. The quality of all imaging obtained was assessed in a blinded consensus reading performed by an experienced neurosurgeon and an experienced neuroradiologist. A 6-point scoring system ranging from excellent to insufficient was used for quality evaluation of CTP and CTA. In 9 of 10 CTP data sets, the quality was rated excellent or good. In the remaining case, the quality was rated insufficient for diagnostic evaluation due to major streak artifacts induced by the titanium pins of the head clamp. In this particular case, the quality of the related CTA was rated good and sufficient for intra-operative decision making. The quality of all 12 CTA data sets was rated excellent or good. In 1 patient with an anterior communicating artery aneurysm, CTP scanning led to a re-positioning of the clip because of an ischemic pattern of the perfusion parameter maps due to clip stenosis of an artery. The subsequent CTP scan obtained in this patient revealed an improved perfusion of the related vascular territory, and follow-up MRI showed only minor ischemia of the anterior cerebral artery territory. The authors concluded that intra-operative CTA and CTP scanning were shown to be feasible with short acquisition time, little interference with the surgical workflow, and very good diagnostic imaging quality. Thus, these modalities might be very helpful in vascular neurosurgery. They stated that having demonstrated their feasibility, the impact of these methods on patients' outcomes has now to be analyzed prospectively in a larger series.

Silvennoinen et al (2010) stated that the routine diagnostic tool of acute ischemic stroke is NCCT. Modern multi-slice CT scanners also allow functional imaging with brain perfusion and CTA. Wider adoption of thrombolytic therapy in acute stroke have advanced their application. Computed tomography perfusion is fast and widely available. It allows verification of cerebral ischemia, and may potentially assist in determining the extent of the ischemic tissue that still is salvageable with
thrombolytic therapy. Major cerebral arteries can also be visualized to detect occlusions or stenosis, which also assists in clinical decision making. Non-contrast CT still remains the mainstay of acute stroke imaging. Furthermore, Warren et al (2010) noted that integrated stroke imaging, including demonstration of potentially salvageable tissue with either MR perfusion/diffusion studies or CT perfusion, is increasingly likely to play a central role in future management strategies and widening of the potential therapeutic window.

Lovblad and Baird (2010) noted that over the past 10 years, there has been a parallel in progress in techniques in both diagnostic and therapeutic options for acute cerebral ischemia. While previously only used for excluding hemorrhage, imaging now has the possibility to detect ischemia, vascular occlusion, and tissue at risk in one setting. It also allow clinicians to monitor treatment and predict/exclude therapeutic complications. Parallel to advances in MRI of stroke, CT has markedly improved over the past 10 years as a result of the development of faster CT scanners, which allow clinicians to acquire CTP or CTA in a reliable way. Computed tomography can detect many signs that might help clinicians detect impending signs of massive infarction, but there is still a lack of experience in the use of these techniques to guide possible therapy.

In a pilot study, Michel and colleagues (2012) examined the feasibility of a trial of perfusion computed tomography (PCT)-guided thrombolysis in patients with ischemic tissue at risk of infarction and unknown stroke onset. Patients with a supratentorial stroke of unknown onset in the middle cerebral artery territory and significant volume of at-risk tissue on PCT were randomized to intravenous thrombolysis with alteplase (0.9 mg/kg) or placebo. Feasibility endpoints were randomization and blinded treatment of patients within 2 hrs after hospital arrival, and the correct application (estimation) of the perfusion imaging criteria. At baseline, there was a trend towards older age [69.5 (57 to 78) versus 49 (44 to 78) years] in the thrombolysis group (n = 6) compared to placebo (n = 6). Regarding feasibility, hospital arrival to treatment delay was
above the allowed 2 hrs in 3 patients (25%). There were 2 protocol violations (17%) regarding PCT, both under-estimating the predicted infarct in patients randomized in the placebo group. No symptomatic hemorrhage or death occurred during the first 7 days. Three of the 4 (75%) and 1 of the 5 (20%) patients were re-canalized in the thrombolysis and placebo group respectively. The volume of non-infarcted at-risk tissue was 84 (44 to 206) cm(3) in the treatment arm and 29 (8 to 105) cm(3) in the placebo arm. The authors concluded that this pilot study shoeds that a randomized PCT-guided thrombolysis trial in patients with stroke of unknown onset may be feasible if issues such as treatment delays and reliable identification of tissue at risk of infarction tissue are resolved. Safety and efficiency of such an approach need to be established.

Recent guidelines regarding CT perfusion for evaluating acute cerebral ischemia included the following:

- The European Federation of Neurological Societies' guideline on neuroimaging in acute stroke (Masdeu et al, 2006) stated that perfusion CT is helpful when MRI is not available and for the study of stroke patients for whom MRI is contraindicated (class IV, level GCPP). Class IV: Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls). Good clinical practice point (GCPP) supported primarily by expert opinion.
- The American Heart Association, American Stroke Association Stroke Council, and Clinical Cardiology Council's guidelines for the early management of adults with ischemic stroke (Adams et al, 2007) stated multi-modal CT and MRI may provide additional information that will improve diagnosis of ischemic stroke (Class I, Level of Evidence A). Class I Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective. Level of Evidence "A" Data derived from multiple randomized clinical trials
- The American Association of Neuroscience Nurses’ guide to the care of the hospitalized patient with ischemic stroke
(2008) stated that the use of CT angiography (CTA) and CT perfusion (CTP) is growing in popularity and usefulness for acute stroke management. CTA/CTP imaging at admission assists in evaluating the cervical vessels and determining infarct localization and site of vascular occlusion. As this technology improves and is studied further, the use of CTA and CTP may increase.

- The American College of Radiology's Appropriateness Criteria on cerebrovascular disease (De La Paz et al, 2010) noted that advanced CTP methods improve sensitivity to acute ischemia and are increasingly used with CTA to evaluate acute stroke as a supplement to the non-contrast head CT.

- The Institute for Clinical Systems Improvement's guideline on the diagnosis and treatment of ischemic stroke (2010) stated that although ischemic brain swelling typically peaks between 3 and 5 days after stroke onset, marked early swelling (in the first 24 to 48 hours) causing mass effect and tissue shift can occur in the most severe cases ("malignant" ischemic brain edema). Low attenuation changes exceeding 2/3 of the middle cerebral artery territory and large areas of hypoperfusion on perfusion scans (CT perfusion or MRI perfusion) on initial radiological evaluation are associated with high risk of developing malignant brain edema. Patients with these features should be strictly monitored with serial neurological examinations, ideally in a stroke unit. Repeating CT scan of the brain to evaluate for progression of regional mass effect is indicated if the patient develops any signs of neurological deterioration. The value of serial CT scans of the brain in the absence of clinical changes remains to be established.

Shibamoto et al (2012) reported the case of a 31-year old male presenting with intra-cranial hemorrhage manifesting as deep coma and anisocoria underwent immediate emergency surgery. Three-dimensional computed tomography (CT) angiography revealed stenosis of the right middle cerebral artery (MCA) and perfusion CT immediately after the surgery suggested severe hypo-perfusion in the right MCA territory.
Post-operative angiography demonstrated right unilateral moyamoya disease. These researchers predicted that brain edema and intra-cranial pressure (ICP) elevation occurring after the hemorrhage might result in cerebral infarction. Hyper-osmotic drugs were contraindicated by dehydration. Therefore, therapeutic hypothermia was induced that controlled the ICP. These researchers considered that the increased ICP, dehydration, vasospasm, and shrinkage of the ruptured vessel comprised the pathogenesis of acute cerebral ischemia after intra-cranial bleeding. They stated that cerebral hemodynamics should be evaluated during the acute phase of cerebral hemorrhage to prevent subsequent cerebral infarction.

Furthermore, an UpToDate review on “Moyamoya disease: Prognosis and treatment” (Suwanwela, 2013) stated that “Preoperative cerebral angiography with bilateral injections of the internal and external carotid arteries and vertebral arteries is generally recommended to evaluate the sites of occlusion and collateral circulation and to identify donor vessels. Cerebral perfusion and autoregulation studies using xenon CT, perfusion CT, and/or perfusion MRI, with or without acetazolamide, may also be helpful in evaluating cerebrovascular reserve".

While CT perfusion may be useful for the evaluation of moyamoya disease patients who present with acute cerebral ischemic attacks, there is inadequate evidence to support CT perfusion for monitoring of the disease.

Cremers and colleagues (2014) stated that delayed cerebral ischemia (DCI) is at presentation a diagnosis per exclusion, and can only be confirmed with follow-up imaging. For treatment of DCI, a diagnostic tool is needed. These researchers performed a systematic review to evaluate the value of CTP in the prediction and diagnosis of DCI. They searched PubMed, Embase, and Cochrane databases to identify studies on the relationship between CTP and DCI. A total of 11 studies (570 patients) were included. On admission, CBF, CBV, MTT, and TTP did not differ between patients who did and did not develop DCI. In the DCI
time-window (4 to 14 days after SAH), DCI was associated with a decreased CBF (pooled mean difference -11.9 ml/100 g per minute (95% CI: -15.2 to -8.6)) and an increased MTT (pooled mean difference 1.5 seconds (0.9 to 2.2)). Cerebral blood volume did not differ and TTP was rarely reported. Perfusion thresholds reported in studies were comparable, although the corresponding test characteristics were moderate and differed between studies. The authors concluded that CTP can be used in the diagnosis but not in the prediction of DCI. They stated that there is a need to standardize the method for measuring perfusion with CTP after SAH, and optimize and validate perfusion thresholds.

Mir and associates (2014) stated that DCI is a significant cause of morbidity and mortality after aneurysmal SAH, leading to poor outcomes. These investigators evaluated the usefulness of CTP in determining DCI in patients with aneurysmal SAH. They conducted a systematic review evaluating studies that assessed CTP in patients with aneurysmal SAH for determining DCI. Studies using any of the following definitions of DCI were included in the systematic review: (i) new onset of clinical deterioration, (ii) cerebral infarction identified on follow-up CT or MRI, and (iii) functional disability. A random-effects meta-analysis was performed assessing the strength of association between a positive CTP result and DCI. The systematic review identified 218 studies that met the screening criteria, of which 6 cohort studies met the inclusion criteria. These studies encompassed a total of 345 patients, with 155 (45%) of 345 patients classified as having DCI and 190 (55%) of 345 patients as not having DCI. Admission disease severity was comparable across all groups. Four cohort studies reported CTP test characteristics amenable to the meta-analysis. The weighted averages and ranges of the pooled sensitivity and specificity of CTP in the determination of DCI were 0.84 (0.7 to 0.95) and 0.77 (0.66 to 0.82), respectively. The pooled odds ratio of 23.14 (95% CI: 5.87 to 91.19) indicated that patients with aneurysmal SAH with positive CTP test results were approximately 23 times more likely to experience DCI compared with patients with negative CTP test results. The authors
concluded that perfusion deficits on CTP are a significant finding in determining DCI in aneurysmal SAH. They noted that this may be helpful in identifying patients with DCI before development of infarction and neurologic deficits.

Rawal et al (2015) stated that DCI is a serious complication after aneurysmal SAH. If DCI is suspected clinically, imaging methods designed to detect angiographic vasospasm or regional hypoperfusion are often used before instituting therapy. Uncertainty in the strength of the relationship between imaged vasospasm or perfusion deficits and DCI-related outcomes raises the question of whether imaging to select patients for therapy improves outcomes in clinical DCI. These researchers performed a decision analysis using Markov models. Strategies were either to treat all patients immediately or to first undergo diagnostic testing by digital subtraction angiography or CTA to assess for angiographic vasospasm, or CTP to assess for perfusion deficits. According to current practice guidelines, treatment consisted of induced hypertension. Outcomes were survival in terms of life-years and quality-adjusted life-years. When treatment was assumed to be ineffective in non-vasospasm patients, treat all and digital subtraction angiography were equivalent strategies; when a moderate treatment effect was assumed in non-vasospasm patients, treat all became the superior strategy. Treating all patients was also superior to selecting patients for treatment via CTP. One-way sensitivity analyses demonstrated that the models were robust; 2- and 3-way sensitivity analyses with variation of disease and treatment parameters reinforced dominance of the treat all strategy. The authors concluded that imaging studies to test for the presence of angiographic vasospasm or perfusion deficits in patients with clinical DCI do not seem helpful in selecting which patients should undergo treatment and may not improve outcomes. They stated that future directions include validating these results in prospective cohort studies.

Furthermore, an UpToDate review on “Etiology, clinical manifestations, and diagnosis of aneurysmal subarachnoid hemorrhage” (Singer et al, 2015) does not mention CT
perfusion as a diagnostic tool.

**Confirmation of Brain Death:**

Brasil et al (2016) noted that several complications make the diagnosis of brain death (BD) medically challenging and a complimentary method is needed for confirmation. In this context, CTA and CTP could represent valuable alternatives; however, the reliability of CTA and CTP for confirming brain circulatory arrest remains unclear. These investigators performed a systematic review to identify relevant studies regarding the use of CTA and CTP as ancillary tests for BD confirmation. A total of 322 patients were eligible for the meta-analysis, which exhibited 87.5% sensitivity; CTA image evaluation protocol exhibited variations between medical institutions regarding which intra-cranial vessels should be considered to determine positive or negative test results. The authors concluded that for patients who were previously diagnosed with BD according to clinical criteria, CTA demonstrated high sensitivity to provide radiologic confirmation.

An UpToDate review on “Diagnosis of brain death” (Young, 2016) states that “The clinical utility of computed tomographic angiography (CTA) and computed tomographic perfusion in the evaluation of brain death is uncertain. These tests are somewhat more invasive than MRA, in that contrast injection is required. Case reports document findings of absent cerebral circulation perfusion on CTA in patients with brain death. However, systematic reviews of studies comparing CTA to an alternative brain death determination have concluded that the reported sensitivities are variable and appear low overall (ranging from 62 to 99%). The highest sensitivity was achieved when the absence of opacification of the internal cerebral veins was used as a criterion. The absence of studies examining CTA findings in patients who are comatose but not brain dead preclude an assessment of this test’s specificity”.

**Magnetic Resonance Imaging Perfusion Studies:**
Stroke is one of the most common causes of permanent disability and/or death in the Western world. The majority of strokes is caused by acute ischemia as a consequence of occlusion of the cerebral artery by a clot. The minority of strokes is related to intra-cerebral hemorrhage or other sources. Transient ischemic attack (TIA) is defined as symptom duration of less than 24 hrs. Time from onset of symptoms to treatment is considered to be the key variable that influences the indication of re-canalization therapy for treatment of acute brain infarction. Early reperfusion has been reported to improve clinical outcomes, yet the majority of patients with acute stroke do not attend in time for thrombolysis, which is the only approved treatment. To extend the time window for thrombolysis, several imaging parameters in computed tomography and magnetic resonance imaging (MRI) have been investigated. In particular, multi-modal neuroimaging is increasingly employed in the initial evaluation and management of acute stroke patients in parallel with the expansion of therapeutic options. Multi-modal MRI can identify the type of stroke (ischemia or hemorrhage), severity and location of the lesion, the patency of the intra-cranial vessels, the degree of cerebral perfusion, as well as the presence and size of the ischemic penumbra (tissue). This information can be used to guide both acute and long-term treatment decisions for stroke patients (Kloska et al, 2010; Warren et al, 2010; Burgess and Kidwell, 2011; Olivot and Albers, 2011).

Olivot and Albers (2011) noted that preliminary studies suggested that stroke victims with a significant penumbra estimated by the diffusion/perfusion mismatch on MRI benefit from thrombolysis beyond the currently recommended time window of 4.5 hrs. New software programs can automatically produce reliable perfusion and diffusion maps for use in clinical practice. Combined diffusion and perfusion MRI reveals an acute ischemic lesion in about 60% of TIA patients. Patients with transient symptoms and a restricted diffusion lesion on MRI are considered by the American Heart Association (AHA) scientific committee to have suffered a brain infarction and have a very high risk of early stroke recurrence. The authors
concluded multi-modal MRI provides critical real-time information about ongoing tissue injury as well as the risk of additional ischemic damage. It is becoming an essential tool for the diagnosis, management and triage of acute TIA and brain infarction (Olivot and Albers, 2011).

Straka et al (2010) noted that diffusion-perfusion mismatch can be used to identify acute stroke patients that could benefit from re-perfusion therapies. Early assessment of the mismatch facilitates necessary diagnosis and treatment decisions in acute stroke. These researchers developed the RApid processing of Perfusion and Diffusion (RAPID) for unsupervised, fully automated processing of perfusion and diffusion data for the purpose of expedited routine clinical assessment. The RAPID system computes quantitative perfusion maps (CBV, CBF, mean transit time [MTT], and the time until the residue function reaches its peak [T(max)]) using deconvolution of tissue and arterial signals. Diffusion-weighted imaging/perfusion-weighted imaging (DWI/PWI) mismatch is automatically determined using infarct core segmentation of ADC maps and perfusion deficits segmented from T(max) maps. The performance of RAPID was evaluated on 63 acute stroke cases, in which diffusion and perfusion lesion volumes were outlined by both a human reader and the RAPID system. The correlation of outlined lesion volumes obtained from both methods was r(2) = 0.99 for DWI and r(2) = 0.96 for PWI. For mismatch identification, RAPID showed 100 % sensitivity and 91 % specificity. The mismatch information is made available on the hospital's PACS within 5 to 7 mins. Results indicate that the automated system is sufficiently accurate and fast enough to be used for routine care as well as in clinical trials.

Kim et al (2010) developed fully automated software for dynamic susceptibility contrast (DSC) MR PWI to efficiently and reliably derive critical hemodynamic information for acute stroke treatment decisions. Brain MR PWI was performed in 80 consecutive patients with acute non-lacunar ischemic stroke within 24 hrs after onset of symptom. These studies were automatically processed to generate hemodynamic parameters
that included CBF and CBV, and MTT. To develop reliable software for PWI analysis, these investigators used computationally robust algorithms including the piecewise continuous regression method to determine bolus arrival time (BAT), log-linear curve fitting, arrival time independent deconvolution method as well as sophisticated motion correction methods. An optimal arterial input function (AIF) search algorithm using a new artery-likelihood metric was also developed. Anatomical locations of the automatically determined AIF were reviewed and validated. The automatically computed BAT values were statistically compared with estimated BAT by a single observer. In addition, gamma-variate curve-fitting errors of AIF and inter-subject variability of AIFs were analyzed. Lastly, 2 observers independently assessed the quality and area of hypo-perfusion mismatched with restricted diffusion area from motion corrected MTT maps and compared that with time-to-peak (TTP) maps using the standard approach. The AIF was identified within an arterial branch and enhanced areas of perfusion deficit were visualized in all evaluated cases. Total processing time was 10.9 +/- 2.5 s (mean +/- S.D.) without motion correction and 267 +/- 80 s (mean +/- S.D.) with motion correction on a standard personal computer. The MTT map produced with the authors' software adequately estimated brain areas with perfusion deficit and was significantly less affected by random noise of the PWI when compared with the TTP map. Results of image quality assessment by 2 observers revealed that the MTT maps exhibited superior quality over the TTP maps (88 % good rating of MTT as compared to 68 % of TTP). The authors' software allowed fully automated de-convolution analysis of DSC PWI using proven efficient algorithms that can be applied to acute stroke treatment decisions.

Recent guidelines regarding MRI perfusion for evaluating acute cerebral ischemia included the following:

- The European Federation of Neurological Societies' guideline on neuroimaging in acute stroke (Masdeu et al, 2006) stated that MR PWI and MR DWI are very helpful for the evaluation
of patients with acute ischemic stroke (class I, level A). The

- American Heart Association, American Stroke
  Association Stroke Council, and Clinical Cardiology Council's
  guidelines for the early management of adults with ischemic
  stroke (Adams et al, 2007) stated that multi-modal MRI may
  provide additional information that will improve diagnosis of
  ischemic stroke (Class I, Level of Evidence A).

- The American College of Radiology's Appropriateness
  Criteria on cerebrovascular disease (De La Paz et al, 2010)
  noted that MR DWI are highly sensitive and specific for
  acute cerebral ischemia and, when combined with MR PWI,
  may be used to identify potentially salvageable ischemic
  tissue, especially in the period greater than 3 hours after
  symptom onset.

- The Institute for Clinical Systems Improvement (ICSI)'s
  guideline on the diagnosis and treatment of ischemic stroke
  (ICSI, 2010) reported that MRI scans of the brain with
  diffusion- and susceptibility-weighted sequences are much
  more sensitive than CT in detecting new infarction and
  chronic hemorrhage as well as of equal sensitivity for acute
  hemorrhage. If the patient is not having symptoms at the
  time of presentation, a MR DWI is preferred because
  diffusion-weighted sequences may identify patients at
  particularly high risk of early major recurrence.

- On behalf of the Therapeutics and Technology Assessment
  Subcommittee of the American Academy of Neurology
  (AAN), Schellinger et al (2010) evaluated the evidence for
  the use of MR DWI and MR PWI in the diagnosis of patients
  with acute ischemic stroke. These investigators
  systematically analyzed the literature from 1966 to January
  2008 to address the diagnostic and prognostic value of DWI
  and PWI. Diffusion-weighted MRI is established as useful
  and should be considered more useful than non-contrast CT
  for the diagnosis of acute ischemic stroke within 12 hours of
  symptom onset. Diffusion-weighted MRI should be
  performed for the most accurate diagnosis of acute ischemic
  stroke (Level A); however, the sensitivity of MR DWI for the
  diagnosis of ischemic stroke in a general sample of patients
  with possible acute stroke is not perfect. On the basis of
Class II and III evidence, baseline MR DWI volumes probably predict baseline stroke severity in anterior territory stroke (Level B) but possibly do not in vertebro-basilar artery territory stroke (Level C). Baseline MR DWI lesion volumes probably predict (final) infarct volumes (Level B) and possibly predict early and late clinical outcome measures (Level C). Baseline MR PWI volumes predict to a lesser degree the baseline stroke severity compared with DWI (Level C). There is insufficient evidence to support or refute the value of MR PWI in diagnosing acute ischemic stroke.

Howard et al (2011) stated that development of treatments for acute and chronic pain conditions remains a challenge, with an unmet need for improved sensitivity and reproducibility in measuring pain in patients. These investigators used pulsed-continuous arterial spin-labeling (pCASL), a relatively novel perfusion MRI technique, in conjunction with a commonly-used post-surgical model, to measure changes in regional cerebral blood flow [rCBF] associated with the experience of being in ongoing pain. They demonstrated repeatable, reproducible assessment of ongoing pain that is independent of patient self-report. In a cross-over trial design, 16 participants requiring bilateral removal of lower-jaw 3rd molars underwent pain-free pre-surgical pCASL scans. Following extraction of either left or right tooth, repeat scans were acquired during post-operative ongoing pain. When pain-free following surgical recovery, the pre/post-surgical scanning procedure was repeated for the remaining tooth. Voxel-wise statistical comparison of pre and post-surgical scans was performed to reveal rCBF changes representing ongoing pain. In addition, rCBF values in pre-defined pain and control brain regions were obtained. Regional CBF increases (5 to 10 %) representing post-surgical ongoing pain were identified bilaterally in a network including primary and secondary somatosensory, insula and cingulate cortices, thalamus, amygdala, hippocampus, midbrain and brainstem (including trigeminal ganglion and principal-sensory nucleus), but not in a control region in visual cortex. Regional CBF changes were reproducible, with no rCBF differences identified across scans.
within-session or between post-surgical pain sessions. This was the first report of the cerebral representation of ongoing post-surgical pain without the need for exogenous tracers. Regions of rCBF increases are plausibly associated with pain and the technique is reproducible, providing an attractive proposition for testing interventions for on-going pain that do not rely solely on patient self-report. The authors concluded that these findings have the potential to improve the understanding of the cerebral representation of persistent painful conditions, leading to improved identification of specific patient sub-types and implementation of mechanism-based treatments.

Howard et al (2012) determined rCBF changes representing ongoing pain experienced by patients with painful osteoarthritis (OA) of the carpometacarpal (CMC) joint and examined rCBF variability across sessions. These researchers used pCASL, a perfusion MRI technique. The study included 16 patients with CMC OA and 17 matched controls. Two pCASL scans and numerical rating scale (NRS) estimates of ongoing pain were acquired in each of 2 identical sessions. Voxel-wise general linear model analyses were performed to determine rCBF differences between OA and control groups, rCBF differences between sessions within each group, and whether session-wise rCBF differences were related to variability in perceived ongoing pain. In the OA group, rCBF increases representing ongoing pain were identified in the primary and secondary somatosensory, insula, and cingulate cortices; thalamus; amygdala; hippocampus; and dorsal midbrain/pontine tegmentum, including the peri-aqueductal gray/nucleus cuneiformis. Session-wise rCBF differences in the OA group in the post-central, rostral/subgenual cingulate, mid/anterior insula, prefrontal, and premotor cortices were related to changes in perceived ongoing pain. No significant session-wise rCBF differences were observed in controls. The authors concluded that this was the first quantitative endogenous perfusion MRI study of the cerebral representation of ongoing, persistent pain due to OA. Observed rCBF changes potentially indicate dysregulated central nervous system
appraisal and modulation of pain, most likely the maladaptive neuroplastic sequelae of living with painful OA. Moreover, the clinical value of cerebral MRI perfusion studies for evaluating persistent pain has yet to be established.

Liu and colleagues (2013) examined the effects of post-herpetic neuralgia (PHN) on resting-state brain activity utilizing ASL techniques. Features of static and dynamic CBF were analyzed to reflect the specific brain response to PHN pain. A total of 11 consecutive patients suffering from PHN and 11 age- and gender-matched control subjects underwent perfusion functional MRI brain scanning during the resting state. Group comparison was conducted to detect the regions with significant changes of CBF in PHN patients. Then these investigators chose those regions that were highly correlated with the self-reported pain intensity as "seeds" to calculate the functional connectivity of both groups. Absolute CBF values of these regions were also compared across PHN patients and control subjects. Significant increases in CBF of the patient group were observed in left striatum, right thalamus, left primary somatosensory cortex (S1), left insula, left amygdala, left primary somatomotor cortex, and left inferior parietal lobule. Significant decreases in CBF were mainly located in the frontal cortex. Regional CBF in the left caudate, left insula, left S1, and right thalamus was highly correlated with the pain intensity, and further comparison showed that the regional CBF in these regions is significantly higher in PHN groups. Functional connectivity results demonstrated that the reward circuitry involved in striatum, prefrontal cortex, amygdala, and parahippocampal gyrus and the circuitry among striatum, thalamus, and insula were highly correlated with each element in PHN patients. The authors stated that non-invasive brain perfusion imaging at rest may provide novel insights into the central mechanisms underlying PHN pain.

Aquino et al (2014) stated that PWI can be used to measure key aspects of tumor vascularity in-vivo and recent studies suggested that perfusion imaging may be useful in the early assessment of response to angiogenesis inhibitors. These
investigators compared Parametric Response Maps (PRMs) with the Region of Interest (ROI) approach in the analysis of tumor changes induced by bevacizumab and irinotecan in recurrent glioblastomas (rGBM), and evaluated if changes in tumor blood volume measured by perfusion MRI may predict clinical outcome. A total of 42 rGBM patients with KPS greater than or equal to 50 were treated until progression, as defined by MRI with Response Assessment in Neuro-Oncology (RANO) criteria. Relative CBV variation after 8 weeks of treatment was calculated through semi-automatic ROI placement in the same anatomic region as in baseline. Alternatively, relative CBV variations with respect to baseline were calculated into the evolving tumor region using a voxel-by-voxel difference. Parametric Response Maps were created showing where relative CBV significantly increased, decreased or remained unchanged. An increased blood volume in PRM (PRMCBV+) higher than 18 % (1st quartile) after 8 weeks of treatment was associated with increased progression free survival (PFS; 24 versus 13 weeks, p = 0.045) and overall survival (OS; 38 versus 25 weeks, p = 0.016). After 8 weeks of treatment ROI analysis showed that mean relative CBV remained elevated in non-responsive patients (4.8 ± 0.9 versus 5.1 ± 1.2, p = 0.38), whereas decreased in responsive patients (4.2 ± 1.3 versus 3.8 ± 1.6 p = 0.04), and re-increased progressively when patients approached tumor progression. The authors concluded that these findings suggested that PRMs can provide an early marker of response to anti-angiogenic treatment and warrant further confirmation in a larger cohort of GBM patients.

Ziegelitz et al (2014) demonstrated in idiopathic normal pressure hydrocephalus (iNPH) patients by DSC MRI a reduced pre-operative CBF that correlated with the severity of clinical symptoms and predicted shunt outcome. In cortical, sub-cortical, peri-ventricular regions and along peri-and para-ventricular profiles absolute perfusion values were estimated by multi-slice DSC MRI in 21 iNPH patients and 16 age-matched healthy individuals (HI). Relative CBF, calculated with the occipital cortex as internal reference, was used for comparison between groups and for correlation analysis.
between regional rCBF and symptoms or outcome. Idiopathic NPH patients showed significantly decreased rCBF in the basal medial frontal cortex, hippocampus, lentiform nucleus, periventricular white matter (PVWM), central grey matter and the global parenchyma as compared to Hl. Idiopathic NPH patients with higher pre-operative rCBF in the PVWM performed better in clinical tests. A lower overall pre-operative function resulted in a more obvious recovery after shunt insertion. Shunt-responders had higher rCBF values in the basal medial frontal cortex than non-responders. The authors concluded that DSC MRI perfusion is a potentially useful diagnostic tool in iNPH and perfusion based criteria might be possible predictors of shunt response.

Ziegelitz et al (2015) explored relationships between clinical improvement and rCBF changes after shunt-insertion in iNPH as measured by DSC MRI. In 20 iNPH patients, rCBF was measured pre-operatively and 3 months post-operatively. Because of shunt-induced right-sided artefacts, evaluation was restricted to 12 left sided cortical, sub-cortical, and peri-ventricular regions of interest. Correlations between rCBF and clinical symptoms were analyzed in shunt responders. In responders, the post-operative regions of interest-based rCBF increase of 2 % to 9 % was significant in the parenchyma, the hippocampus, and the anterior periventricular white matter. Perfusion improvement in the cingulus, caudate head, and thalamus correlated with decreased disturbance in 1 or more of the domains neuropsychology, gait, balance, and total performance. The authors concluded that DSC MRI can measure post-operative perfusion changes in responders; post-operative perfusion increase in some grey matter structures seems to determine the degree of clinical improvement.

Furthermore, an UpToDate review on “Normal pressure hydrocephalus” (Graff-Radford, 2015) states that “Other MRI techniques such as cine-MRI and perfusion-weighted MRI have had either mixed or negative results in the evaluation of patients with NPH. A small pilot study of magnetic resonance
spectroscopy has shown findings in NPH that appear to correlate with cognitive deterioration”.

Reardon et al (2014) provided historical and scientific guidance on imaging response assessment for incorporation into clinical trials to stimulate effective and expedited drug development for recurrent glioblastoma by addressing 3 fundamental questions: (i) What is the current validation status of imaging response assessment, and when are we confident assessing response using today's technology? (ii) What imaging technology and/or response assessment paradigms can be validated and implemented soon, and how will these technologies provide benefit? (iii) Which imaging technologies need extensive testing, and how can they be prospectively validated? These researchers noted that assessment of T1 +/- contrast, T2/FLAIR, diffusion, and perfusion-imaging sequences are routine and provide important insight into underlying tumor activity. Nonetheless, utility of these data within and across patients, as well as across institutions, are limited by challenges in quantifying measurements accurately and lack of consistent and standardized image acquisition parameters. Currently, there exists a critical need to generate guidelines optimizing and standardizing MRI sequences for neuro-oncology patients. Additionally, more accurate differentiation of confounding factors (pseudo-progression or pseudo-response) may be valuable. The authors concluded that although promising, diffusion MRI, perfusion MRI, MR spectroscopy, and amino acid positron emission tomography (PET) require extensive standardization and validation. Moreover, they stated that additional techniques to enhance response assessment, such as digital T1 subtraction maps, warrant further investigation.

Boxerman and Ellingson (2015) noted that there exist multiple challenges associated with the current response assessment criteria for high-grade gliomas, including the uncertain role of changes in non-enhancing T2 hyper-intensity, and the phenomena of pseudo-response and pseudo-progression in the setting of anti-angiogenic and chemo-radiation therapies, respectively. Advanced physiological MRI, including diffusion
and perfusion (DSC MRI and dynamic contrast-enhanced MRI)
sensitive techniques for overcoming response assessment
challenges, has been proposed, with their own potential
advantages and inherent shortcomings. Measurement
variability exists for conventional and advanced MRI
techniques, necessitating the standardization of image
acquisition parameters in order to establish the utility of these
imaging methods in multi-center trials for high-grade gliomas.
This review chapter highlighted the important features of MRI
in clinical brain tumor trials, focusing on the current state of
response assessment in brain tumors, advanced imaging
techniques that may provide additional value for determining
response, and imaging issues to be considered for multicenter
trials.

Huang et al (2015) stated that glioblastoma is a devastating
diagnosis with an average survival of 14 to 16 months using the
current standard of care treatment. The determination of
treatment response and clinical decision making is based on the
accuracy of radiographic assessment. Notwithstanding,
challenges exist in the neuroimaging evaluation of patients
undergoing treatment for malignant glioma. Differentiating
treatment response from tumor progression is problematic and
currently combines long-term follow-up using standard MRI,
with clinical status and corticosteroid-dependency assessments.
In the clinical trial setting, treatment with gene therapy,
vaccines, immunotherapy, and targeted biologicals similarly
produces MRI changes mimicking disease progression. A
neuroimaging method to clearly distinguish between pseudo-
progression and tumor progression has unfortunately not been
found to-date. With the incorporation of anti-angiogenic
therapies, a further pitfall in imaging interpretation is pseudo-
response. The Macdonald criteria that correlate tumor burden
with contrast-enhanced imaging proved insufficient and
misleading in the context of rapid blood-brain barrier
normalization following anti-angiogenic treatment that is not
accompanied by expected survival benefit. Even improved
criteria, such as the RANO criteria, which incorporate non-
enhancing disease, clinical status, and need for
corticosteroid use, fall short of definitively distinguishing tumor progression, pseudo-response, and pseudo-progression. These investigators focused on advanced imaging techniques including perfusion MRI, diffusion MRI, MR spectroscopy, and new positron emission tomography imaging tracers. They discussed the relevant image analysis algorithms and interpretation methods of these promising techniques in the context of determining response and progression during treatment of glioblastoma both in the standard of care and in clinical trial context.

Filice and Crisi (2016) evaluated the differences in dynamic contrast-enhanced (DCE) MRI perfusion estimates of high-grade gliomas (HGG) due to the use of an input function (IF) obtained respectively from arterial (AIF) and venous (VIF) approaches by 2 different commercially available software applications. This prospective study includes 20 patients with pathologically confirmed diagnosis of HGG. The data source was processed by using 2 DCE dedicated commercial packages, both based on the extended Toft model, but the 1st customized to obtain input function from arterial measurement and the 2nd from sagittal sinus sampling. The quantitative parametric perfusion maps estimated from the 2 software packages were compared by means of a region of interest (ROI) analysis. The resulting input functions from venous and arterial data were also compared. No significant difference has been found between the perfusion parameters obtained with the 2 different software packages ($p < 0.05$). The comparison of the VIFs and AIFs obtained by the 2 packages showed no statistical differences. The authors concluded that direct comparison of DCE-MRI measurements with IF generated by means of arterial or venous waveform led to no statistical difference in quantitative metrics for evaluating HGG. Moreover, they noted that additional research involving DCE-MRI acquisition protocols and post-processing would be beneficial to further substantiate the effectiveness of venous approach as the IF method compared with arterial-based IF measurement.

Verclytte et al (2016) noted that early-onset Alzheimer's disease
(EOAD) is frequently associated with atypical clinical presentations and its early detection remains a challenging issue. In this study, these researchers used arterial spin labeling (ASL), a non-invasive perfusion MRI sequence, and [18 F]-FDG-PET to detect the perfusion and metabolic features in patients with EOAD. All patients were investigated in the French reference center for young-onset dementia and were assessed by MRI, including a pseudo-continuous ASL (pCASL) sequence, and [18 F]-FDG-PET. Quantitative analyses and inter-modality comparison with correlation analysis were made after data processing including correction of partial volume effects, cortical projection, and specific intensity normalization. These investigators prospectively included 37 patients with EOAD with a mean age of 58.3 years. The areas of most severe hypoperfusion detected with ASL were located in the parietal lobes, the pre-cuneus, the right posterior cingulate cortex, and the frontal lobes (p < 0.05). The areas of lowest glucose metabolism detected by [18 F]-FDG-PET were identified in the temporo-parietal cortex and the pre-cuneus (p < 0.05). Hypo-metabolic regions were more extensive than hypoperfused regions on ASL maps whereas ASL highlighted alterations in the frontal lobes without apparent hypo-metabolism on [18 F]-FDG-PET maps. The authors concluded that ASL and [18 F]-FDG-PET detected pathological areas of similar distribution mainly located in the inferior parietal lobules and local zones in the temporal cortex in patients with EOAD. They stated that the findings of this preliminary study showed that ASL and [18 F]-FDG-PET may have a complementary role in combination with structural MRI for the assessment of suspected EOAD.

Blauwblomme et al (2015) noted that ASL-MRI is becoming a routinely used sequence for ischemic strokes, as it quantifies CBF without the need for contrast injection. As brain arteriovenous malformations (AVMs) are high-flow vascular abnormalities, increased CBF can be identified inside the nidus or draining veins. These researchers analyzed the relevance of ASL-MRI in the diagnosis and follow-up of children with brain AVM. They performed a retrospective analysis of 21 patients
who had undergone digital subtraction angiography (DSA) and pseudo-continuous ASL-MRI for the diagnosis or follow-up of brain AVM after radiosurgery or embolization. They compared the AVM nidus location between ASL-MRI and 3D contrast-enhanced T1 MRI, as well as the CBF values obtained in the nidus (CBFnidus) and the normal cortex (CBFcortex) before and after treatment. The ASL-MRI correctly demonstrated the nidus location in all cases. Nidal perfusion (mean CBFnidus of 137.7 ml/100 mg/min) was significantly higher than perfusion in the contralateral normal cortex (mean CBFcortex of 58.6 ml/100 mg/min; p < 0.0001, Mann-Whitney test). Among 3 patients followed-up after embolization, a reduction in both AVM size and CBF values was noted. Among 5 patients followed-up after radiosurgery, a reduction in the nidus size was observed, whereas CBFnidus remained higher than CBFcortex. The authors concluded that ASL-MRI revealed nidus location and patency after treatment due to its ability to demonstrate focal increased CBF values. They stated that absolute quantification of CBF values could be relevant in the follow-up of pediatric brain AVM after partial treatment, although this must be confirmed in larger prospective trials.

Innes and colleagues (2015) examined gray matter volume and concentration and cerebral perfusion in people with untreated obstructive sleep apnea (OSA) while awake. These investigators employed voxel-based morphometry to quantify gray matter concentration and volume and ASL perfusion imaging to quantify cerebral perfusion. A total of 19 people with OSA (6 females and 13 males; mean age of 56.7 years, range of 41 to 70; mean apnea hypopnea index [AHI] 18.5, range of 5.2 to 52.8) and 19 controls (13 females and 6 males; mean age of 50.1 years, range of 41 to 81). There were no differences in regional gray matter concentration or volume between participants with OSA and controls. Neither was there any difference in regional perfusion between controls and people with mild OSA (n = 11). However, compared to controls, participants with moderate-severe OSA (n = 8) had decreased perfusion (while awake) in 3 clusters. The largest cluster incorporated, bilaterally, the para-cingulate gyrus, anterior
cingulate gyrus, and sub-callosal cortex, and the left putamen and left frontal orbital cortex; the 2nd cluster was right-lateralized, incorporating the posterior temporal fusiform cortex, para-hippocampal gyrus, and hippocampus; the 3rd cluster was located in the right thalamus. The authors concluded that there is decreased regional perfusion during wakefulness in participants with moderate-severe OSA, and these are in brain regions that have shown decreased regional gray matter volume in previous studies in people with severe OSA. Thus, these researchers hypothesized that cerebral perfusion changes are evident before (and possibly underlie) future structural changes. These preliminary findings need to be validated by well-designed studies.

Wang et al (2015) evaluated CBF in chronic pediatric mild traumatic brain injury (mTBI) using ASL MRI perfusion. Patients with mTBI showed lower CBF than controls in bilateral fronto-temporal regions, with no between-group cognitive differences. The authors concluded that these findings suggested ASL MRI perfusion may be useful in evaluating functional abnormalities in pediatric mTBI. These preliminary findings need to be validated by well-designed studies.

Fernández-Seara et al (2015) stated that neurophysiological changes within the cortico-basal ganglia-thalamocortical circuits appear to be a characteristic of Parkinson's disease (PD) pathophysiology. The sub-thalamic nucleus (STN) is one of the basal ganglia components showing pathological neural activity patterns in PD. In this study, perfusion imaging data, acquired non-invasively using ASL perfusion MRI, were used to assess the resting state functional connectivity (FC) of the STN in 24 early-to-moderate PD patients and 34 age-matched healthy controls, to determine whether altered FC in the very low frequency range of the perfusion time signal occurs as a result of the disease. The results showed that the healthy STN was functionally connected with other nuclei of the basal ganglia and the thalamus, as well as with discrete cortical areas including the insular cortex and the hippocampus. In PD patients, connectivity of the STN was increased with 2 cortical
areas involved in motor and cognitive processes. The authors concluded that these findings suggested that hyperconnectivity of the STN could underlie some of the motor and cognitive deficits often present even at early stages of PD. They stated that FC measures provided good discrimination between controls and patients, suggesting that ASL-derived FC metrics could be a putative PD biomarker.

Evaluation of Head and Neck Cancers:

Noij and colleagues (2015) provided an extensive overview of the current state of perfusion-weighted MRI for head and neck squamous cell carcinoma (HNSCC). PubMed and Embase were searched for literature until July 2014 assessing the diagnostic and prognostic performance of perfusion-weighted MRI in HNSCC. A total of 21 diagnostic and 12 prognostic studies were included for qualitative analysis; 4 studies used a T2(∗) sequence for dynamic susceptibility (DSC)-MRI, 29 studies used T1-based sequences for dynamic contrast enhanced (DCE)-MRI. Included studies suffered from a great deal of heterogeneity in study methods showing a wide range of diagnostic and prognostic performance. Thus, these researchers could not perform any useful meta-analysis. Perfusion-weighted MRI showed potential in some aspects of diagnosing HNSCC and predicting prognosis; 3 studies reported significant correlations between hypoxia and tumor heterogeneity in perfusion parameters (absolute correlation coefficient |ρ| >0.6, p < 0.05); 2 studies reported synergy between perfusion-weighted MRI and PET parameters; 4 studies showed a promising role for response prediction early after the start of chemo-radiotherapy. In 2 studies perfusion-weighted MRI was useful in the detection of residual disease. The authors concluded that more research with uniform study and analysis protocols with larger sample sizes are needed before perfusion-weighted MRI can be used in clinical practice.

Differentiation of Radiation-Induced Necrosis from Recurrent Brain Tumor:
In a meta-analysis, Chuang and associates (2016) examined roles of several metabolites in differentiating recurrent tumor from necrosis in patients with brain tumors using MR perfusion and spectroscopy. Medline, Cochrane, Embase, and Google Scholar were searched for studies using perfusion MRI and/or MR spectroscopy published up to March 4, 2015 which differentiated between recurrent tumor versus necrosis in patients with primary brain tumors or brain metastasis. Only 2-armed, prospective or retrospective studies were included. A meta-analysis was performed on the difference in relative cerebral blood volume (rCBV), ratios of choline/creatine (Cho/Cr) and/or choline/N-acetyl aspartate (Cho/NAA) between participants undergoing MRI evaluation. A χ²-based test of homogeneity was performed using Cochran's Q statistic and I². Of 397 patients in 13 studies who were analyzed, the majority had tumor recurrence. As there was evidence of heterogeneity among 10 of the studies which used rCBV for evaluation (Q statistic = 31.634, I² = 97.11 %, p < 0.0001) a random-effects analysis was applied. The pooled difference in means (2.18, 95 % CI: 0.85 to 3.50) indicated that the average rCBV in a contrast-enhancing lesion was significantly higher in tumor recurrence compared with radiation injury (p = 0.001). Based on a fixed-effect model of analysis encompassing the 6 studies which used Cho/Cr ratios for evaluation (Q statistic = 8.388, I² = 40.39 %, p = 0.137), the pooled difference in means (0.77, 95 % CI: 0.57 to 0.98) of the average Cho/Cr ratio was significantly higher in tumor recurrence than in tumor necrosis (p = 0.001). There was significant difference in ratios of Cho to NAA between recurrent tumor and necrosis (1.02, 95 % CI: 0.03 to 2.00, p = 0.044). The authors concluded that 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.

An UpToDate review on “Delayed complications of cranial irradiation” (Dietrich et al, 2016) states that “Differentiating recurrent tumor from radiation necrosis can be very difficult by imaging. Conventional MRI typically shows a contrast-enhancing mass lesion with central necrosis and reactive
edema within or immediately adjacent to the site of the original tumor and/or the site of highest dose of radiation. These imaging features are entirely overlapping with the radiographic appearance of high-grade primary brain tumors and brain metastases, and therefore image interpretation can be challenging. Other imaging modalities have been investigated in an attempt to differentiate radiation necrosis from active tumor, however, no single imaging modality has proven to be sufficiently specific to establish a diagnosis. Perfusion-weighted MRI may show decreased cerebral blood volume (CBV) associated with radiation necrosis, whereas active tumor is more likely to be associated with increased CBV. Restricted diffusion on diffusion-weighted MRI suggests active tumor. A high lipid peak on MR spectroscopy suggests necrosis. Increased uptake with FDG or methionine PET or thallium chloride-201 SPECT all suggest tumor, whereas lack of uptake is more suggestive of necrosis. Ultimately, biopsy of the suspicious lesion may be required for a definitive diagnosis, particularly in patients who are symptomatic and have worsening imaging findings over time.

<table>
<thead>
<tr>
<th>CPT Codes / HCPCS Codes / ICD-10 Codes</th>
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<tr>
<td><strong>Information in the [brackets] below has been added for clarification purposes.</strong> Codes requiring a 7th character are represented by &quot;+&quot;:</td>
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**ICD-10 codes will become effective as of October 1, 2015:**

**Cerebral CT Perfusion Studies:**

CPT codes covered if selection criteria are met:

| 0042T | Cerebral perfusion analysis using computed tomography with contrast administration, including post-processing of parametric maps with determination of cerebral blood flow, cerebral blood volume, and mean transit time |

**Other CPT codes related to the CPB:**

<p>| 37195 | Thrombolysis, cerebral, by intravenous infusion |</p>
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>61623</td>
<td>Endovascular temporary balloon arterial occlusion, head or neck (extracranial/intracranial) including selective catheterization of vessel to be occluded, positioning and inflation of occlusion balloon, concomitant neurological monitoring, and radiologic supervision and interpretation of all angiography required for balloon occlusion and to exclude vascular injury post occlusion</td>
</tr>
<tr>
<td>70450 - 70470</td>
<td>Computed tomography, head or brain; without contrast material, with contrast material(s), or without contrast material followed by contrast material(s) and further sections</td>
</tr>
<tr>
<td>70496</td>
<td>Computed tomographic angiography, head, with contrast material(s), including noncontrast images, if performed, and image post-processing</td>
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**ICD-10 codes covered if criteria are met:**

<table>
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<tr>
<th>Code</th>
<th>Description</th>
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<tr>
<td>I65.01 - I65.9</td>
<td>Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction</td>
</tr>
<tr>
<td>I66.01 - I66.9</td>
<td>Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction</td>
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**ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tr>
<td>B00.4</td>
<td>Herpesviral encephalitis</td>
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<tr>
<td>C71.0 - C71.9</td>
<td>Malignant neoplasm of brain</td>
</tr>
<tr>
<td>C79.31</td>
<td>Secondary malignant neoplasm of brain</td>
</tr>
<tr>
<td>C79.49</td>
<td>Secondary malignant neoplasm of other parts of nervous system [spinal cord]</td>
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<tr>
<td>G45.0 - G45.9</td>
<td>Transient cerebral ischemic attacks and related syndromes</td>
</tr>
<tr>
<td>G46.3 - G46.8</td>
<td>Vascular syndromes of brain in cerebrovascular diseases</td>
</tr>
<tr>
<td>G47.33</td>
<td>Obstructive sleep apnea (adult) (pediatric)</td>
</tr>
<tr>
<td>G91.0</td>
<td>Communicating hydrocephalus</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>G91.2</td>
<td>(Idiopathic) normal pressure hydrocephalus</td>
</tr>
<tr>
<td>I60.00 - I62.9</td>
<td>Nontraumatic subarachnoid, intracerebral and other and unspecified intracranial hemorrhage</td>
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<tr>
<td>I67.1 - I67.2 I67.4 -I68.8</td>
<td>Other cerebrovascular diseases and cerebrovascular disorders in diseases classified elsewhere</td>
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<td>I69.00 - I69.998</td>
<td>Sequelae of cerebrovascular disease</td>
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<tr>
<td>I73.89 - I73.9</td>
<td>Other and unspecified peripheral vascular disease</td>
</tr>
<tr>
<td>S02.0xx+ - S02.42x+ S02.60x+ - S02.92x+</td>
<td>Fracture of skull and facial bones [traumatic brain injury]</td>
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<tr>
<td>S06.0x0+ - S06.9x9+</td>
<td>Intracranial injury, excluding those with skull fracture [traumatic brain injury]</td>
</tr>
<tr>
<td>S09.10x+ - S09.11x+ S09.19x+ S09.8xx+ - S09.90x+</td>
<td>Head injury, unspecified</td>
</tr>
</tbody>
</table>

**Cerebral MRI Perfusion Studies:**

No specific code

**Other HCPCS codes related to the CPB:**

- C9257 Injection, bevacizumab, 0.25 mg
- J9035 Injection, bevacizumab, 10 mg

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

- C71.0 - C71.9 Malignant neoplasm of brain [not covered for assessment of response to angiogenesis inhibitors in persons with glioblastoma]
- G20 Parkinson’s disease
- G30.0 - G30.9 Alzheimer’s disease
- G89.21 Chronic pain due to trauma
The above policy is based on the following references:

Computed Tomography Perfusion Imaging:

16. Schellinger PD, Fiebach JB, Hacke W. Imaging-based decision making in thrombolytic therapy for ischemic


47. Greenberg ED, Gold R, Reichman M, et al. Diagnostic


57. American Heart Association (AHA) Website. Guidelines for the early management of patients with acute ischemic


60. American College of Radiology (ACR) Website. ACR-ASNR-SPR practice parameter for the performance of computed tomography (CT) perfusion in neuroradiologic imaging. 2014.


65. Young CB. Diagnosis of brain death. UpToDate Inc., Waltham, MA. Last reviewed May 2016.

Magnetic Resonance Imaging Perfusion Imaging:


5. Institute for Clinical Systems Improvement (ICSI). Diagnosis and treatment of ischemic stroke. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI);


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There are no amendments for Pennsylvania Medicaid.

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