BlueCross BlueShield of Alabama

Name of Policy:
Computed Tomography Perfusion Imaging of the Brain

Policy #: 204
Category: Radiology

Latest Review Date: October 2018
Policy Grade: B

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

Computed tomography perfusion (CTP) imaging provides an assessment of cerebral blood flow that may help identify ischemic regions of the brain. This technology is proposed to aid treatment decisions in patients being evaluated for acute ischemic stroke, subarachnoid hemorrhage, cerebral vasospasm, brain tumors, and head trauma.

Acute Stroke

The goal of acute stroke thrombolytic treatment is to rescue the ischemic penumbra, an area of brain that surrounds the infarct core and is hypoperfused but does not die quickly. Multimodal computed tomography (CT) and magnetic resonance imaging (MRI) can be used to assess the cerebral parenchyma, vasculature, and tissue viability in the acute ischemic stroke setting, and are used to detect ischemic tissue, and exclude hemorrhage and other conditions that mimic acute cerebral ischemia.

- Noncontrast CT is used to rule out intracranial hemorrhage, tumor or infection. Diffusion-weighted MRI is used to identify acute infarction, and a gradient-recalled echo (GRE) sequence is used to exclude intracerebral hemorrhage.
- CT angiography (CTA) and MR angiography (MRA) are used to evaluate intra-and extra-cranial vasculature to detect the vascular occlusion and potentially guide therapy (e.g., intravenous thrombolysis or mechanical thrombectomy).

The approved therapy, use of an intravenous tissue plasminogen activator (tPA), requires only a non-contrast CT scan to exclude the presence of hemorrhage (a contraindication to the use of the drug). Current guidelines are to administer (tPA) within the first three hours after an ischemic event, preceded by a CT scan. Many patients, however, do not present to the emergency room within the three-hour window, and thrombolysis carries a risk of intracranial hemorrhage. Thus, more sophisticated imaging may be needed to select the proper use of intra-arterial thrombolysis or mechanical thrombectomy in patients who present more than three hours after an ischemic stroke. Perfusion imaging is also being evaluated in the management of other neurological conditions, such as subarachnoid hemorrhage and head trauma.

The potential utility of perfusion imaging of acute stroke is as follows:

- Identification of brain regions with extremely low cerebral blood flow, which represents the core;
- Identification of patients with at-risk brain regions (acutely ischemic but viable penumbra) that may be salvageable with successful intra-arterial thrombolysis beyond the standard three-hour window;
- Triage of patients with at-risk brain regions to other available therapies, such as induced hypertension or mechanical clot retrieval;
- Decisions regarding intensive monitoring of patients with large abnormally perfused brain regions;
- Biologically-based management of patients who awaken with a stroke for which the precise time of onset is unknown.

Additional potential uses of CT perfusion (CTP) in acute stroke may include the following:

- detection and differential diagnosis (e.g., excluding stroke mimics such as transient ischemic attack, complex migraine, seizure, conversion disorders, hypoglycemia, or brain tumors);
- determination of stroke subtype;
- determination of stroke extent including additional vascular territories at risk;
- identification of patients at high early risk for stroke following transient ischemic attack;
- determining the need for blood pressure management;
- establishing prognosis

Similar information can be provided by CT and MRI regarding infarct core and penumbra. However, multimodal CT has a short protocol time (5-6 min), and because it can be performed with any modern CT equipment, is more widely available in the emergency department setting. CT perfusion (CTP) is performed by capturing images as an iodinated contrast agent bolus passes through the cerebral circulation and accumulates in the cerebral tissues. (Older perfusion methodologies such as single-photon emission CT [SPECT] and xenon-enhanced CT [XeCT] scanning use a diffusible tracer.) The quantitative perfusion parameters are calculated from density changes for each pixel over time with commercially available deconvolution-based software, in which cerebral blood flow (CBF) is equal to regional cerebral blood volume (CBV) divided by mean transit time (MTT). CT angiography and CTP imaging require ionizing radiation and iodinated contrast. It is estimated that a typical CT perfusion deposits a slightly greater radiation dose than a routine unenhanced head CT (~ 3.3 mSv).

Subarachnoid Hemorrhage and Cerebral Vasospasm

Cerebral vasospasm is a major cause of morbidity and mortality following aneurysmal subarachnoid hemorrhage (ASAH) in patients who survive the initial hemorrhage and can be seen in about two-thirds of patients with ASAH. The typical onset of cerebral vasospasm occurs at three to five days after hemorrhage, with maximal narrowing on digital subtraction angiography at 5-14 days. Currently, the diagnosis of vasospasm and the management decisions rely on clinical examination, transcranial Doppler sonography, and digital subtraction angiography. Although symptomatic vasospasm affects 20% to 30% of patients with ASAH, not all patients with angiographic vasospasm manifest clinical symptoms and the symptoms can be nonspecific. Also, patients do not always have both clinical and imaging findings of vasospasm. Due to these limitations, more accurate and reliable methods to detect cerebral vasospasm are being investigated.

Brain Tumors

The current standard for tumor grading is histopathologic assessment of tissue. Limitations of histologic assessment include sampling error due to regional heterogeneity and interobserver variation. These limitations can result in inaccurate classification and grading of gliomas. Because malignant brain tumors are characterized by neovascularity and increased angiogenic activity, perfusion imaging has been proposed as a method to assess tumor grade and prognosis. In addition, perfusion imaging can be repeated and may help to assess the evolution of tumors and the treatment response. Traditionally, perfusion imaging of brain tumors has been performed with MRI, which can estimate tumor blood volume, blood flow, and permeability. More recently, CT perfusion has been investigated for glioma grading. Potential advantages, compared with

magnetic resonance perfusion, include the wider availability, faster scanning times, and lower cost. CTP imaging may also be useful in distinguishing recurrent tumor from radiation necrosis.

Policy:

Effective for dates of service on and after February 10, 2016:

CT-based perfusion imaging meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage in **select patients with anterior large-vessel stroke for mechanical embolectomy**. (Please see MP# 263- *Endovascular Procedures for Intracranial Arterial Disease (Atherosclerosis and Aneurysm* for criteria related to mechanical embolectomy)

CT-based perfusion imaging of the brain does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational for all other indications.**

Effective for dates of service prior to February 10, 2016:

Computed tomography perfusion imaging does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage for all indications including the diagnosis and management of acute cerebral ischemia (stroke) and is considered **investigational**.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination

Key Points:

The most recent literature update was performed through August 9, 2018.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Acute Stroke

Clinical Context and Test Purpose

The purpose of computed tomography perfusion (CTP) imaging in patients with acute stroke is to guide treatment decisions.

The question addressed in this evidence review is: Does CTP improve the net health outcome of patients with stroke?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant populations of interest are patients with acute stroke who are being evaluated for thrombolysis or mechanical embolectomy, and patients with acute stroke who are being evaluated for prognosis.

Interventions

The interventions of interest are CTP imaging.

Comparators

The comparator of interest is standard stroke management without CTP (non-contrast computed tomography [NCCT], computed tomography angiography [CTA]).

Outcomes

The outcomes of interest are function measured with the National Institutes of Health Stroke Scale (NIHSS) or modified Rankin Scale (mRS) scores following thrombolysis or mechanical embolectomy.

Timing

The timing for CTP is during the first 12 hours after stroke onset. Functional outcomes are measured at 90 days after stroke.

Setting

CTP is an add-on to NCCT and CTA and is widely available in hospital emergency departments.

Technical Reliability

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Evaluation for Thrombolysis

Systematic Reviews

In 2015, Burton et al reported a meta-analysis of 13 studies (three RCTs, six prospective cohort studies) that used CTP imaging and provided intravenous thrombolytic treatment. The objectives of the studies included comparisons of thrombolytic agents and predictions of clinical outcomes. Relatively few patients received tPA based on CTP imaging results. One study (2012) in the review prospectively compared outcomes between 172 patients treated within 4.5 hours based on non-contrast CT criteria and 43 patients treated after 4.5 hours based on CTP mismatch criteria. Another 49 patients who presented beyond 4.5 hours (54%) were excluded according to CTP imaging criteria. This exploratory study found similar rates of symptomatic intracranial hemorrhagic (2.9% in the <4.5-hour group vs. 2.3% in the >4.5-hour group) and good long-term outcome (64.5% vs 60.5%, respectively) in both groups, supporting further study in a randomized trial.

Prospective Cohort Studies

A 2015 study by Bivard et al examined the effectiveness of CTP imaging by assessing health outcomes in patients who qualified for tissue plasminogen activator (tPA) based on standard clinical/non-contrast CT criteria, who were treated or not treated based on qualitative CTP results. Patients selected for a tissue plasminogen activator (tPA) based on qualitative analysis of CTP imaging (n=366) had higher odds of an excellent outcome (modified Rankin Scale [mRS] score 0-1; odds ratio [OR], 1.59, p=0.009) and lower mortality (OR=0.56, p=0.021) than historical controls (n=396) selected for tPA based on clinical/non-contrast CT information. In addition, of patients treated with tPA, those who had target mismatch by CTP imaging had significantly better outcomes than patients treated with tPA who did not (OR=13.8 for three-month mRS score, ≤2). However, 83 (31%) of 269 untreated patients had target mismatch, and 56 (15%) of 366 treated patients had a large ischemic core. This observational study suggested that CTP imaging might identify those patients with acute stroke who are likely and unlikely to respond to thrombolysis. However, questions remain about whether CTP imaging is sufficiently reliable to select individual stroke patients for treatment.

Another area of research is whether CTP imaging can help select ischemic stroke patients for thrombolysis after the standard three-hour time window. Sztriha et al (2011) studied a cohort of 254 thrombolyzed patients; 174 received tPA at zero to three hours using NCCT, and 80 received tPA at three to six hours by using CTP imaging criteria. At three months, there were no differences between patient's thrombolyzed at zero to three hours and those at three to six hours who had a symptomatic intracerebral hemorrhage (3% vs 4%) or in any intracerebral hemorrhage (7% vs 9%). There were also no differences at three months in mortality rates (16% vs 9%) or the mRS score of zero to two (55% vs 54%), all respectively. The authors noted that their results could not be generalized to patients with symptoms in the posterior circulation, an area where CTP imaging is known to underperform.

In 2011, Obach et al compared outcomes for 106 patients with acute stroke assessed with multi-modal CT (CT, computed tomography angiography [CTA], and CTP) to a cohort of 262 patients with acute stroke assessed without full multimodal brain imaging during a five-year period. Clinical and imaging data were collected prospectively, and all imaging studies were assessed by investigators blinded to prognostic data. Good outcome (mRS score, <2) at three months was

higher in the multimodal group compared with controls (adjusted odds ratio [OR] of 2.88) in models adjusted for age, gender, NIHSS, glucose level, and treatment delay or modality. In a sensitivity analysis, multimodal-assisted thrombolysis yielded superior benefits in those patients treated after three hours (adjusted OR=4.48) than in patients treated within three hours (adjusted OR=1.31). For patients treated after three hours, 63% of patients assessed by multimodal CT had a Rankin score of two or less compared with 24% of controls. Mortality (14% and 15%) and symptomatic hemorrhage (5% and 7%) rates were similar in the two groups, respectively.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

No RCTs were identified assessing use of CTP for stroke patients being evaluated for thrombolysis.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.
Because the clinical validity of CTP for this population has not been established, a chain of evidence supporting the clinical utility of CTP cannot be constructed.

Subsection Summary: Evaluation for Thrombolysis

Evidence from nonrandomized comparative studies with either concurrent or historical controls has suggested that outcomes after thrombolysis are better in patients who have target mismatch on perfusion imaging than in patients without target mismatch, and that patients with target mismatch treated after a three-hour time window have outcomes similar to those treated within three hours. However, randomized trials are needed to provide greater certainty whether a strategy employing CTP imaging leads to improved health outcomes compared with traditional treatment strategies for acute stroke.

Evaluation for Mechanical Embolectomy

Randomized Controlled Trials

CTP imaging was used to select patients for mechanical embolectomy in the 2015 EXTEND-IA randomized controlled trial (RCT). This trial enrolled patients with ischemic stroke who were receiving IV tPA within 4.5 hours after stroke onset. Eligible patients had an occlusion of the internal carotid artery or M1 or M2 segments of the middle cerebral artery on CTA, were able to receive endovascular therapy within six hours of stroke onset, and were functionally independent before the stroke. Patients were evaluated before enrollment with CTP imaging and were required to have evidence of salvageable brain tissue and an ischemic core with a volume of less than 70 mL. CTP imaging was analyzed with an operator-independent postprocessing software.

Enrollment was planned for 100 patients, but the trial's data safety and monitoring board stopped the study for efficacy after the first 70 enrolled patients. The trial used two coprimary end points: reperfusion (measured as the percentage reduction in perfusion-lesion volume between the initial imaging and imaging at 24 hours) and early neurologic improvement (defined as a reduction of >8 points on the NIHSS or a score of 0 or 1 at day 3).

About 25% of clinically eligible patients were excluded by perfusion imaging criteria. Endovascular therapy subjects had increased reperfusion at 24 hours, with a median reperfusion of 100% (percentage reduction in perfusion-lesion volume), compared with 37% for the tPA-only group (adjusted OR=4.7; 95% CI, 2.5 to 9.0; p<0.001). Of the endovascular therapy subjects, 28 (80%) of 35 had early neurologic improvement compared with 13 (37%) of 35 of the tPA-only subjects (adjusted OR=6.0; 95% CI, 2.0 to 18.0; p=0.002). Rates of reperfusion of at least 90% at 24 hours without symptomatic intracerebral hemorrhage were higher in endovascular therapy patients (89% vs 34%; adjusted OR=27.0; 95% CI, 5.5 to 135.0; p<0.001). Safety outcomes, including death, symptomatic intracerebral hemorrhage, and parenchymal hematoma, did not differ significantly between groups.

It should be noted that other comparable trials of mechanical embolectomy from the same period (e.g., ESCAPE, MR CLEAN, and SWIFT PRIME) also used time from stroke onset, multiphase CTA, or Alberta Stroke Program Early CT score to select patients for treatment. Overall, these trials found a significant benefit of mechanical embolectomy with stent retrievers.

The value of CTP imaging-based patient selection for intra-arterial acute ischemic stroke treatment was assessed by Borst et al in 2015 using data from the MR CLEAN trial. In this trial, inclusion was not limited to CTP imaging, so investigators could perform it if it was a standard procedure at their institution. Of 500 patients in MR CLEAN, 333 (67%) underwent CTP imaging and 175 (52.6%) had adequate images. Of the 175, 102 fulfilled the CTP mismatch criteria. The primary outcome was mRS score at 90 days, which was assessed for patients with and without CTP mismatch. There was no significant interaction for mismatch and treatment (mechanical embolectomy or usual care) for the mRS score at 90 days, suggesting that CTP imaging cannot reliably identify patients who will not benefit from mechanical embolectomy. In both treatment groups, there was a shift towards better outcomes in patients who had CTP mismatch compared with those who did not, suggesting a benefit for prognosis (see the Evaluation for Prognosis section).

Rai et al (2013) evaluated rates of recanalization and functional outcomes in a cohort of 99 patients selected by CT perfusion for treatment with endovascular stroke therapy and compared results with historical controls from the MERCI [Mechanical Embolus Removal in Cerebral Ischemia], Multi-MERCI, and Penumbra device trials that treated all comers. Patients were included if they had anterior circulation symptoms at presentation with a baseline NIHSS score of 8 or greater and intracerebral vascular occlusion on admission CT angiography correlating with the neurologic deficit. There was no cut-off time for treatment, and the type of endovascular therapy was thrombolytics in 33 (33.3%) of patients, mechanical device only in 24 (24.2%), and both treatments in 42 (42.4%). Successful recanalization was achieved in 55.6%, with a good outcome in 41.4% of patients. The recanalization rate in this study did not differ significantly from the 46% for MERCI and 68% for Multi-MERCI, but was significantly lower than the 82%

recanalization rate in the Penumbra trial. In patients successfully recanalized, good outcomes were obtained in 67% in this study in comparison with 46% in MERCI, 49% in Multi-MERCI, and 29% in Penumbra. The rate of futile recanalization (defined as a poor outcome despite successful recanalization) was 33% in Rai et al compared with 54% in MERCI, 51% in Multi-MERCI, and 71% for Penumbra.

Cohort Studies

Results of the CRISP (CT Perfusion to Predict Response to Recanalization in Ischemic Stroke Project) study were published by Lansberg et al (2017). CRISP was a multicenter cohort study of 190 acute stroke patients who were assessed by CTP prior to endovascular therapy, although the decision to proceed with endovascular therapy (stent retrievers, manual aspiration, intra-arterial thrombolytic agents, and/or angioplasty with or without stenting, depending on the operator's preference) was not dependent on the CTP results (automated analysis with RAPID software). Patients up to 18 hours after symptom onset were included. Patients with target mismatch (n=131) had higher odds of a favorable clinical response based on the NIHSS (83% vs 44%, p=0.002; adjusted OR=6.6; 95% CI, 2.1 to 20.9).

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs were identified assessing use of CTP for stroke patients being evaluated for mechanical embolectomy.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

A chain of evidence can be constructed based on the clinical validity of CTP for this population. The available evidence suggests the acute stroke patients who receive CTP and receive mechanical embolectomy benefit and therefore it can be inferred that defining viable ischemic tissue using CTP will lead to management changes facilitating better outcomes

Subsection Summary: Evaluation for Mechanical Embolectomy

CTP imaging is one of several approaches used in acute stroke to better define viable ischemic tissue that may benefit from mechanical endovascular intervention. One RCT showed improved outcomes with mechanical embolectomy when patients were selected based on CTP imaging results, supporting the use of CTP for evaluation for mechanical embolectomy. Other RCTs have used time from stroke onset, multiphase CTA, and Alberta Stroke Program Early CT as selection

criteria. CTP may be considered an effective method to determine suitability for mechanical embolectomy.

Evaluation for Prognosis
In 2015, Borst et al (discussed above) reported on the relation between CTP imaging-derived parameters and functional outcomes from the MR CLEAN trial. Functional outcome as measured by mRS score at 90 days was associated with the CTP imaging-derived ischemic core volume (OR=0.79 per 10 mL; 95% CI, 0.73 to 0.87 per 10 mL; p<0.001) and percentage ischemic core (OR=0.82 per 10%; 95% CI, 0.66 to 0.99 per 10%; p=0.002), but not the penumbra. This trial population had been selected for treatment using mechanical embolectomy.

A prognostic model, developed with data from the Dutch Acute Stroke Study (DUST), was reported by van Seeters et al in 2015. They analyzed an unselected population of 1374 patients with suspected anterior circulation stroke who underwent multimodal CT. Images were evaluated by an observer blinded to all clinical information except for the side of stroke symptoms. The analysis used 60% of patients for a prediction model and 40% for a validation cohort. Poor outcome (90 day mRS score 3-6) occurred in 501 (36.5%) patients. Included in the basic prediction model were patient characteristics (age, stroke severity, time from onset to imaging, dependency prior to stroke symptoms, glucose level, whether treatment had been given) and non-contrast CT measures. CTA and CTP imaging also were predictive of clinical outcome. However, adding CTA and CTP imaging to the basic prediction model did not improve it. For example, in the validation cohort, the area under the curve (AUC) was 0.78 (95% CI, 0.73 to 0.82) when using patient characteristics and NCCT. When CTA and CTP imaging were added to the basic prediction model, the AUC was 0.79 (95% CI, 0.75 to 0.83).

In 2017, DUST investigators evaluated prediction models with NCCT, CTA, or CTP at baseline and day 3 to predict the outcome at 90 days. A total of 224 patients from the DUST trial were selected who had anterior circulation occlusion on CTA with an ischemic deficit on CTP at admission and also had follow-up imaging on day 3. An unfavorable outcome (mRS score of 3-6) at 90 days was identified in 44% of the patients. For models that included baseline variables plus one of the three imaging modalities at day 3, the area under the receiver operating characteristics curve was 0.85 for NCCT, 0.86 for CTA, and 0.86 for CTP. All three models improved prediction compared with no imaging at day 3, but there was no difference between the models. CTP at day 3 was no better than NCCT in predicting the clinical outcome.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs were identified assessing use of CTP for stroke patients being evaluated for prognosis.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.
Because the clinical validity of CTP for this population has not been established, a chain of evidence supporting the clinical utility of CTP cannot be constructed.

Subsection Summary: Evaluation of Prognosis
Retrospective analyses of data from the MR CLEAN and DUST trials found that the ischemic core detected on CTP imaging was predictive of functional outcomes. However, analysis of data from the DUST study found no improvement in a prediction model when CTP imaging was added to a basic model that used only patient characteristics and non–contrast CT. CTP at day 3 did not outperform NCCT for stroke prognosis.

Subarachnoid Hemorrhage and Cerebral Vasospasm
Clinical Context and Test Purpose
The purpose of CTP imaging in patients with aneurysmal subarachnoid hemorrhage (SAH) is to evaluate those at high risk for vasospasm or delayed cerebral ischemia and to improve treatment decisions.

The question addressed in this evidence review is: Does CTP improve the net health outcome of patients with aneurysmal SAH?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is patients with SAH who are being evaluated for vasospasm or delayed cerebral ischemia.

Interventions
The intervention of interest is CTP imaging.

Comparators
The comparator of interest is standard management without CTP.

Outcomes
The outcomes of interest are function measured with NIHSS or mRS scores.

Timing
Functional outcomes (NIHSS, mRS) are measured at 90 days after aneurysmal SAH.

Setting
CTP is an add-on to NCCT and is widely available in hospitals.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and

unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews

A 2010 meta-analysis on the diagnostic accuracy of CTA and CTP for cerebral vasospasm identified three studies (total N=64 patients) that met the inclusion criteria and contained the appropriate data for statistical analysis. In these studies, "vasospasm" was defined on CTP as a perfusion deficit demonstrating prolonged mean transit time and decreased cerebral blood flow. However, there were no standardized thresholds for mean transit time or cerebral blood flow to determine vasospasm, contributing to the heterogeneity among these studies. For this meta-analysis, "angiographic vasospasm" was defined as evidence of arterial narrowing compared with the parent vessel or with a baseline examination; symptomatic and asymptomatic patients included. Compared with digital subtraction angiography, CT perfusion pooled estimates had 74% sensitivity and 93% specificity. Given the small pooled sample size and the heterogeneity in the CTP data, these results should be considered preliminary.

A 2014 systematic review and meta-analysis by Cremers et al included 11 studies (total N=570 patients) on the use of CTP to identify delayed cerebral ischemia. CTP imaging measures at admission did not differ between patients who did and did not develop delayed cerebral ischemia. Some measures of CTP (cerebral blood flow and mean transit time, but not cerebral blood volume [CBV]) differed between groups during the 4 to 14 days after subarachnoid hemorrhage, suggesting a possible role in diagnoses of delayed cerebral ischemia.

Cohort Studies

One study included in the Cremers meta-analysis is the 2011 prospective study with 97 patients that evaluated the accuracy of CTP imaging to diagnose delayed cerebral ischemia following aneurysmal subarachnoid hemorrhage. CTP imaging was performed between days 6 and 8 in asymptomatic patients and on the day of clinical deterioration in symptomatic patients. Perfusion maps were qualitatively evaluated by two neuroradiologists who were blinded to clinical and imaging data and compared to the reference standard. Based on a multistage hierarchical reference standard that incorporated both imaging and clinical criteria, 40 (41%) patients were diagnosed with delayed cerebral ischemia. Overall diagnostic accuracy for CT perfusion, determined from receiver operating characteristic (ROC) curves, was 93% for cerebral blood flow, 88% for mean transit time, and 72% for cerebral blood volume. The study also sought to determine a quantitative threshold for delayed cerebral ischemia with CTP imaging, although it was noted that absolute thresholds may not be generalizable due to differences in scanner equipment and post-processing methods. Clinical outcomes of the delayed cerebral ischemia group included 19 (48%) patients with no permanent neurologic deficit, 16 (40%) with permanent neurologic deficit, and 5 (13%) who died during hospitalization.

Sanelli et al (2011) also retrospectively studied the development of vasospasm in 75 patients with the aneurysmal subarachnoid hemorrhage who had a CTP imaging assessment (likely

overlap in subjects with the study described above). Based on a multistage reference standard, 28 (37%) patients were classified using vasospasm. CTP imaging values (cerebral blood flow and mean transit time) on days 0 to 3 were found to be significantly lower in the vasospasm group. Optimal thresholds were then determined for cerebral blood flow (50% sensitivity and 91% specificity), mean transit time (61% sensitivity and 70% specificity) and cerebral blood volume (36% sensitivity and 89% specificity). Clinical outcomes of the vasospasm group included 15 patients (54%) with no permanent neurologic deficit, 11 (39%) with permanent neurologic deficit, and two (7%) who died during hospitalization.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs were identified assessing use of CTP for patients with SAH being evaluated for vasospasm or delayed cerebral ischemia.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of CTP for this population has not been established, a chain of evidence supporting the clinical utility of CTP cannot be constructed.

Section Summary: Subarachnoid Hemorrhage and Cerebral Vasospasm

One prospective study has shown a qualitative measure of cerebral blood flow to have 93% accuracy for the detection of delayed cerebral ischemia with lower accuracy for cerebral blood volume. No studies identified provided evidence of a change in management leading to improved function following CTP imaging. Further study is needed to evaluate whether CTP in patients with aneurysmal subarachnoid hemorrhage leads to the early identification of patients at high risk for vasospasm or delayed cerebral ischemia, alters treatment decisions, and improves health outcomes.

Brain Tumors

Clinical Context and Test Purpose

The purpose of CTP imaging in patients with patients with brain tumors is for grading of gliomas. Potential uses are to guide biopsy and to monitor low-grade gliomas.

The question addressed in this evidence review is: Does CTP improve the net health outcome of patients with brain tumors?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is patients with gliomas.

Interventions
The intervention of interest is CTP imaging.

Comparators
The comparator of interest is standard management without CTP.

Outcomes
The outcome of interest is glioma grade.

Timing
Outcomes are measured at the time of CTP imaging.

Setting
CTP is an add-on to NCCT and is widely available in hospitals.

Technical Reliability
There is limited data on the technical reliability of CTP for brain tumors.

In 2011, Xyda et al reported a prospective study of the feasibility and efficacy of volume perfusion computed tomography (VPCT) for the preoperative assessment of suspected cerebral gliomas in 46 consecutive patients. (Whereas typical CTP imaging covers a relatively narrow range of brain tissue, the VPCT system with multi-spiral acquisition covers the entire tumor.) Two blinded readers independently evaluated VPCT by drawing volumes of interest (VOIs) around the tumor according to maximum intensity projection volumes. The VOIs were mapped onto the cerebral blood volume, CBF, and permeability perfusion datasets, which correspond to histopathologic microvascular density. VPCT was followed by stereotactic biopsy or surgery to evaluate the histopathology of the tumor and classified into low-grade (I and II) and high-grade (III and IV). The diagnostic power of the perfusion parameters was assessed using receiver operating characteristic (ROC) curve analysis. Permeability demonstrated the highest diagnostic accuracy (97% sensitivity, 100% specificity), positive predictive value (100%), and negative predictive value (94%) to identify or exclude high-grade tumors.

A 2011 review by Jain indicated that most of the literature on the utility of perfusion imaging for glioma grading is based on various MR perfusion techniques. One study (2007) compared CTP imaging with conventional MRI in 19 patients. With a cut-off point of greater than 1.92 normalized cerebral blood volume (nCBV), there was sensitivity of 85.7% and specificity of 100% to differentiate high-grade gliomas. There were no significant differences in nCBV between Grade III or IV tumors. A subsequent study by Jain et al (2008) correlated CTP imaging findings with histopathologic grade in 32 patients with astroglial tumors. Eight additional patients with oligodendrogliomas were excluded from analysis because of the known higher blood volume compared with astroglial tumors. Of the 32 patients included in the study, 8 had

low-grade gliomas and 24 had high-grade gliomas. In this select set of patients, CTP imaging showed significant differences in the Grade III and Grade IV tumors.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs were identified assessing use of CTP for patients with brain tumors undergoing grading of gliomas.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of CTP for this population has not been established, a chain of evidence supporting the clinical utility of CTP cannot be constructed.

Section Summary: Brain Tumors
For indications such brain tumors, data on CTP imaging are limited. One study assessed the diagnostic accuracy of CTP imaging to differentiate high-grade from low-grade gliomas. Prospective studies in an appropriate patient population are needed to evaluate the sensitivity and specificity of CTP glioma grading, with histopathologic assessment of tumors as the independent reference standard. One prospective study performed ROC analysis to evaluate the diagnostic accuracy of VPCT. This is the first report using VPCT to differentiate gliomas; therefore, replication of these findings in an independent sample is needed. Consistency in the thresholds used is also needed. Studies are also needed to show an improvement in health outcomes with CTP imaging. No recent reports on the use of CTP imaging for the evaluation of brain tumors were identified.

Summary of Evidence
Acute Stroke
For individuals who have acute stroke who are being evaluated for thrombolysis who receive CTP imaging, the evidence includes a systematic review with meta-analysis and cohort studies. Relevant outcomes are overall survival, test accuracy, symptoms, morbid events, and functional outcomes. One potential area of benefit is greater individualization of therapy for acute stroke by better defining at risk ischemic areas that may benefit from thrombolysis. Evidence from nonrandomized comparative studies has suggested that outcomes after thrombolysis are better in patients who have target mismatch on perfusion imaging than in patients without target mismatch and that patients with target mismatch treated after a three-hour time window have outcomes similar to patients treated within three hours. However, the therapeutic changes that

would be associated with identifying specific target mismatch pattern on CTP are not well-defined. Therefore, randomized controlled trials are needed to determine with greater certainty whether a strategy employing CTP imaging improves health outcomes compared with traditional strategies for the treatment of acute stroke. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have acute stroke who are being evaluated for prognosis who receive CTP imaging, the evidence includes a retrospective analysis of data from large prospective randomized trials. Relevant outcomes are overall survival, test accuracy, symptoms, morbid events, and functional outcomes. Retrospective analysis of data from the MR CLEAN and DUST trials have found that the ischemic core detected on CTP imaging was predictive of functional outcomes. However, analysis of data from the DUST study found no improvement in a prediction model when CTP imaging was added to a basic model that used only patient characteristics and non-contrast computed tomography. The evidence is insufficient to determine the effects of the technology on health outcomes.

Acute Anterior Large-Vessel Stroke

For individuals who have acute anterior large-vessel stroke who are being evaluated for mechanical embolectomy who receive CTP imaging, the evidence includes a randomized controlled trial. Relevant outcomes are overall survival, test accuracy, symptoms, morbid events, and functional outcomes. CTP is one of the several approaches used in acute stroke to define viable ischemic tissue better and therefore may benefit from mechanical endovascular intervention. Alternative methods of patient selection for mechanical embolectomy have included time from stroke onset, multiphase computed tomography angiography, or Alberta Stroke Program Early CT score. One randomized controlled trial showed improved outcomes with mechanical embolectomy when patients were selected based on CTP results. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Subarachnoid Hemorrhage and Cerebral Vasospasm

For individuals who have suspected subarachnoid hemorrhage and cerebral vasospasm who receive CTP imaging, the evidence includes a prospective study. Relevant outcomes are overall survival, test accuracy, symptoms, morbid events, and functional outcomes. CTP imaging is being evaluated for the diagnosis of vasospasm and delayed cerebral ischemia following aneurysmal subarachnoid hemorrhage. One prospective study showed a qualitative measure of cerebral blood flow to have 93% accuracy for the detection of delayed cerebral ischemia, with lower accuracy for cerebral blood volume. Prospective trials are needed to determine whether CTP imaging in patients with aneurysmal subarachnoid hemorrhage leads to the early identification of patients at high risk for vasospasm or delayed cerebral ischemia, alters treatment decisions, and improves health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Brain Tumors

For individuals who have brain tumors who receive CTP imaging, the evidence includes studies on diagnostic accuracy. Relevant outcomes are test accuracy, symptoms, morbid events, and functional outcomes. For indications such as brain tumors and head trauma, the data on CTP

imaging are limited. One study assessed the diagnostic accuracy of CTP imaging to differentiate high-grade from low-grade gliomas. Prospective studies in an appropriate population of patients are needed to evaluate the sensitivity and specificity of CTP glioma grading, with histopathologic assessment of tumors as the independent reference standard. One prospective study performed receiver operating characteristic curve analysis to evaluate the diagnostic accuracy of volume perfusion computed tomography. This is the first report using volume perfusion computed tomography to differentiate gliomas; therefore, replication of these findings in an independent sample of patients is needed as well as clarification of the clinical utility of this information. Studies showing the consistency in the thresholds used are needed as are studies showing improvement in health outcomes with CTP imaging. No recent reports on the use of CTP imaging for the evaluation of brain tumors have been identified. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

American Heart Association and American Stroke Association

The 2012 American Heart Association (AHA) and American Stroke Association (ASA) joint guidelines for the management of aneurysmal subarachnoid hemorrhage recommend that perfusion imaging with CT or MR can be useful to identify regions of potential brain ischemia (Class IIa; Level of Evidence B). The guidelines state that there are emerging data that perfusion imaging, demonstrating regions of hypoperfusion, may be more accurate for identification of delayed cerebral ischemia than anatomic imaging of arterial narrowing or changes in blood flow velocity by transcranial Doppler. The guidelines concluded that CTP imaging is a promising technology, although repeat measurements are limited by the risks of dye load and radiation exposure.

The AHA and ASA's 2013 guidelines on the early management of adults with ischemic stroke recommend that CTP and magnetic resonance perfusion, and diffusion imaging, including measures of infarct core and penumbra, may be considered for selecting patient for acute reperfusion therapy beyond IV fibrinolytic time windows. The guidelines state that these techniques provide additional information that may improve diagnosis, mechanism, and severity of ischemic stroke and permit more informed clinical decision making (Class IIb, Level of Evidence B).

In 2018, AHA and ASA revised their joint 2015 statement on the use of CTP for the early management of adults with ischemic stroke. Table 1 summarizes the new recommendations were made.

Table 1. New Guidelines Recommendations on Use of Computed Tomography Perfusion

Recommendation	SOE	LOB	LOE
Administration of IV alteplase should not be delayed based on "multimodal CT and MRI, including perfusion imaging" because trial analysis "has failed to demonstrate clinical efficacy in patients with various pretreatment imaging biomarkers compared with those without those markers"	III	Strong Harm	B-NR (non-randomized)
In selected patients with acute ischemic stroke and large vessel occlusion, CTP is recommended for clinical decision	I	Strong benefit	A (high quality evidence from multiple RCTs)

making regarding mechanical thrombectomy, "but only when imaging and other eligibility criteria from RCTs showing benefit are being strictly applied in selecting patients for mechanical thrombectomy"			
In selected patients with acute ischemic stroke (> 16-24 hours of last normal) and large vessel occlusion, DAWN criteria (which may include imaging findings from CTP) may be used for clinical decision making regarding mechanical thrombectomy	IIa	Moderate benefit	B-R (non-randomized)

CT: computed tomography; CTP: computed tomography perfusion; IV: intravenous; LOC: level of benefit; LOE: level of evidence; MRI: magnetic resonance imaging; RCT; randomized controlled trial; SOE: strength of evidence.

American Society of Neuroradiology et al

In 2013, the American Society of Neuroradiology, the American College of Radiology, and the Society of Neuro-Interventional Surgery issued a joint statement on imaging recommendations for acute stroke and transient ischemic attack patients. The following statements were made regarding perfusion imaging:

- "In acute stroke patients who are candidates for endovascular therapy, vascular imaging (CTA, MRA, DSA) [digital subtraction angiography]) is strongly recommended during the initial imaging evaluation. Perfusion imaging may be considered to assess the target tissue "at risk" for reperfusion therapy. However, the accuracy and usefulness of perfusion imaging to identify and differentiate viable tissue have not been well-established."
- "Determination of tissue viability based on imaging has the potential to individualize thrombolytic therapy and extend the therapeutic time window for some acute stroke patients. Although perfusion imaging has been incorporated into acute stroke imaging algorithms at some institutions, its clinical utility has not been proved."
- "It is important to note that perfusion imaging has many applications beyond characterization of the penumbra and triage of patients to acute revascularization therapy. These applications include, but are not limited to, the following: 1) improving the sensitivity and accuracy of stroke diagnosis (in some cases, a lesion on PCT [perfusion CT] leads to more careful scrutiny and identification of a vascular occlusion that was not evident prospectively, particularly in the M2 and more distal MCA branches); 2) excluding stroke mimics; 3) better assessment of the ischemic core and collateral flow; and 4) prediction of hemorrhagic transformation and malignant edema."

In 2017, ACR, ASNR, and the Society for Pediatric Radiology revised their joint practice parameter on the performance of computed tomography perfusion in neuroradiologic imaging. The primary indications for CTP imaging of the brain were described as acute neurologic change suspicious for stroke, suspected vasospasm following subarachnoid hemorrhage, and cerebral hemorrhage with secondary local ischemia. Secondary indications included follow-up of acute cerebral ischemia or infarction, to assist in planning and evaluating the effectiveness of therapy, in patients with a contraindication to MRI, in the setting of acute traumatic brain injury, and intracranial tumors. There were "little data" to support a role of brain CTP imaging in pediatric stroke.

American College of Radiology

American College of Radiology (ACR) Appropriateness Criteria, updated in 2016, provide the following ratings for head CTP imaging with contrast:

- Rating of 5 (may be appropriate) for asymptomatic individuals with structural lesion on physical examination (cervical bruit) and/or risk factors.
- Rating of 5 (may be appropriate) if directly employed in decision making and planning treatment for carotid territory or vertebrobasilar transient ischemic attack on the initial screening survey.
- Rating of 6 (may be appropriate) for a new focal neurologic defect, fixed or worsening; less than 6 hours.
- Rating of 5 (may be appropriate) for a new focal neurologic defect, fixed or worsening; longer than 6 hours.
- Rating of 5 (may be appropriate) for evaluation for cerebral vasospasm after aneurysmal subarachnoid hemorrhage.
- The ACR also notes that CT stroke protocols combining a brain non-contrast CT, CTA, and CTP may produce a relative radiation level of 1 to 10 mSv, and repeated use of this protocol in an individual patient might result in high radiation exposure to the scalp and eyes.

Agency for Healthcare Research and Quality

The Agency for Healthcare Research and Quality (AHRQ) published a report on acute stroke in 2005. It addressed multiple issues related to how the CTP imaging and angiography modalities affect the use of thrombolytic therapy for acute ischemic stroke. This report did not identify any studies on the prospective use of CTP imaging and angiography techniques in patient selection for thrombolysis.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Key Words:

Computed tomography (CT), computed tomography perfusion (CTP), perfusion CT (PCT), acute stroke, ischemic stroke, hemorrhagic stroke, anterior large vessel stroke, volume perfusion computed tomography(VPCT).

Approved by Governing Bodies:

Several postprocessing software packages (e.g., Siemens' syngo® Perfusion-CT, GE Healthcare's CT Perfusion 4, Philips Medical System's Brain Perfusion Option) have been cleared for marketing by the U.S. Food and Drug Administration for use with a CT system to perform perfusion imaging. The software is being distributed with new CT scanners.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP contracts: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT Codes:

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

Previous Coding:

CPT Codes:

76497	Unlisted computed tomography procedure (e.g., diagnostic, interventional)

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Policy History:

Medical Policy Group, September 2004 **(3)**
Medical Policy Administration Committee, October 2004
Available for comment October 15-November 29, 2004
Medical Policy Group, September 2006 **(1)**
Medical Policy Group, December 2007 **(1)**
Medical Policy Group, December 2008 **(2)**
Medical Policy Group, May 2010 **(1):** Policy updated, no coverage changes
Medical Policy Panel, September 2012
Medical Policy Group, September 2012 **(1):** Update to Descriptions, Key Points and References; no change to policy statement
Medical Policy Panel, August 2013
Medical Policy Group, March 2014 **(3):** 2013 Update to Description, Key Points & References; no change in policy statement
Medical Policy Panel, August 2014
Medical Policy Group, August 2014 **(3)**: 2014 Updates to Key Points & References; no change in policy statement
Medical Policy Panel, September 2015
Medical Policy Group, September 2015 **(3)**: 2015 Updates to Key Points & References; no change in policy statement
Medical Policy Panel, October 2015
Medical Policy Group, February 2016 **(3):** 2015 updates to Key Points and References; Policy statement added for CT-based perfusion imaging to meet medical criteria for coverage; another statement added for CT-based perfusion imaging investigational in all other situations
Medical Policy Administration Committee, February 2016
Available for comment February 10 through March 25, 2016
Medical Policy Panel, October 2016
Medical Policy Group, November 2016 **(3)**: 2016 Updates to Key Points & References; no change in policy statement.
Medical Policy Panel, September 2017
Medical Policy Group, October 2017 **(3):** 2017 Updates to Title, Description, Key Points & References; No change in policy statement.
Medical Policy Panel, September 2018
Medical Policy Group, October 2018 (**3**): Updates to Key Points, Approved by Governing Bodies, References and Key Words: Added: anterior large vessel stroke, volume perfusion computed tomography (VPCT), and CTP. No changes to policy statement.
