Computed Tomography Perfusion Imaging of the Brain

Policy # 00495
Original Effective Date: 03/16/2016
Current Effective Date: 03/15/2017

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:
- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider Computed tomography perfusion (CTP) imaging to select patients with anterior large-vessel stroke for mechanical embolectomy to be eligible for coverage.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers Computed tomography perfusion (CTP) imaging of the brain for all other indications to be investigational.*

Background/Overview
Computed tomography perfusion 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.

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.
- Non-contrast CT is used to rule out intracranial hemorrhage, tumor, or infection. Magnetic resonance diffusion-weighted imaging demonstrates acute infarction, and a gradient-recalled echo sequence excludes intracerebral hemorrhage.
- Computed tomography angiography (CTA) and magnetic resonance angiography are used to evaluate intra- and extracranial vasculature to detect the vascular occlusion and potentially guide therapy (eg, intravenous thrombolytics, or intra-arterial or mechanical thrombolysis).

The approved therapy, 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 3 hours after an ischemic event, preceded by a CT scan. Many
Computed Tomography Perfusion Imaging of the Brain

Policy # 00495
Original Effective Date: 03/16/2016
Current Effective Date: 03/15/2017

patients, however, do not present within the 3-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 3 hours after an ischemic stroke. Perfusion imaging is also being evaluated in the management of other neurologic conditions, such as subarachnoid hemorrhage and head trauma.

The potential utility of perfusion imaging of acute stroke is described as the following:
- 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 3-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 in acute stroke may include the following:
- detection and differential diagnosis (eg, excluding stroke mimics such as transient ischemic attack, complex migraine, seizure, conversion disorders, hypoglycemia, 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 in terms of infarct core and penumbra. However, multimodal CT has a short protocol time (5-6 minutes) and, because it can be performed with any modern CT equipment, is more widely available in the emergency department setting. CT perfusion 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 computed tomography and xenon-enhanced CT 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 is equal to regional cerebral blood volume divided by mean transit time. CTA and CTP imaging require ionizing radiation and iodinated contrast. It is estimated that a typical CTP imaging 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 3 to 5 days after hemorrhage, with maximal narrowing on digital subtraction angiography at 5 to 14 days. Currently, the diagnosis of vasospasm and the management decisions rely on clinical examination, transcranial Doppler sonography,
Computed Tomography Perfusion Imaging of the Brain

Policy # 00495
Original Effective Date: 03/16/2016
Current Effective Date: 03/15/2017

and digital subtraction angiography. Although symptomatic vasospasm affects 20% to 30% of patients with ASAHI, not all patients with angiographic vasospasm manifest clinical symptoms, and the symptoms can be nonspecific. In addition, 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, CTP imaging has been investigated for glioma grading. Potential advantages, compared with MR perfusion, include the wider availability, faster scanning times, and lower cost. CTP imaging may also be useful in distinguishing recurrent tumor from radiation necrosis.

FDA or Other Governmental Regulatory Approval
Several post processing software packages (eg, Siemens’ syngo® Perfusion-CT, GE Healthcare’s CT Perfusion 4, Philips Medical System’s Brain Perfusion Option) have been cleared for marketing by the FDA through the 510(k) process for use with a CT system to perform perfusion imaging. The software is being distributed with new CT scanners. FDA product code: JAK.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source
The most recent literature review was performed through August 23, 2016.

Acute Stroke
In 2009, the American Heart Association published a scientific statement that included a review of the evidence on CTP imaging. The scientific review determined that:

- Creation of accurate, quantitative CTP imaging has been validated in comparison with xenon-CT, positron emission tomography (PET), and magnetic resonance perfusion imaging (MRPI). CTP imaging appears to have greater spatial resolution than MRPI, and MRPI may be more sensitive to contamination by large vascular structure, leading to the possibility that visual assessment of core/penumbra mismatch is more reliable with CTP imaging than with MRPI.
- Even relatively imprecise measures of core/penumbra mismatch may be used to select patients for treatment beyond a strict 3-hour time window for intravenous thrombolysis. Multimodal CT may also determine suitability for other therapies, such as mechanical clot retrieval and intra-arterial thrombolysis, and increase patient access to new treatments.
Computed Tomography Perfusion Imaging of the Brain

Policy # 00495
Original Effective Date: 03/16/2016
Current Effective Date: 03/15/2017

- CTP imaging has the potential to serve as a surrogate marker of stroke severity (final size of infarction), possibly exceeding current predictors of outcome such as the National Institutes of Health Stroke Score (NIHSS). Because of the superior quantitative capability compared with MRPI, application of specific CTP imaging thresholds to predict tissue survival or infarction appears promising; however, these thresholds must be validated in larger patient cohorts for which reperfusion status is known.

More recent literature that addresses these issues follows.

One area of active research is to define the technical CT parameters that best detect perfusion mismatches. For example, in 2011, Bivard et al reported a prospective clinical validation study of CTP imaging for acute (<6 hours) ischemic stroke in 314 consecutive patients. Using a threshold of cerebral blood flow less than 40% of contralateral with a relative delay time less than 2 seconds, the correlation between the extent of CTP mismatch tissue (volume of “at-risk” tissue) salvaged from infarction and clinical improvement was a coefficient of determination (R2) of 0.59 (p=0.04) at 24 hours (National Institutes of Health Stroke Scale [NIHSS] score) and an R2 of 0.42 (p=0.02) at 90 days (Rankin Scale score). In 2016, this group of investigators reported a validation study on the threshold settings for whole-brain 320-detector CTP imaging and compared its performance to limited-coverage CTP imaging.

Evaluation for Thrombolysis

In 2015, Bivard et al examined the effectiveness of CTP imaging by assessing health outcomes in patients who qualified for tPA based on standard clinical/non-contrast CT criteria, who were either treated or not treated based on qualitative CTP results, and later had quantitative analysis of CTP imaging data. Patients selected for 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) who had been selected for tPA based on clinical/non-contrast CT information. In addition, of the patients treated with tPA, those who had target mismatch by CT perfusion had significantly better outcomes than patients treated with tPA who did not have target mismatch (OR=13.8 for 3-month mRS of ≤2). However, 83 of 269 (31%) untreated patients had target mismatch and 56 of 366 (15%) treated patients had a large ischemic core. This observational study suggests that CTP imaging has the potential to 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 could help select ischemic stroke patients for thrombolysis after the 3-hour time window. Sztriha et al studied a cohort of 254 thrombolysed patients; 174 received tPA at 0 to 3 hours using non-contrast CT, and 80 received tPA at 3 to 6 hours by using CT perfusion criteria. At 3 months, there were no differences between patients thrombolysed at 0 to 3 hours or at 3 to 6 hours in symptomatic intracerebral hemorrhage (3% vs 4%), or in any intracerebral hemorrhage (7% vs 9%). There were also no differences at 3 months in mortality (16% vs 9%) or the mRS score of 0 to 2 (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 multimodal CT (CT, computed tomography angiography [CTA], or CTP) to a cohort of 262 patients with acute stroke assessed without full multimodal brain imaging during a 5-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 3 months was higher in the multimodal group than in controls (adjusted OR=2.88) in models adjusted for age, sex, NIHSS score, glucose level, and treatment delay or modality. In a sensitivity analysis, multimodal-assisted thrombolysis yielded superior benefits in those patients treated after 3 hours (adjusted OR=4.48) than in patients treated within 3 hours (adjusted OR=1.31). For patients treated after 3 hours, 63% of patients assessed by multimodal CT had a Rankin Scale score of 2 or less compared with 24% of controls. Mortality (14% and 15%) and symptomatic hemorrhage (5% and 7%) were similar in the 2 groups, respectively.

In 2015, Burton et al reported a meta-analysis of 13 studies (3 randomized controlled trials [RCTs], 6 prospective cohort studies, 3 retrospective cohort studies) that used CTP imaging and gave 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 of the studies in the review was a prospective comparison of 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 imaging 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 the 2 groups, supporting further study in a randomized trial.

Section 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 3-hour time window have outcomes similar to those treated within 3 hours. However, randomized trials are needed to determine with 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
CTP imaging was used to select patients for mechanical embolectomy in the 2015 EXTEND-IA RCT. Other comparable trials of mechanical embolectomy from the same time period (e.g., ESCAPE, MR CLEAN, SWIFT PRIME) used time from stroke onset, multiphase CTA, or Alberta Stroke Program Early CT (ASPECTS) score to select patients for treatment.

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, but 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 compared between patients with and without CTP mismatch. There was no significant interaction for
Computed Tomography Perfusion Imaging of the Brain

Policy # 00495
Original Effective Date: 03/16/2016
Current Effective Date: 03/15/2017

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 to those who did not, suggesting a benefit for prognosis (see the Evaluation for Prognosis section).

In 2013, Sheth et al retrospectively studied the effect of multimodal CT on outcomes from endovascular therapy in 556 patients from 10 stroke centers. Patients were included if they presented within 8 hours of symptom onset and were then divided into groups based on the imaging modality employed before treatment. Non–contrast CT was used in 51% of patients, CT perfusion in 34%, and MRI in 14% of patients. Patients were selected for endovascular therapy based on specific imaging criteria. Non–contrast CT patients had significantly lower median times to groin puncture (61 minutes) than with CTP imaging (114 minutes) or MRI (124 minutes) patients. There were no differences in clinical outcomes, hemorrhage rates, or final infarct volumes among the groups.

Rai et al evaluated rates of recanalization and functional outcomes in a cohort of 99 patients selected by CT perfusion for treatment with endovascular stroke therapy and results compared 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 CTA correlating with the neurologic deficit. There was no cutoff time for treatment, and the type of endovascular therapy was thrombolitics in 33 (33.3%), 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.

Section 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. However, other RCTs have used time from stroke onset, multiphase CTA, and ASPECTS as selection criteria. Additional study is needed to determine whether selection for mechanical embolectomy based on CTP imaging mismatch leads to superior outcomes compared with other methods of patient selection.

Evaluation for Prognosis
A large number of case series have assessed how contrast CT patients had significantly lower median times to groin puncture (61 minutes) than with CTP imaging at admission might facilitate clinical decision making and predict outcomes in patients with suspected acute ischemic stroke.
In 2015, Borst et al (discussed above) reported on the relationship 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 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).

Section Summary: Evaluation for Prognosis
Retrospective analysis 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.

Subarachnoid Hemorrhage and Cerebral Vasospasm
A 2010 meta-analysis on the diagnostic accuracy of CTA and CT perfusion for cerebral vasospasm identified 3 studies (64 patients) that met the inclusion criteria and contained the appropriate data for statistical analysis. In these studies, “vasospasm” was defined on CT perfusion 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 were included. Compared with digital subtraction angiography, CT perfusion pooled estimates had 74% sensitivity and 93% specificity. Given the small sample size and the heterogeneity of the CT perfusion data, these results are considered preliminary. A 2014 meta-analysis by Cremers et al included 11 studies (570 patients) on the use of CT perfusion 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 CT perfusion (cerebral blood flow and mean transit time, but not cerebral blood volume) differed between the 2 groups during the 4 to 14 days after subarachnoid hemorrhage, suggesting a possible role in diagnoses of delayed cerebral ischemia.
One of the studies included in the meta-analysis was a prospective 2011 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 2 neuroradiologists, who were blinded to clinical and imaging data, and compared with the reference standard. Based on a multistage hierarchical reference standard that incorporated both imaging and clinical criteria, 40 patients (41%) 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 postprocessing 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 also retrospectively studied the development of vasospasm in 75 patients with aneurysmal subarachnoid hemorrhage who had had 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, mean transit time) on days 0 to 3 were significantly lower in the vasospasm group. Optimal thresholds were then determined for cerebral blood flow (50% sensitivity, 91% specificity), mean transit time (61% sensitivity, 70% specificity), and cerebral blood volume (36% sensitivity, 89% specificity). Clinical outcomes of the vasospasm group included 15 (54%) patients with no permanent neurologic deficit, 11 (39%) with permanent neurologic deficit, and 2 (7%) who died during hospitalization.

**Section Summary: Subarachnoid Hemorrhage and Cerebral Vasospasm**

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. RCTs are needed to evaluate 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.

**Brain 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 compared CTP imaging with conventional MRI in 19 patients. With a cutoff 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 and IV tumors. A subsequent study by Jain et al 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 IV tumors.
Computed Tomography Perfusion Imaging of the Brain

Policy # 00495
Original Effective Date: 03/16/2016
Current Effective Date: 03/15/2017

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 cerebral gliomas in 46 consecutive patients with suspected cerebral gliomas. (Whereas typical CTP imaging covers a relatively narrow range of brain tissue, the VPCT system with multispiral 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, cerebral blood flow, 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 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. Potential uses of VPCT are to guide biopsy and to monitor low-grade gliomas.

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.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01622517</td>
<td>Computed Tomography Perfusion (CTP) to Predict Response to Recanalization in Ischemic Stroke Project (CRISP)</td>
<td>200</td>
<td>Feb 2016 (ongoing)</td>
</tr>
<tr>
<td>NCT01387113</td>
<td>Expanding the Time Window for IV Thrombolysis With Rt-PA in Acute Ischemic Stroke Patients Using Computed Tomography Perfusion Imaging: The PERFusion Use in Stroke Evaluation (PERFUSE) Study</td>
<td>100</td>
<td>Jan 2017</td>
</tr>
<tr>
<td>NCT02360670</td>
<td>Penumbra and Recanalisation Acute Computed Tomography in Ischaemic Stroke Evaluation (PRACTISE)</td>
<td>400</td>
<td>May 2017</td>
</tr>
<tr>
<td>NCT01923922</td>
<td>CT Perfusion in the Prognostication of Cerebral High Grade Glioma</td>
<td>100</td>
<td>Dec 2017</td>
</tr>
<tr>
<td>NCT02586415</td>
<td>Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3 (DEFUSE 3)</td>
<td>476</td>
<td>Jun 2020</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
Clinical Input Received From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 4 physician specialty societies (8 reviewers) and 3 academic medical centers while this policy was under review in 2012. Most input supported some uses of CTP imaging; however, there was little consensus on the specific indications that would be considered medically necessary. For use in late stroke, most reviewers agreed that CTP imaging can identify patients with late stroke who may benefit from thrombolysis, but there was no consensus whether the benefits of using this strategy to select patients with late stroke for thrombolysis outweigh the risks. Some additional indications recommended by reviewers included differential diagnosis, eg, excluding stroke mimics, determination of stroke subtype, determination of stroke extent, identification of patients at high early risk for debilitating stroke following transient ischemic attack, determining the need for blood pressure management, guiding disposition decisions such as the need for intensive care unit placement, and establishing prognosis. Evaluation of chronic cerebral ischemia and head trauma were also noted as potential indications. There was near consensus that CTP imaging is investigational for head trauma and for the staging and management of brain tumors. Additional references were provided and subsequently reviewed.

Summary of Evidence

For individuals with acute stroke who are being evaluated for thrombolysis who receive CTP imaging, the evidence includes nonrandomized comparative 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 had 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 3-hour time window have outcomes similar to patients treated within 3 hours. However, the therapeutic changes that would be associated with identifying specific target mismatch pattern on CTP are not well defined. Therefore, RCTs 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 with acute anterior large-vessel stroke who are being evaluated for mechanical embolectomy who receive CT perfusion imaging, the evidence includes a randomized controlled trial. Relevant outcomes are overall survival, test accuracy, symptoms, morbid events, and functional outcomes. CT perfusion is one of several approaches that have been used in acute stroke to better define viable ischemic tissue 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 ASPECTS score. One RCT showed improved outcomes with mechanical embolectomy when patients were selected based on CT perfusion results. The evidence is insufficient to determine the effects of the technology on health outcomes.
Computed Tomography Perfusion Imaging of the Brain

Policy # 00495
Original Effective Date: 03/16/2016
Current Effective Date: 03/15/2017

sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals with acute stroke who are being evaluated for prognosis who receive CTP imaging, the evidence includes 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.

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.

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 like 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 (VPCT). This is the first report using VPCT 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.

References
Computed Tomography Perfusion Imaging of the Brain

Policy #  00495
Original Effective Date:  03/16/2016
Current Effective Date:  03/15/2017

Computed Tomography Perfusion Imaging of the Brain

Policy # 00495
Original Effective Date: 03/16/2016
Current Effective Date: 03/15/2017


Policy History

Original Effective Date: 03/16/2016
Current Effective Date: 03/15/2017
03/04/2016 Medical Policy Committee review
03/16/2016 Medical Policy Implementation Committee approval. New Policy.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
03/02/2017 Medical Policy Committee review
03/15/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date: 03/2018

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®), copyright 2016 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.
Computed Tomography Perfusion Imaging of the Brain

Policy # 00495
Original Effective Date: 03/16/2016
Current Effective Date: 03/15/2017

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>0042T</td>
</tr>
<tr>
<td>HCPCS Diagnosis</td>
<td>No codes</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>All related diagnoses</td>
</tr>
</tbody>
</table>

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
   1. Consultation with the Blue Cross and Blue Shield Association TEC or other nonaffiliated technology evaluation center(s);
   2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
   3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.