



Louisiana

Computed Tomography Perfusion Imaging of the Brain

Policy # 00495

Original Effective Date: 03/16/2016

Current Effective Date: 04/13/2020

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.

Note: Endovascular Procedures for Intracranial Arterial Disease (Atherosclerosis and Aneurysms) is addressed separately in medical policy 00198.

When Services Are 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.***

Policy Guidelines

Selection criteria for the EXTEND-IA trial included patients with an anterior large-vessel stroke who: were receiving a tissue plasminogen activator; were able to receive endovascular therapy within 6 hours of stroke onset; were functionally independent prior to the stroke; and had evidence of salvageable brain tissue and an ischemic core with a volume of less than 70 mL on computed tomography perfusion imaging.

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Background/Overview

Acute Stroke

The goal of acute stroke thrombolytic treatment is to rescue the ischemic penumbra, an area of the 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. Diffusion-weighted MRI is used to identify acute infarction, and a gradient-recalled echo sequence is used to exclude intracerebral hemorrhage.

CT angiography and magnetic resonance angiography are used to evaluate intra- and extracranial vasculature to detect the vascular occlusion and potentially guide therapy (eg, intravenous thrombolysis or mechanical thrombectomy).

The approved therapy, use of an intravenous tissue plasminogen activator, requires only a non-contrast CT scan to exclude the presence of hemorrhage (a contraindication to use of the drug). Current guidelines are to administer tissue plasminogen activator within the first three hours after an ischemic event, preceded by a CT scan. Many patients, however, do not present to the emergency department 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 neurologic conditions, such as subarachnoid hemorrhage and head trauma.

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

- identification of brain regions with extremely low cerebral blood flow, which represent 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

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- 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 (eg, excluding stroke mimics such as a 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 of stroke following a 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 minutes) and, because it can be performed with any modern CT equipment, is more widely available in the emergency department setting. 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 and xenon-enhanced CT scanning use a diffusible tracer.) The quantitative perfusion parameters are calculated from density changes for each pixel over time with the commercially available deconvolution-based software, in which cerebral blood flow is equal to regional cerebral blood volume divided by mean transit time. CT angiography and CTP imaging require ionizing radiation and iodinated contrast. It is estimated that 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 SAH in patients who survive the initial hemorrhage and can be seen in about two-thirds of patients with aneurysmal SAH. 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

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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 aneurysmal SAH, 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 a 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. Also, 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 magnetic resonance perfusion, include the wider availability, faster scanning times, and lower cost. CTP imaging may also be used to distinguish recurrent tumor from radiation necrosis.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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 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. Food and Drug Administration product code: JAK.

Rationale/Source

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.

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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, a randomized controlled trial (RCT), and cohort studies. The relevant outcomes are overall survival (OS), 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. Additionally, although available evidence from the RCT suggests some modest benefit for acute stroke patients who receive CTP or magnetic resonance imaging and receive alteplase up to nine hours post-stroke, the overall net health outcome is unclear because there was also a lack of significant benefit on the secondary outcome of functional improvement and a trend toward increased risk of symptomatic intracranial hemorrhage and there were important limitations in relevance and potential limitations in statistical power. 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 who have acute anterior large-vessel stroke who are being evaluated for mechanical embolectomy who receive CTP imaging, the evidence includes RCTs and cohort studies. The relevant outcomes are OS, 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 identify patients who might 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. Three RCTs showed improved outcomes with mechanical embolectomy when patients were selected based on CTP results within 6 hours, at 6 to 16 hours, and at 6 to 24 hours. The evidence is sufficient to quantitatively determine that the technology results in a meaningful improvement in the net health outcome.

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For individuals who have acute stroke who are being evaluated for prognosis who receive CTP imaging, the evidence includes retrospective analyses of large randomized trials. The relevant outcomes are OS, 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.

Subarachnoid Hemorrhage

For individuals who have SAH and cerebral vasospasm who receive CTP imaging, the evidence includes a systematic review with meta-analysis and a cohort study. The relevant outcomes are OS, test accuracy, symptoms, morbid events, and functional outcomes. CTP imaging is being evaluated for the diagnosis of vasospasm and delayed cerebral ischemia following aneurysmal SAH. 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 SAH 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. The 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 is 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 a histopathologic assessment of tumors as the independent reference standard. One prospective study performed a 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

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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.

Supplemental Information

Clinical Input 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 inputs supported some uses of computed tomography perfusion (CTP) imaging; however, there was little consensus on specific indications that would be considered medically necessary. For use in late stroke, most reviewers agreed that CTP imaging could 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 outweighed 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.

Practice Guidelines and Position Statements

American Heart Association and American Stroke Association

The American Heart Association (AHA) and American Stroke Association (ASA; 2012) joint guidelines on the management of aneurysmal subarachnoid hemorrhage recommended that perfusion imaging with computed tomography or magnetic resonance can be useful to identify regions of potential brain ischemia (class IIa; level of evidence B). The guidelines stated there are emerging data that perfusion imaging, demonstrating regions of hypoperfusion, may be more

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accurate for identifying 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 recommended that CTP, magnetic resonance perfusion, and diffusion imaging, including measures of infarct core and penumbra, may be considered for selecting a patient for acute reperfusion therapy beyond intravenous fibrinolytic time windows. The guidelines stated these techniques provide additional information that may improve diagnosis, mechanism, and severity of the ischemic stroke and permit more informed clinical decision making (class IIb, level of evidence B).

The AHA and ASA (2018) 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 (nonrandomized)
In selected patients with acute ischemic stroke and large vessel occlusion, CTP is recommended for clinical decision 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"	I	Strong benefit	A (high-quality evidence from multiple RCTs)
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)	IIa	Moderate benefit	B-R (nonrandomized)

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may be used for clinical decision making regarding mechanical thrombectomy			
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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

The American Society of Neuroradiology, the American College of Radiology (ACR), and the Society of NeuroInterventional Surgery (2013) issued a joint statement on imaging recommendations for acute stroke and transient ischemic attack. The following statements were made on perfusion imaging:

- "In acute stroke patients who are candidates for endovascular therapy, vascular imaging (CTA [computed tomography angiography], MRA [magnetic resonance angiography], 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 [middle cerebral artery] branches); 2) excluding stroke mimics; 3) better assessment of the ischemic core and collateral flow; and 4) prediction of hemorrhagic transformation and malignant edema."

The American Society of Neuroradiology, the Society for Pediatric Radiology, and ACR (2017) revised their joint practice parameters on the performance of CTP in neuroradiologic imaging. The primary indications for CTP imaging of the brain were described as acute neurologic change

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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 therapy effectiveness, in patients with a contraindication to magnetic resonance imaging, in the setting of acute traumatic brain injury, and intracranial tumors. There was "little data" to support the role of brain CTP imaging in pediatric stroke.

American College of Radiology

The ACR Appropriateness Criteria, updated in 2016, have provided the following ratings for head CTP imaging with contrast (see Table 2).

Table 2. Appropriateness of Head Computed Tomography Perfusion Imaging With Contrast

Recommendation	

Ratings of 5 and 6 "may be appropriate."

The ACR also noted that computed tomography stroke protocols combining a brain noncontrast computed tomography, computed tomography angiography, and CTP might 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.

U.S. Preventive Services Task Force Recommendations

Not applicable.



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Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT02360670	Penumbra and Recanalisation Acute Computed Tomography in Ischaemic Stroke Evaluation	400	Nov 2018
NCT01387113	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	100	Jan 2021
<i>Unpublished</i>			
NCT01923922	CTperfusion in the Prognostication of Cerebral High Grade Glioma	100	Dec 2017 (unknown)

NCT: national clinical trial.

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Louisiana

Computed Tomography Perfusion Imaging of the Brain

Policy # 00495

Original Effective Date: 03/16/2016

Current Effective Date: 04/13/2020

Policy History

Original Effective Date: 03/16/2016

Current Effective Date: 04/13/2020

- 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.
- 03/01/2018 Medical Policy Committee review
- 03/21/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 03/07/2019 Medical Policy Committee review
- 03/20/2019 Medical Policy Implementation Committee approval Coverage eligibility unchanged.
- 03/05/2020 Medical Policy Committee review
- 03/11/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 03/2021

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

Code Type	Code
CPT	0042T
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*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 U.S. Food and Drug Administration (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 technology assessment program (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.

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****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.

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NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

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.

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