Medical Policy

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Title: CT (Computed Tomography) Perfusion Imaging of the Brain

Description/Background

Perfusion imaging using computed tomography (CT) provides an assessment of cerebral blood flow that may assist in the identification of ischemic regions of the brain. This technology is proposed as a method 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 hypo-perfused 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 (DWI) demonstrates acute infarction, and a gradient-recalled echo (GRE) sequence excludes intracerebral hemorrhage.

Computed tomography angiography (CTA) and magnetic resonance angiography (MRA) are used to evaluate intra- and extra-cranial vasculature to detect the vascular occlusion and potentially guide therapy (e.g., intravenous thrombolytics, or intra-arterial or mechanical thrombolysis).

The approved thrombolytic therapy, 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 3 hours after an ischemic event, preceded by a CT scan. Many 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 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 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 perfusion CT (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, 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 min), 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 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/CT perfusion requires 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 ($\approx$3.3 mSv).

SUBARACHNOID HEMORRHAGE AND CEREBRAL VASOSPASM
Cerebral vasospasm is one of the major causes 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 3 to 5 days after hemorrhage, with maximal narrowing on digital subtraction angiography at 5-14 days. Currently, the diagnosis of vasospasm and 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. 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, CT perfusion has been investigated for glioma grading. Potential advantages, compared with MR perfusion, include the wider availability, faster scanning times, and lower cost. CT perfusion may also be useful in distinguishing recurrent tumor from radiation necrosis.

Regulatory Status:

Several post-processing 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 (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

Medical Policy Statement

Computed tomography (CT)–based perfusion imaging may be considered established to select patients with stroke for mechanical embolectomy.

CT-based perfusion imaging of the brain is considered experimental/investigational for all other indications. It has not been scientifically demonstrated to improve patient clinical outcomes.

Inclusionary and Exclusionary Guidelines

Inclusions
- Computed tomography (CT)–based perfusion imaging to select patients with stroke for mechanical embolectomy.

Exclusions

- CT-based perfusion imaging of the brain for all other indications not specified under the inclusions.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

  0042T

Other codes (investigational, not medically necessary, etc.):

  N/A

Rationale

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

Evaluation for Thrombolysis

Clinical Context and Test Purpose
The purpose of computed tomography perfusion (CTP) imaging in individuals with acute stroke who are being evaluated for thrombolysis is to guide treatment decisions.

The following **PICOs** were used to select literature to inform this review.

Populations
The relevant population of interest is individuals 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.

Study Selection Criteria

For the evaluation of CTP imaging, studies that meet the following eligibility criteria were considered:

- Reported on outcomes associated with the use of CTP to guide therapy decisions in a relevant patient population
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

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

Burton et al (2015) reported on a meta-analysis of 13 small but generally good-quality studies (including 3 RCTs and 6 prospective cohort studies) that used CTP imaging and provided intravenous thrombolytic treatment (Tables 1 and 2).[5] The objectives of the studies included comparisons of thrombolytic agents and predictions of clinical outcomes. Although relatively few patients received tPA based on CTP imaging results, the meta-analysis found rates of 90-day mortality, mRS scores ≤ 2 and in-hospital symptomatic intracranial hemorrhage rates (Table 2) that meta-analysis authors indicated "are comparable with those in studies that used other image modalities." However, to definitively determine the clinical utility of CTP imaging, RCT's are still needed that directly compare CTP imaging-guided thrombolytic therapy vs thrombolytic therapy guided by another imaging modality.

Table 1. Thrombolysis SR & M-A Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Burton (2015)[5,]	Search dates: 1946-2012; Publication dates: 2000-2012	13	Patients with acute ischemic stroke who underwent CTP neuroimaging for thrombolytic therapy selection	557 (2 to 140)	RCTs (3), prospective cohorts (7), retrospective cohorts (3)	In hospital to 90 days

CT: computed tomography; M-A: meta-analysis; RCT: randomized controlled trial; SR: systematic review.

Table 2. Results From Burton 2015 Systematic Review

Study		90-day mortality	mRS score ≤ 2 at 90 days	In-Hospital Symptomatic Intracranial Hemorrhage
Burton (2015)				
All patients	N	118	100	171
	Pooled effect (95% CI)	10.0% (5.4 to 15.9)	59.4% (38.2 to 78.9)	3.6% (1.4 to 6.8)
	I^2	0	73.1	0
Treated ≤ 3 hrs	N	95	47	94
	Pooled effect (95% CI)	12.5% (6.7 to 19.7)	42.5 (16.6 to 70.9)	3.3% (0.7 to 7.7)
	I^2	0	NA	0
Treated > 3 hrs	N	23	53	77
	Pooled effect (95% CI)	2.9% (0 to 12.7)	69.9% (0 to 83.5)	3.9% (0.8 to 9.2)

CI: confidence interval; CT: computed tomography; mRS: modified Rankin Scale; NA: not available; SICH: symptomatic intracranial hemorrhage.

Randomized Controlled Trials

The use of CTP imaging to select ischemic stroke patients for thrombolysis after the standard 4.5-hour time window has been evaluated. Ma et al (2019) reported the international Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND) RCT.[6] Automated computed tomography (CT) or magnetic resonance imaging (MRI) perfusion imaging was used in all patients (median NIHSS score range, 10 to 12) to detect hypo perfused but salvageable regions of the brain. Patients randomized to receive intravenous alteplase up to 9 hours after stroke onset (n=113) had no or minor neurological deficits compared to those who received placebo (n=112) (35.4% vs. 29.4%; adjusted rate ratio, 1.44; 95% confidence interval [CI], 1.01 to 2.06). However, symptomatic intracerebral hemorrhage occurred in a non-statistically significant greater number of patients in the alteplase group (6.2% vs. 0.9%; adjusted rate ratio, 7.22; 95% CI, 0.97 to 53.5). Although EXTEND provides information about the potential clinical utility of perfusion imaging to guide thrombolysis beyond 4.5 hours, conclusions cannot be drawn about CTP specifically. No information was provided about what proportion of participants received CT versus MRI. Results were also not reported by perfusion imaging type. A previous systematic review[5] and 2 previous prospective cohort studies[7,8] consistently found that use of CTP imaging to select patients for thrombolysis after 3 hours or 4.5 hours post-acute stroke led to generally favorable outcomes compared to using CTP imaging to select patients for treatment within 3 hours [5] and compared to using NCCT to select patients for treatment within 3 hours[8] or 4.5 hours.[7] In the prospective cohort study by Garcia-Bemejo et al (2012) that 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, there were 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 outcomes (64.5% vs. 60.5%, respectively) in both groups. A prospective cohort study by Medina-Rodriguez et al (2020) compared 53 patients receiving CTP with 657 control patients receiving standard of care to guide selection of thrombolysis within 4.5 hours of stroke onset.[9] The authors found no significant differences between groups at 90 days in symptomatic intracranial hemorrhage (3.8% vs. 3.8%; p=1.0) and mRS < 2 (72.0% vs. 60.4%; p=.107).

Nonrandomized Studies

Bivard et al (2015) reported a comparison of CTP imaging-guided thrombolytic therapy versus thrombolytic therapy guided by another imaging modality in a study that compared the qualitative analysis of CTP imaging (n=366) to historical controls (n=396) selected for tPA based on clinical and NCCT information.[10] Patients selected for tPA based on qualitative analysis of CTP imaging had higher odds of an excellent outcome (mRS score, 0 to 1; odds ratio [OR], 1.59; p=.009) and lower mortality (OR, 0.56; p=.021) than historical controls. In patients treated with tPA, those who had a target mismatch by CTP imaging had significantly better outcomes than patients without target mismatch (OR, 13.8 for 3-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 likely to respond to thrombolysis.

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. Evidence from an RCT (EXTEND) and nonrandomized comparative studies also provides general support of the clinical rationale of selecting patients for thrombolysis based on perfusion imaging (MRI or CTP) after a 3 or 4.5-hour time window. The EXTEND RCT had the potential to establish a general clinical rationale of using CTP imaging to select patients for thrombolysis. However, the net health benefit is not clear because the magnitude of improvement on the primary outcome of mRS of 0 or 1 at 90 days was modest and inconsistent between adjusted and unadjusted analyses, there was no significant difference on the secondary outcome of functional improvement, and there was a large increased risk of symptomatic intracranial hemorrhage. Also, the EXTEND RCT had important methodological and relevance limitations, including (1) baseline imbalance in age and NIHSS; (2) indirect intervention – CT or MRI with no stratification; and (3) not an optimal comparator. Therefore, further RCTs are still 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

Review of Evidence

Systematic Reviews

Kobeissi et al (2023) compared outcomes between CTP and NCCT for late window (6 to 24 hours) stroke thrombectomy.[11] The systematic review and meta-analysis included 5 cohort studies (N=3384) and the primary outcome was rate of functional independence, defined as modified Rankin scale 0 to 2 and secondary outcomes included rates of successful reperfusion, mortality, and symptomatic intracranial hemorrhage (sICH). Overall, in the pool analysis between the CTP and NCCT groups, rates of functional independence (OR 1.03; 95% CI, 0.87 to 1.22; p=.71) and sICH (OR, 1.09; 95% CI, 0.58 to 2.04; p=.80) were comparable. The CTP group had higher rates of successful reperfusion (OR ,1.31; 95% CI ,1.05 to 1.64; p =.015) along with lower rates of mortality (OR, 0.79; 95% CI, 0.65 to 0.96; p=.017) compared to the NCCT group.

Randomized Controlled Trials

The clinical utility of CTP imaging-based patient selection for thrombectomy has not yet been proven in an RCT in which inclusion of patients was not based on perfusion imaging findings. Numerous RCTs have shown that in patients with ischemic stroke with a proximal cerebral artery or internal carotid artery occlusion that were selected based on having a region of salvageable tissue on CTP imaging, thrombectomy within 6 hours,[12] at 6 to 16 hours,[13] and at 6 to 24 hours[14] results in better outcomes than standard medical therapy alone. Also, it should be noted that other comparable trials of mechanical embolectomy from the same period (e.g., Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in The Netherlands [MR CLEAN], Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke) also used time from stroke onset, multiphase CTA, or Alberta Stroke Program Early Computed Tomography Score to select patients for treatment.[15,16,17] Overall, these trials found a significant benefit of mechanical embolectomy with stent retrievers, and generally support a clinical rationale for CTP imaging-based patient selection. (See evidence review 2.01.54, which addresses endovascular procedures for intracranial arterial disease, for discussion of these trials.) However, such studies do not allow any conclusions on whether CTP imaging can reliably differentiate between those who will and will not benefit from thrombectomy.

One of the most recent RCTs that used CTP imaging-based patient selection for thrombectomy was the Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (DEFUSE 3) trial by Albers et al (2018), which compared endovascular therapy plus medical therapy (n=92) with medical therapy alone (n=90).[13] The DEFUSE 3 trial enrolled patients with proximal middle cerebral artery or internal carotid artery occlusion based on whether their initial infarct volume was ≤ 70 mL, their ratio of volume of ischemic tissue to initial infarct volume was ≥ 1.8, and their absolute volume of potentially reversible ischemia was ≥ 15 mL. Infarct and ischemia parameters were calculated using automated image processing software (RAPID) following selective application of either CTP (73%) or MRI diffusion and perfusion scans (27%). Enrollment was planned for up to 476 patients over 4 years but it was stopped early for efficacy after enrolling 182 patients. The DEFUSE 3 trial was designed to evaluate the effectiveness of endovascular treatment initiated later than the recommended 6 hours after patients were last seen well (6 to 16 hours) and had the primary outcome of ordinal score on the mRS at 90 days. Patients were 51% female, had a median age of 70 years, and a median NIHSS score of 16.

Compared to medical therapy alone in DEFUSE 3, thrombectomy improved the 90-day mRS (median scores, 3 vs. 4; OR, 2.77; 95% CI, 1.63 to 4.70) and rate of 90-day functional independence (45% vs. 17%; OR, 2.67; 95% CI, 1.60 to 4.48).[13] Additionally, there were no differences in 90-day death (14% vs. 26%; OR, 0.55; 95% CI, 0.30 to 1.02) or symptomatic intracranial hemorrhage (7% vs. 4%; OR, 1.47; 95% CI, 0.40 to 6.55). Furthermore, in a sensitivity analysis based on imaging modality (CT vs. MRI), there was no interaction by modality type in the effects of thrombectomy on 90-day functional independence. However, small sample size, selection bias (CT and MRI selectively used) and potential for residual confounding (no multivariable regression) are major limitations of the subanalysis.

Consistent with DEFUSE 3,[13] the Diffusion Weighted Imaging or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo (DAWN) RCT[14] and the EXTEND-IA trial[12] provide evidence that CTP imaging may be useful in identifying people who may benefit from thrombectomy within 6 hours[12] and 6 to 24 hours after stroke.[14] However, because neither DAWN nor EXTEND-IA

involves a comparison of patients who were selected for thrombectomy using other non-CTP imaging approaches or who were not selected for thrombectomy, these RCTs also do not provide definitive evidence of the clinical utility of CTP imaging. The PerfusiOn imaging Selection of Ischemic sTroke patients for endoVascular theErapy (POSITIVE) trial was also designed to evaluate functional outcomes in patients with emergent large vessel occlusion presenting within 0 to 12 hours who were selected for endovascular thrombectomy after perfusion imaging.[18] The POSITIVE trial was stopped early having enrolled 33 participants after the release of the DEFUSE 3 trial results. The overall proportion of patients achieving an mRS score of 0 to 2 was 75% in the thrombectomy cohort and 43% in the medical management group (OR, 4.00; 95% CI, 0.84 to 19.2), consistent with previous trials.

Nonrandomized Trials
Findings from 2 previous nonrandomized studies[19,20] have raised questions about whether CTP imaging can reliably differentiate between those who will and will not benefit from thrombectomy. First, a subanalysis of data from the MR CLEAN trial by Borst et al (2015) suggests that CTP imaging cannot reliably identify patients who would not benefit from mechanical embolectomy.[19] In this trial, inclusion was not limited to CTP imaging, so CTP was permitted if it were standard procedure at an institution. Of 500 patients in MR CLEAN, 333 (67%) underwent CTP imaging. Of 175 (52.6%) patients with adequate images, 102 fulfilled the CTP mismatch criteria. The primary outcome, mRS score at 90 days, 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 would not benefit from mechanical embolectomy. In both treatment groups, there was a shift toward 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 CTP for treatment with endovascular stroke therapy and compared results with historical controls from the Mechanical Embolus Removal in Cerebral Ischemia (MERCI), Multi-MERCI, and Penumbra device trials that treated all comers.[20] 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 thrombolytics in 33 (33.3%), the 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 device trial. In patients successfully recanalized, good outcomes were obtained in 67% in this study compared 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 (2013) compared with 54% in MERCI, 51% in Multi-MERCI, and 71% for Penumbra.

Further, real-world experience from a high-volume center in the Czech Republic using RAPID imaging analysis processing software to select patients for thrombectomy raises questions about the applicability of findings from RCTs of CTP imaging in everyday clinical practice.[21] In the EXTEND-IA RCT[12] - in which thrombectomy was initiated within a median of 210 minutes post-stroke - rates of 90-day mRS score of 0 to 2 were 71%. In contrast, in everyday clinical practice at the Czech Republic center, despite a similar median time from stroke to reperfusion

of 230 minutes, rates of 90-day mRS score of 0 to 2 were much lower at 37%. The authors of the Czech Republic study suggested this may have been due to the somewhat smaller ischemic cores and penumbras in their patients, but noted that many other factors that can vary in real-life clinical practice may also play a role (e.g., level/time of successful reperfusion, localization of core and penumbra).[21.]

Cohort Studies

Results of the CT Perfusion to Predict Response to Recanalization in Ischemic Stroke Project study were published by Lansberg et al (2017).[22.] This study was a multicenter cohort study of 190 acute stroke patients 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=.002; adjusted OR, 6.6; 95% CI, 2.1 to 20.9).

A single-center retrospective cohort study by De Muynck et al (2020) evaluated functional outcomes following introduction of CTP as a selection tool for thrombectomy compared with historical data from a similar local retrospective study.[23.] Among patients with acute ischemic stroke who underwent thrombectomy and provided evaluable data, there was no significant difference between CTP-guided selection (n=76) and historical controls (n=65) at 90 days in good functional outcome (mRS score of 0 to 2; 48.4% vs. 44%, respectively; p=1.0), excellent functional outcome (mRS score of 0 to 1; 34.4% vs. 29%; p=1.0), and significant intracranial hemorrhage (4.1% vs. 5%; p-value not reported).

Nogueira et al (2021) reported data from a prospective multicenter registry of patients who underwent mechanical embolectomy.[24.] Patients were included in the study if they had occlusions involving the intracranial internal carotid artery or the M1- or M2-segments of the middle cerebral artery, a premorbid mRS score of 0 to 2, and time-last-seen-well to arterial puncture of 0 to 24 hours. Among patients with time-last-seen-well to arterial puncture of 0 to 6 hours, 332 patients were selected for mechanical embolectomy based on NCCT (with or without CTA) alone, while 373 also underwent CTP. After adjusting for confounders, there were no differences between patients selected with CTP and patients selected with NCCT with or without CTA in terms of 90-day functional disability (ordinal mRS shift: adjusted OR, 0.936; 95% CI, 0.709 to 1.238 p=.644) or independence (mRS 0 to 2: adjusted OR, 1.178; 95% CI, 0.833 to 1.666; p=.355). Among patients with time-last-seen-well to arterial puncture of 6 to 24 hours, 68 patients were selected for mechanical embolectomy based on NCCT (with or without CTA) alone, while 180 also underwent CTP. After adjusting for confounders, there were no differences between patients selected with CTP and patients selected with NCCT with or without CTA in terms of 90-day functional disability (adjusted OR, 0.983; 95% CI, 0.81 to 1.662; p=.949) or independence (adjusted OR, 0.640; 95% CI, 0.318 to 1.289; p=.212). The findings of this study suggest that selection using CTP imaging may not be associated with better outcomes than selection using NCCT with or without CTA alone. This study was a retrospective analysis of registry data and susceptible to selection bias, therefore, findings require confirmation in an RCT.

Subsection Summary: Evaluation for Mechanical Embolectomy

Computed tomography perfusion imaging is one of several approaches used in acute stroke to better define viable ischemic tissue and identify patients who might benefit from mechanical

endovascular intervention. Randomized controlled trials have shown improved outcomes with mechanical embolectomy when patients were selected based on CTP imaging within 6 hours,[12,] at 6 to 16 hours,[13,] and at 6 to 24 hours,[14,] 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 Score as selection criteria. Computed tomography perfusion may be considered an effective method to determine suitability for mechanical embolectomy.

Evaluation for Prognosis

Review of Evidence

Investigators from the Dutch Acute Stroke Trial (DUST) trial (2017) evaluated prediction models with NCCT, CTA, or CTP at baseline and day 3 to predict outcomes at 90 days.[25,] 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 to 6) at 90 days was identified in 44% of patients. For models that included baseline variables plus 1 of the 3 imaging modalities on 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 3 models improved prediction compared with no imaging on day 3 but there was no difference between the models. Computed tomography perfusion imaging at day 3 was no better than NCCT in predicting the clinical outcome.

A prognostic model, developed with data from DUST, was reported by van Seeters et al (2015).[26,] The authors 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 to 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 before stroke symptoms, glucose level, whether the treatment had been given) and NCCT measures. Computed tomography angiography and CTP imaging also were predictive of clinical outcome. However, adding CTA and CTP imaging to the basic prediction model did not improve prediction. For example, in the validation cohort, the area under the curve 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 model, the area under the curve was 0.79 (95% CI, 0.75 to 0.83).

Borst et al (2015), discussed above, reported on the relation between CTP imaging-derived parameters and functional outcomes from the MR CLEAN trial.[19,] 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<.001) and percentage ischemic core (OR, 0.82 per 10%; 95% CI, 0.66 to 0.99 per 10%; p=.002), but not the penumbra. This trial population had been selected for treatment using mechanical embolectomy.

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. 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 individuals with aneurysmal subarachnoid hemorrhage (SAH) is to evaluate those at high risk for vasospasm or delayed cerebral ischemia and to improve treatment decisions.

The following **PICOs** were used to select literature to inform this review.

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

Interventions
The intervention of interest is CTP imaging as an add-on to NCCT.

Comparators
The following practice is currently being used to make decisions about managing SAH: standard management without CTP.

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

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).

Review of Evidence

Cerebral Ischemia
A meta-analysis by Greenberg et al (2010) assessing the diagnostic accuracy of CTA and CTP for cerebral vasospasm identified 3 studies (N=64) that met the inclusion criteria and contained data appropriate for statistical analysis.[27] In these studies, "vasospasm" was defined on CTP as a perfusion deficit demonstrating prolonged mean transit time and decreased cerebral blood flow (CBF). However, there were no standardized thresholds for mean transit time or CBF 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, CTP pooled estimates had 74% sensitivity and 93% specificity.

A systematic review and meta-analysis by Bergin et al (2023) compared CTA to CTP in the diagnosis of cerebral vasospasm.[28] Authors included 22 studies (8 CTA studies;12 CTP studies; 2 CTA and CTP studies; N=836); the meta-analysis for pooled estimates only included 13 studies (7 CTA studies; 6 CTP studies) due to insufficient result reporting in the other studies. In the pooled estimates, CTP had a sensitivity of 0.86 (95% CI, 0.81 to 0.92), specificity of 0.97 (95% CI, 0.95 to 0.98), positive predictive value (PPV) of 0.94 (95% CI, 0.89

to 0.98), and negative predicative value (NPV) of 0.94 (95% CI, 0.91 to 0.97). Comparatively, CTA had a sensitivity of 0.76 (95% CI, 0.72 to 0.80), specificity of 0.93 (95% CI, 0.92 to 0.95), PPV of 0.77 (95% CI, 0.76 to 0.79), and NPV of 0.81 (95% CI, 0.79 to 0.82). Authors noted that analysis of results is limited by heterogeneity between the studies and study data not always being present or in alignment (e.g., no accuracy outcomes compared with the gold standard were provided).

Table 3. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Greenberg et al (2010)[27.]					
Bergin et al (2023)[28.]					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 4. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Greenberg et al (2010)[27.]					2. small number of included studies, limited data with high inconsistency index values	
Bergin et al (2023)[28.]					2. small number of included studies, heterogeneity between included studies, and data sourced from studies not always in alignment	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Cohort Studies

The pattern of sensitivity and specificity with CTP were similar in a retrospective study by Stecco et al (2018) (70% and 100%, respectively).[29.] Stecco et al evaluated 19 patients selected for a combined CTA and CTP approach based on clinical signs of arterial vasospasm and positive transcranial Doppler. However, given the small sample sizes and the heterogeneity of the CTP imaging data, these results should be considered preliminary.

Sanelli et al (2011) also retrospectively studied the development of vasospasm in 75 patients with aneurysmal SAH who had a CTP imaging assessment (there was likely overlap in subjects with the study described above).[30] Based on a multistage reference standard, 28 (37%) patients were classified as having vasospasm. Computed tomography perfusion imaging values (CBF, mean transit time) on days 0 to 3 were significantly lower in the vasospasm group. Optimal thresholds were then determined for CBF (50% sensitivity, 91% specificity), mean transit time (61% sensitivity, 70% specificity), and cerebral blood volume (CBV) (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.

Delayed Cerebral Ischemia
A systematic review and meta-analysis by Cremers et al (2014) included 11 studies (N=570) on the use of CTP to identify delayed cerebral ischemia.[31] Computed tomography perfusion imaging measures at admission did not differ between patients who did and did not develop delayed cerebral ischemia. Some measures of CTP (CBF and mean transit time but not CBV) differed between groups during the 4 to 14 days after SAH, suggesting a possible role in diagnosis of delayed cerebral ischemia.

A meta-analysis by Sun et al (2019) evaluated the use of CTP to identify patients at risk for delayed cerebral ischemia in the acute phase (< 4 days) after aneurysmal SAH.[32] The meta-analysis included 3 studies (N=128), 2 of which were included in the meta-analysis by Cremers et al (2014). The authors reported that patients with positive CTP in the acute phase were significantly more likely to develop delayed cerebral ischemia (OR, 32.15; 95% CI, 9.92 to 104.21).

A meta-analysis by Han et al (2022) evaluated CTP parameters for predicting delayed cerebral ischemia after aneurysmal SAH.[33] Fifteen studies were included (N=882) in the analysis. Authors noted that most studies chose the cutoff values of their own tests as thresholds, instead of prespecified ones, which could overestimate test performance (high risk of bias in the index test domain of the QUADAS-2 methodological assessment tool). Authors reported that the best threshold for the prediction was 0.9 using the relative CBF parameter (sensitivity 97% and specificity 89%). Meta-analysis of the quantitative parameters reported that mean transit time represented the most valuable predictor when the calculation of the mean value was uniformed. Perfusion thresholds in the included studies were incomparable (results needed further validation). Authors concluded that CTP is a promising tool for predicting DCI in aneurysmal SAH, however the parameters require further standardization and validation.

Mitchelle et al (2024) conducted a meta-analysis evaluating CTP for screening vasospasm and delayed cerebral ischemia in aneurysmal SAH.[34] Thirty studies were included (N=1786) in the analysis. For the assessment of delayed cerebral ischemia using CTP, the pooled sensitivity was 82.1% (95% CI; 74.5% to 87.8%) and the specificity was 79.6% (95% CI; 73.0% to 84.9%). The positive likelihood ratio was 4.01 (95% CI; 2.94 to 5.47); and the negative likelihood ratio was 0.23 (95% CI; 0.12 to 0.33). For the assessment of vasospasm using CTP, the pooled sensitivity was 85.6% (95% CI; 74.2% to 92.5%) and the specificity was 87.9% (95% CI; 79.2% to 93.3%). The positive likelihood ratio was 7.10 (95% CI; 3.87 to 13.04); and the negative likelihood ratio was 0.16 (95% CI; 0.09 to 0.31). The authors note various reporting methods as a limitation of the meta-analysis. Standardization of CTP techniques and randomized controlled trials are still needed.

Table 5. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Cremers et al (2014)[31.]			4. Control patients differed between various studies	6. Most studies used different methods for measuring perfusion	
Sun et al (2019)[32.]				6. Different CTP parameters with various thresholds were used to evaluate results	
Han et al (2022)[33.]		1. Most studies chose cutoff values of their own tests as thresholds, instead of prespecifed ones			
Mitchelle et al (2024)			3. Not compared to other tests	6. Different CTP parameters were used	

CTP, computed tomography perfusion
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose; 4. Other
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests); 6. Other
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 6. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Cremers et al (2014)[31.]					2. small sample size	
Sun et al (2019)[32.]					2. small sample size	
Han et al (2022)[33.]					2. majority data from each study included were from a single center with small sample size (n<100)	
Mitchelle et al (2024)						

Cohort Studies

One study included in the Cremers et al (2014) meta-analysis is the prospective study by Sanelli et al (2011) of 97 patients that evaluated the accuracy of CTP imaging to diagnose delayed cerebral ischemia following aneurysmal SAH.[34] Computed tomography perfusion 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, both 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 (41%) patients were diagnosed with delayed cerebral ischemia. Overall diagnostic accuracy for CTP, determined from receiver operating characteristic curves, was 93% for CBF, 88% for mean transit time, and 72% for CBV. The study also sought to determine a quantitative threshold for delayed cerebral ischemia with CTP imaging, although it was noted that absolute thresholds might 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.

A retrospective cohort study by Starnoni et al (2019) of 38 patients with aneurysmal SAH evaluated CTP within 48 hours after hemorrhage.[35] The occurrence of delayed cerebral ischemia was significantly correlated with lower mean early CBF values (p=.049) and vasospasm with lower mean CBF (p=.01) and mean transit time (p<.00001) values. Mean transit time threshold values of 5.5 seconds were shown to have 94% specificity and 100% sensitivity for predicting the risk of developing vasospasm.

Section Summary: Subarachnoid Hemorrhage and Cerebral Vasospasm

One prospective study has shown a qualitative measure of CBF to have 93% accuracy for the detection of delayed cerebral ischemia, with lower accuracy for CBV. No studies identified provided evidence of a change in management leading to improved function following CTP imaging. Meta-analyses have found high diagnostic accuracy determined for both CTA and CTP in cerebral vasospasms, however, note that the evidence is limited and data is highly variable. Further study is needed to evaluate whether CTP 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.

BRAIN TUMORS

Clinical Context and Test Purpose

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

The following **PICOs** were used to select literature to inform this review.

Populations
The relevant population of interest is individuals with gliomas.

Interventions
The intervention of interest is CTP imaging as an add-on to NCCT.

Comparators
The comparator of interest is standard management without CTP.

Outcomes
The outcome of interest is glioma grade.

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).

Review of Evidence
Xyda et al (2011) reported on 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.[37,] 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 around the tumor according to maximum intensity projection volumes. The volumes of interest were mapped onto the CBV, CBF, and permeability perfusion datasets, which correspond to histopathologic microvascular density. The VPCT imaging was followed by stereotactic biopsy or surgery to evaluate the histopathology of the tumor and classified into a low grade (I to II) and high grade (III to IV). The diagnostic power of the perfusion parameters was assessed using receiver operating characteristic 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 review by Jain (2011) indicated that most of the literature on the utility of perfusion imaging for glioma grading is based on various magnetic resonance perfusion techniques.[38] A study by Ellika et al (2007) compared CTP imaging with conventional MRI in 19 patients.[39] With a cutoff point of greater than 1.92 normalized CBV, there was a sensitivity of 85.7% and a specificity of 100% to differentiate high-grade gliomas. There were no significant differences in normalized CBV between grade III and IV tumors. A subsequent study by Jain et al (2008) correlated CTP imaging findings with histopathologic grade in 32 patients with astroglial tumors.[40] 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 grade III and IV tumors.

Section Summary: Brain Tumors
The data on CTP imaging for brain tumors are limited. One study assessed the diagnostic accuracy of CTP imaging to differentiate between high-grade and low-grade gliomas. Prospective studies in an appropriate patient population 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 receiver operating characteristic 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 following the use of 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 with acute stroke who are being evaluated for thrombolysis who receive computed tomography perfusion (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. The evidence is sufficient 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 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 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 CTP results. The evidence is 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 sufficient to determine the effects of the technology on health outcomes.

Subarachnoid Hemorrhage
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 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.

Ongoing and Unpublished Clinical Trials

Some currently 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
Ongoing			
NCT04879615	Treatment With Intravenous Alteplase in Ischemic Stroke Patients With Onset Time Between 4.5 and 24 Hours	372	Dec 2025
NCT05276934	Prospective Assessment of Brain Imaging After Aneurysmal of AVM-related Intracranial Hemorrhage	100	Dec 2025
NCT05230914	NOn-contrast Computed Tomography Versus Computed Tomography Perfusion Selection in Stroke Patients for Endovascular Treatment: the NO-CTP Cluster-randomized, Crossover Trial	3400	Nov 2026
NCT02056769	CT Perfusion Imaging to Predict Vasospasm in Subarachnoid Hemorrhage	41	Jun 2026
Unpublished			
NCT01923922	CT perfusion in the Prognostication of Cerebral High Grade Glioma	100	Dec 2017 (unknown)
NCT02360670	Penumbra and Recanalisation Acute Computed Tomography in Ischaemic Stroke Evaluation	400	Nov 2018 (unknown)

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	48	Jan 2022

NCT: national clinical trial

SUPPLEMENTAL INFORMATION

Clinical Input Received through 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 by Blue Cross Blue Shield Association (BCBSA) from 4 physician specialty societies (8 reviewers) and 3 academic medical centers while this policy was under review in 2012. The majority input supported some uses of CTP; 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 can identify patients with late stroke who may benefit from thrombolysis, but there was no consensus on 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, e.g., 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 is investigational for head trauma and for the staging and management of brain tumors. Additional references were provided, which were subsequently reviewed.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Heart Association and American Stroke Association

The American Heart Association (AHA) and American Stroke Association (ASA; 2023) joint guidelines on the management of aneurysmal subarachnoid hemorrhage [aSAH]state that "in patients with aSAH with suspected vasospasm or limited neurological examination, CTA [computed tomography angiography] or CT perfusion (CTP) can be useful to detect vasospasm and predict DCI [delayed cerebral ischemia] (Class 2a; level of evidence B-NR [nonrandomized])"[41]The guideline states that CTP can aid in the early prediction of perfusion abnormalities, and has a positive predictive value of 0.67 for DCI. However, the guideline also states that "further validation of CTP thresholds to guide more invasive angiographic evaluation or medical therapy is needed".

AHA/ASA's 2013 guidelines for the early management of adults with ischemic stroke recommended that CTP and MRI 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.[42] The guidelines state that these techniques provide additional information that may improve diagnosis, mechanism, and severity of

ischemic stroke and allow more informed clinical decision making. (class IIb, level of evidence B).[43]

Table 7. New Guidelines Recommendations on Use of Computed Tomography Perfusion

Recommendation	SOE	LOB	LOE
In patients eligible for IV alteplase, because benefit of therapy is time dependent, treatment should be initiated as quickly as possible and not delayed for additional multimodal neuroimaging, such as CT and MRI perfusion imaging.	I	Strong benefit	B-NR (nonrandomized)
When selecting patients with AIS within 6 to 24 hours of last known normal who have large vessel occlusion in the anterior circulation, obtaining CTP or DW-MRI, with or without MRI perfusion, is recommended to aid in patient selection for mechanical thrombectomy, but only when patients meet other eligibility criteria from one of the RCTs that showed benefit from mechanical thrombectomy in this extended time window.	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) may be used for clinical decision making regarding mechanical thrombectomy	IIa	Moderate benefit	B-R (nonrandomized)

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 (ACR), and the Society of NeuroInterventional Surgery issued a joint statement on imaging recommendations for acute stroke and transient ischemic attack patients.[44] The following statements were made regarding perfusion imaging:

- "In acute stroke patients who are candidates for endovascular therapy, vascular imaging (CTA, MRA, DSA) 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 2022, the American Society of Neuroradiology, the Society for Pediatric Radiology, and ACR revised their joint practice parameters on the performance of CTP in neuroradiologic imaging.[45] The primary indications for CTP imaging of the brain were described as diagnosis of ischemic stroke, differentiation of salvageable ischemic penumbra from unsalvageable ischemic core, distinguishing true "at-risk" ischemic penumbra from benign oligemia, identifying patients most likely to benefit from thrombolysis or thrombectomy, predicting hemorrhagic transformation in acute ischemic stroke, identifying patients with malignant profiles,   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, identifying cerebral hyperperfusion syndrome, 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 a role of brain CTP imaging in pediatric stroke.

American College of Radiology
ACR Appropriateness Criteria, updated in 2016, have provided the following ratings for head CTP imaging with contrast (see Table 5).[46]

Table 8. Appropriateness of Head Computed Tomography Perfusion Imaging With Contrast

Recommendation	Rating
For asymptomatic individuals with a structural lesion on physical examination (cervical bruit) and/or risk factors	5
If directly employed in decision making and planning treatment for carotid territory or vertebrobasilar transient ischemic attack on the initial screening survey	5
For a new focal neurologic defect, fixed or worsening; less than 6 hours	6
For a new focal neurologic defect, fixed or worsening; longer than 6 hours	5
For evaluation for cerebral vasospasm after aneurismal subarachnoid hemorrhage	5

Ratings of 5 and 6: "may be appropriate"

ACR also noted that CT stroke protocols combining a brain noncontrast CT, CTA, 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.

Government Regulations
National/Local:
There is no national coverage determination on this topic.

WPS does have a local coverage determination (LCD): Category III Codes (L35490) Effective on or after 11/17/2024.

CMS considers the concordant level I evidence of a large clinical benefit after CTP imaging (using automated post-processing software algorithmic analysis) in acute ischemic stroke (AIS) secondary to large vessel occlusion (LVO), to assist in late endovascular mechanical thrombectomy (EVT) eligibility determination per AHA/ASA guidelines, medically reasonable and necessary when the following conditions are fulfilled:

1. Intracranial internal carotid artery (ICA) **OR** middle cerebral artery (MCA) occlusion
2. The medical record documents the patient is being considered for endovascular mechanical thrombectomy (EVT) and does not have contraindications to the EVT (based on DAWN or DEFUSE3 trial criteria)
3. Treatment (femoral puncture) can be started within 6-24 hours of the last time known to be at neurologic baseline

While there is a promise to CTP technology applied to other neuroimaging areas, there is still insufficient evidence. Other stroke or non-stroke indications, including routine assessment of AIS, determination of hemorrhagic transformation (HT), and other indications, are not considered medically reasonable and necessary at this time.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

PET/CT Fusion

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through January2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
9/1/09	7/15/09	6/16/09	Joint policy established
7/1/11	4/19/11	5/3/11	Policy reformatted; additional references added.
11/1/12	8/21/12	8/21/12	Routine maintenance; title changed from "Cerebral Perfusion Analysis Using Computed Tomography" to "CT (Computed Tomography) Perfusion Imaging."
11/1/13	8/22/13	8/27/13	Routine review; updated references and rationale.
3/1/15	12/12/14	12/29/14	Routine maintenance; updated references and rationale.
5/1/16	2/16/16	3/16/16	Policy position changed from experimental/investigational to established for select patients with stroke for mechanical embolectomy. All other indications remain experimental/investigational.
5/1/17	2/21/17	2/21/17	Updated rationale section and reference section (adding 3, 15,18 and 30). No change in policy status.
5/1/18	2/20/18	2/20/18	Updated rationale, added reference # 4, 18, 20 and 31. No change in policy status.
5/1/19	2/19/19		Routine policy maintenance, added reference #27. No change in policy status.
5/1/20	2/18/20		Rationale reorganized, added references 5, 9, 10, 16 and 21. No changes in policy status.
5/1/21	2/16/21		Rationale reorganized and updated, references 8, 19, 26 and 28 added. Government section updated. No change in policy status.

5/1/22	2/15/22		Routine policy maintenance, added reference #20, no change in policy status.
5/1/23	3/9/23		Routine maintenance, no changes in policy status. (ds)
5/1/24	2/20/24		Routine policy maintenance, no change in policy status. Vendor managed: N/A (ds)
5/1/25			Rationale updated, added reference #34. No change in policy status. Vendor managed: N/A (ds)

Next Review Date: 1st Qtr. 2026

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: CT (COMPUTED TOMOGRAPHY) PERFUSION IMAGING OF THE BRAIN

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	According to policy guidelines
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

N/A