6.01.49	Computed Tomography Perfusion Imaging of the Brain		
Original Policy Date:	June 28, 2007	**Effective Date:**	November 1, 2023
Section:	6.0 Radiology	**Page:**	Page 1 of 27

Policy Statement

I. Computed tomography perfusion (CTP) imaging may be considered **medically necessary** to select individuals with anterior large-vessel stroke for mechanical embolectomy.

II. Computed tomography perfusion (CTP) imaging of the brain is considered **investigational** for all other indications.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Selection criteria for the Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial (EXTEND-IA) trial included participants 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.

Coding

There is a CPT category III code specific to this test:

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

Description

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 (SAH), cerebral vasospasm, brain tumors, and head trauma.

Related Policies

- Endovascular Procedures for Intracranial Arterial Disease (Atherosclerosis and Aneurysms)

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

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

Rationale

Background

Acute Stroke

In the United States (U.S.), approximately 795,000 individuals experience a stroke annually, making stroke the fifth most common cause of death in the U.S.[1,] Black individuals experience a 2-fold greater risk of first-ever stroke compared to White individuals, and stroke incidence can differ according to geographic region.[2,] Additionally, the Hispanic population has experienced an increase in stroke incidence since 2013. The quality of stroke care in minority individuals is impacted by several factors that lead to disparities, most notably being overall access to quality health care. A systematic review (Ikeme et al 2022) found racial disparities in emergency medical service utilization and time to treatment.[3,] White patients were estimated to use emergency medical services at a greater rate (59.8%) compared to African American (55.6%), Asian (54.7%), and Hispanic patients (53.2%). A greater proportion of White patients (37.4%) were estimated to arrive within 3 hours from onset of stroke symptoms compared to African American (26.0%) and Hispanic (28.9%) patients. Additionally, a greater proportion of White patients (2.8%) were estimated to receive tissue plasminogen activator (tPA) compared with African American (2.3%), Hispanic (2.6%), and Asian (2.3%) patients. Another recent retrospective study by Tarko et al (2022) found that among 37,790 patients in the Veterans Health Administration system, absolute risk of 30-day mortality after intracerebral hemorrhage was 3.2% higher for Black patients and, after subarachnoid hemorrhage, was 10.3% higher for Hispanic patients compared with White patients.[4,]

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 (NCCT) 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.

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

The approved thrombolytic therapy, an intravenous tPA, requires only a NCCT scan to exclude the presence of hemorrhage (a contraindication to 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 to the emergency department within the 3-hour window, and thrombolysis carries a risk of intracranial hemorrhage. Thus, more sophisticated imaging may be needed to inform 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 (SAH) 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 3-hour window
- triage of patients with at-risk brain regions to other available therapies, such as induced hypertension or mechanical clot retrieval
- decisions regarding intensive monitoring of patients with large, abnormally perfused brain regions
- biologically-based management of patients who awaken with a stroke for which the precise time of onset is unknown.

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

- detection and differential diagnosis (e.g., 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 to 6 minutes) and, because it can be performed with any modern CT equipment, is more widely available in the emergency department setting. Computed tomography perfusion imaging 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. Computed tomography 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 (approximately 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 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. Computed tomography perfusion imaging may also be used to distinguish recurrent tumor from radiation necrosis.

Literature Review

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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Acute Stroke

Evaluation for Thrombolysis

Clinical Context and Test Purpose

The purpose of computed tomography perfusion (CTP) imaging in patients with acute stroke who are being evaluated for thrombolysis is to guide treatment decisions.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients with acute stroke who are being evaluated for thrombolysis.

Interventions

The interventions of interest are CTP imaging as an add-on to non-contrast computed tomography (NCCT) and computed tomography angiography (CTA).

Comparators

The following practice is currently being used to make decisions about managing acute stroke: standard workup without CTP (e.g., NCCT, CTA).

Outcomes

The general outcomes of interest are overall survival (OS), test accuracy, symptoms, morbid events, and functional outcomes. The specific outcomes of interest are function measured with the National Institutes of Health Stroke Scale (NIHSS) or modified Rankin Scale (mRS) scores at least 90 days following thrombolysis.

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).

Review of Evidence

Systematic Reviews

Burton et al (2015) performed a meta-analysis of 13 small but generally good-quality studies (including 3 randomized controlled trials [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. Relatively few patients received tissue plasminogen activator (tPA) based on CTP imaging results. However, the authors reported rates of 90-day mortality, mRS scores ≤2 and in-hospital symptomatic intracranial hemorrhage (Table 2) that they indicated "are comparable with those in studies that used other image modalities." Nonetheless, to more definitively determine the clinical utility of CTP imaging, RCTs are still needed that directly compare thrombolytic therapy guided by CTP imaging versus other imaging modalities.

Table 1. Systematic Review & Meta-Analysis 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

CTP: computed tomography perfusion; RCT: randomized controlled trial.

Table 2. Systematic Review & Meta-Analysis Results (all patients selected for thrombolysis using CTP)

Study		90-day mortality	mRS score ≤ 2 at 90 days	In-Hospital Symptomatic Intracranial Hemorrhage
Burton (2015) [5,]				
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; CTP: computed tomography perfusion; mRS: modified Rankin Scale; NA: not available.

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 hypoperfused 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.

Clinically Useful

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

Direct Evidence

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

Chain of Evidence

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

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 trend toward 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

Clinical Context and Test Purpose

The purpose of CTP imaging in patients with acute anterior large-vessel stroke who are being evaluated for mechanical embolectomy is to guide treatment decisions.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients with acute anterior large-vessel stroke who are being evaluated for mechanical embolectomy.

Interventions

The interventions of interest are CTP imaging as an add-on to NCCT and CTA.

Comparators

The following practice is currently being used to make decisions about managing acute stroke: standard workup without CTP (e.g., NCCT, CTA).

Outcomes

The general outcomes of interest are OS, test accuracy, symptoms, morbid events, and functional outcomes. The specific outcomes of interest are function measured with the NIHSS or mRS scores at least 90 days following 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).

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 (OR1.31; 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.

Clinically Useful

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

Direct Evidence

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

Chain of Evidence

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

Section 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

Clinical Context and Test Purpose

The purpose of CTP imaging in patients with acute stroke who are being evaluated for prognosis is to guide treatment decisions.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients with acute stroke who are being evaluated for prognosis.

Interventions

The interventions of interest are CTP imaging as an add-on to NCCT and CTA.

Comparators

The following practice is currently being used to make decisions about managing acute stroke: standard workup without CTP (e.g., NCCT, CTA).

Outcomes

The general outcomes of interest are OS, test accuracy, symptoms, morbid events, and functional outcomes. The specific outcomes of interest are function measured with the NIHSS or mRS scores at least 90 days 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 the prognostic value of CTP 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).

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.

Clinically Useful

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

Direct Evidence

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

Chain of Evidence

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

Section Summary: Evaluation of Prognosis

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

Subarachnoid Hemorrhage and Cerebral Vasospasm

Clinical Context and Test Purpose

The purpose of CTP imaging in patients with subarachnoid hemorrhage (SAH) is to evaluate those at high risk for vasospasm or delayed cerebral ischemia and to improve treatment decisions.

The following PICO was used to select literature to inform this review.

Populations

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

Interventions

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

Comparators

The following practice is currently being used to make decisions about managing SAH: clinical evaluation.

Outcomes
The general outcomes of interest are OS, test accuracy, symptoms, morbid events, and functional outcomes. The specific outcomes of interest are function as measured with NIHSS or mRS scores at 90 days after aneurysmal SAH.

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

- Reported on the accuracy of CTP in diagnosing cerebral vasospasm
- Included a suitable reference standard
- 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).

Review of Evidence
Cerebral Ischemia

Meta-analyses
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

Meta-analyses

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.

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 15respecified ones			

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)	

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

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.

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

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

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

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 patients with brain tumors is grading gliomas. Potential uses are to guide biopsy and to monitor low-grade gliomas.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is patients with brain tumors; specifically, gliomas.

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 brain tumors: MRI.

Outcomes
The general outcomes of interest are test accuracy, symptoms, morbid events, and functional outcomes. Specific outcomes of interest include glioma grade.

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

- Reported on the use of CTP for assessing gliomas
- Included a suitable reference standard
- 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).

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.[36,] 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.[37,] A study by Ellika et al (2007) compared CTP imaging with conventional MRI in 19 patients.[38,] 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.[39,] 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.

Clinically Useful

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

Direct Evidence

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

Chain of Evidence

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

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.

Supplemental information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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.

2012 Input

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, 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 imaging is investigational for head trauma and for the staging and management of brain tumors.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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])"[40,]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".

The AHA and ASA (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.[41,] 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). This guideline was then updated in 2018, however, in 2019 the AHA and ASA revised their 2018 guideline statement on the use of CTP for the early management of adults with ischemic stroke.[42,] Table 3 summarizes the new recommendations that were made.

Table 7. AHA and ASA 2019 Guideline Recommendations on Use of CTP

Recommendation	SOR	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 acute ischemic stroke 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 to 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)

AHA: American Heart Association; ASA: American Stroke Association; CT: computed tomography; CTP: computed tomography perfusion; DW-MRI: diffusion-weighted magnetic resonance imaging; IV: intravenous; LOB: level of benefit; LOE: level of evidence; MRI: magnetic resonance imaging; RCT; randomized controlled trial; SOR: strength of recommendation.

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.[43,] 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-computed tomography] 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 (2022) revised their joint practice parameters on the performance of CTP in neuroradiologic imaging.[44,] 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 [MRI], 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 4).[45,]

Table 8. Appropriateness of Head CTP 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 aneurysmal subarachnoid hemorrhage	5

Rating scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate.
CTP: computed tomography perfusion.

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.

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 5.

Table 9. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
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	Jul 2022
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	Feb 2024
Unpublished			
NCT01923922	CT perfusion in the Prognostication of Cerebral High Grade Glioma	100	Dec 2017 (unknown)

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT02360670	Penumbra and Recanalisation Acute Computed Tomography in Ischaemic Stroke Evaluation	400	Nov 2018 (unknown)

NCT: national clinical trial.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes
- Reason for CT perfusion imaging

Post Service (in addition to the above, please include the following):

- CT Imaging report

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for

clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0042T	Cerebral perfusion analysis using computed tomography with contrast administration, including post-processing of parametric maps with determination of cerebral blood flow, cerebral blood volume, and mean transit time
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
06/28/2007	BCBSA Medical Policy adoption
10/01/2010	Policy Revision with title change from CT (Computed Tomography) Cerebral Perfusion Imaging
08/23/2013	Title change from Computed Tomography Perfusion Imaging and policy revision without position change. Policy placed on No Further Routine Literature Review and Update status.
10/31/2014	Policy revision with no position change
12/04/2015	Policy title change from Computed Tomography (CT) Perfusion Imaging of the Brain Policy revision with position change
12/01/2016	Policy revision without position change
11/01/2017	Policy revision without position change
11/01/2018	Policy revision without position change
12/01/2019	Policy revision without position change
11/01/2020	Annual review. No change to policy statement. Literature review updated.
11/01/2021	Annual review. No change to policy statement. Literature review updated.
11/01/2022	Annual review. Policy statement, guidelines and literature review updated.
11/01/2023	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) 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 the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Computed Tomography Perfusion Imaging of the Brain 6.01.49 **Policy Statement:** I. Computed tomography perfusion (CTP) imaging may be considered **medically necessary** to select individuals with anterior large-vessel stroke for mechanical embolectomy. II. Computed tomography perfusion (CTP) imaging of the brain is considered **investigational** for all other indications.	**Computed Tomography Perfusion Imaging of the Brain 6.01.49** **Policy Statement:** I. Computed tomography perfusion (CTP) imaging may be considered **medically necessary** to select individuals with anterior large-vessel stroke for mechanical embolectomy. II. Computed tomography perfusion (CTP) imaging of the brain is considered **investigational** for all other indications.