July 2, 2014

Janet McCauley, MD
Senior Medical Director
Blue Cross and Blue Shield of North Carolina
Corporate Headquarters
5901 Chapel Hill Road
Durham, NC 27707

Subject: Corporate Medical Policy: Endovascular Procedures for Intracranial Arterial Disease "Notification"

Dear Dr. McCauley:

On behalf of the American Association of Neurological Surgeons (AANS), Congress of Neurological Surgeons (CNS), AANS/CNS Cerebrovascular Section, North Carolina Neurosurgical Society, American Society of Neuroradiology (ASNR), and Society of Neurointerventional Surgery (SNIS), we are writing you in response to the proposed coverage policy entitled Endovascular Procedures for Intracranial Arterial Disease (Atherosclerosis and Aneurysms), which went into effect on July 1, 2014. In this document the following are identified as investigational:

- Balloon Angioplasty for treatment of Subarachnoid Hemorrhage Induced Vasospasm
- Intracranial Angioplasty and Stenting for Atherosclerotic Disease
- Treatment of Large and Wide-necked Aneurysms with Flow Diversion
- Mechanical Embolectomy

As such, Blue Cross and Blue Shield of North Carolina does not consider these medical necessary in the treatment of the intracranial vascular diseases for which they are used. Based on a review of the literature — which is summarized below and described in more detail in the attached literature reviews — we respectfully disagree with your assessment and urge you to reconsider this policy.

Balloon angioplasty for vasospasm induced by subarachnoid hemorrhage is used only as a procedure of last resort for those in whom spasm of their intracranial vessels persists despite

maximal medical management (including 'triple-H therapy'). In these patients with intractable vasospasm, large ischemic strokes will result without angioplasty, resulting in a significant morbidity, requiring a higher level of subsequent care, as well as a greater cost burden. The safety and efficacy of angioplasty for vasospasm is well documented in the literature, as we will discuss. While these patients can be treated with repeated intra-arterial vasodilator infusions, this does not result in equal efficacy and lasts for only a short time (<24 hours), requiring multiple angiograms during the period of vasospasm, increasing risk of complications, radiation exposure and cost. We believe that your evaluation of angioplasty for vasospasm from subarachnoid hemorrhage may have erroneously fallen under your evaluation of angioplasty for intracranial atherosclerotic disease, which is a very different disease.

Regarding ***intracranial angioplasty and stenting***, the SAMMPRIS trial demonstrated higher safety in the medical arm than in the stenting arm for intracranial atherosclerosis, and we agree that medical therapy should be the first line therapy for this patient population. However, there remains a subgroup of patients that fails medical therapy and benefits from treatment with intracranial angioplasty and stenting. The FDA has acknowledged this in their recent evaluation of the Wingspan stent, and has approved its application specifically for this patient population.

In the ***endovascular treatment of certain wide-necked cerebral aneurysms***, the specialized stents that are categorized as flow diversion devices were developed to treat intracranial aneurysms that have demonstrated high recurrence rates with other endovascular and open vascular techniques, namely wide-neck aneurysms. The need for a randomized controlled trial was deemed unnecessary by the FDA during the clinical trials as the significant benefits offered by the device would make such a trial unethical and historical controls could be used as the control population. These devices have allowed us to treat these aneurysms with a higher efficacy while reducing the cost of treatment significantly, lowering radiation exposure and aneurysm recurrences.

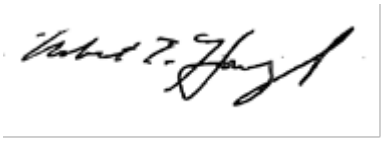
Mechanical embolectomy for stroke has been of increased interest for physicians as well as patients. Although three recent randomized trials have not shown an obvious benefit, they did not show inferiority, and there are several significant shortcomings in those studies that make their applicability to our modern patient population impossible in most instances. These were largely trials of thrombolysis using intra-arterial t-PA rather than the modern mechanical embolectomy. As mentioned above, in the literature review attachment, we will discuss several recently published studies that conclude that mechanical embolectomy may be a treatment option in patients with large vessel occlusion in whom intravenous tissue plasminogen activator (IV t-PA) is contraindicated, patients who have failed IV t-PA or those who present outside the IV t-PA treatment window. In addition, we have provided a summary on the background of the disease state, current treatment options, limitations of currently approved therapies and the evolution of alternative treatment and devices to address this unmet medical need. This patient population has no other alternative to address the acute ischemia, and a significant care and cost burden should they proceed to a large vessel stroke.

Based on the review of the literature, we respectfully request that you immediately reconsider your coverage policy to ensure that our patients receive all appropriate treatment options – including these vital endovascular procedures.

Janet McCauley, MD
Blue Cross and Blue Shield of North Carolina
Endovascular Procedures for Intracranial Arterial Disease Coverage Policy
July 2, 2014

Thank you for your time and consideration. We look forward to a favorable reply. In the meantime, if you have any questions, or need additional information, please contact us.

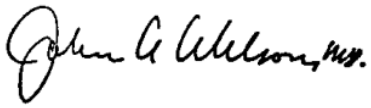
Sincerely,



Robert E. Harbaugh, MD, President
American Association of Neurological Surgeons

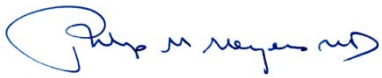
Daniel K. Resnick, MD, President
Congress of Neurological Surgeons

Brian L. Hoh, MD, Chairman
AANS/CNS Joint Cerebrovascular Section



John A. Wilson, MD
North Carolina Neurosurgical Society

Joshua A Hirsch, MD
American Society of Neuroradiology



Philip M. Meyers, MD, President
Society of Neurointerventional Surgery

Attachment: Overview of Endovascular Procedures and Literature References

Staff Contact:
Catherine Jeakle Hill
Senior Manager, Regulatory Affairs
AANS/CNS Washington Office
725 15th Street NW Ste. 500
Washington, DC 20005
Phone: 202-446-2026
E-mail: chill@neurosurgery.org

Attachment

Overview of Endovascular Procedures and Literature References

BALLOON ANGIOPLASTY FOR VASOSPASM SECONDARY TO SUBARACHNOID HEMORRHAGE

Approximately, one-third of patients with arterial subarachnoid hemorrhage (SAH) die from the vasospasm, and another one third are left permanently disabled from stroke, making vasospasm a potentially catastrophic complication (6). Additionally half of patients with angiographic vasospasm after subarachnoid hemorrhage develop delayed ischemic neurological deficits with resultant stroke or death [1, 2, 3]. Cerebral vasospasm tends to be more severe in younger patients with poor neurological grade, thick subarachnoid clot (Fisher Grade 2 and 3), and history of smoking [4, 5]. Because of this, randomized trials examining vasospasm are limited [1].

Oral or intravenous administration of nimodipine is currently recommended as the first-line medication to prevent vasospasm. For symptomatic vasospasm refractory to Triple-H therapy (Hypervolemia, Hemodilution and Hypertension), endovascular therapies such as super-selective intra-arterial infusion of vasodilators and balloon angioplasty are recommended [7, 8]

Historical Background

The management of SAH has drastically changed over the past decades. The pendulum has swung from treatment with a hypovolemic state to the hypervolemic state as part of the Triple-H therapy. Where hypervolemia used to be the commonstay for patients during the period of 4-14 days after the SAH, more patients are being treated with euvolemia rather than hypervolemia unless transcranial dopplers, clinical examination and/or radiographic evidence suggest vasospasm. Radiographically, vasospasm can be diagnosed directly with either invasive or non-invasive modalities such as computed tomography angiogram (CTA), magnetic resonance imaging (MRI) or cerebral angiogram. While mild vasospasm can be managed medically, more severe vasospasm can progress to ischemic stroke. It is the more severe radiographic vasospasm that most often can progess to clinical vasospasm; It is this medically refractory, severe radiographic vasospasm that requires more aggressive interventional treatment. If it is refractory to maximal medical management, the spasm can result in an ischemic stroke.

Historically, medically refractory vasospasm was treated with intravenous and/or intrarterial administration of vasodilators. Intra-arterial vasodilators ameliorate distal and diffuse vasospasm but

their effects are transient. Papaverine was the first drug used for this indication with a half-life of approximately 2 hours. Although Papaverine produced clinical improvement in 43% of treated patients, this was a transient effect and thus required multiple treatments and that lead to a variable but increased complication profile [9]: the drug is neurotoxic and can increase intracranial pressure and also provoke seizures, tranient cortical blindness and irrversible brain injury.

Since the early treatment models of intraarterial papaverine, safer alternatives such as Nimodipine, Nicardipine and Verapamil have emerged, albeit as an off label use. Administration of serial injections of intra-arterial Nimodipine has documented a favorable outcome: Biondi et al. [10] treated 25 patients with 30 procedures and obtained clinical improvement in 76% of the patients. Only 43% of the patients demonstrated vascular dilatation, suggesting alternative methods of amelioration of cerebral function other than through improved flow. To allow for a continuous cerebral vasodilatory effect, Wolf et al. [11] left a perfusion catheter in the affected vessels with continued infusion of Nimodipine in the ICU. Patients were heparanized. Of the nine patients, three died from refractory vasospasm and one from lethal sepsis, making this option fairly unattractive. Repeated procedures were advocated by Cho et al. [12] who performed 101 sessions of Nimodipine infusions in 42 patients. Although angiographic improvement was achieved in 82.2% of the patients and favorable clinical outcome in 76.2%, vasospasm related infarction still occurred in 21.4%. While effective, the short durability of these infusions do not negate the need for repeated procedures due to the transient effects of nimodipine on the vessel wall, adding risk and cost to the treatment of these critically ill patients.

Comparing balloon angioplasty to intra-arterial infusion of papaverine in patients treated for vasospasm, [13] only one patient required repeat angioplasty whereas 42% of the patients treated with papaverine required multiple treatments, often with the addition of angioplasty. Papaverine did not result in post-treatment Day 1 reduction in transcranial doppler velocities (a noninvasive method of mesuring vessel stenosis in vasospasm) in comparison to patients who underwent angioplasty with a decrease in 42% velocities, a decrease that was sustained.

Khatri, et al. reviewed their institutional experience prior to the institution of angioplasty, and after its adoption. There was a significant decline in severe disability after the introduction of angioplasty (45 to 33%) without a significant change in mortality [14].

Despite a lack of randomized clinical trials, experienced physicians treating patients with SAH related vasospasm appreciate that early regognition and treatment of medically refractory vasospasm remains critical in the management of these patients. [16] A recent natiowide survey amongst treating physicians reported that 95.9% of the respondents pursue endovascular treatment for patients who have failed maximal medical management with over 95% reporting the use of balloon angioplasty for proximal (large vessel) vasospasm and effective vasospasm resolution in over 80% of the cases.

Given the data from Zwienenberg-Lee, et al.who incurred several fatal complications assoicated with prophylactic angioplasty in patients with radiographic but not medically refractory clinical vasospasm we agree that prophylactic angioplasty is not indicated. We support its use in medically refractory vasospasm, as there was no change in outcome of patients randomized to early or symptomatic angioplasty [8].

In conclusion, while there is a lack of randomized clinical trials comparing medically refractory vasospasm to medical therapy versus intra-arterial chemical vasodilatation versus balloon angioplasty, conducting such a trial would be unethical, as there is no clinical equipoise. Treating physicians could not ethically enroll young patients with impending vasospasm induced strokes into a “watch and see” control group.

We hope that this clarifies that balloon angioplasty for subarachnoid induced vasospasm is not “investigational”, and that you will cover your patients for this uncommon yet vitally important procedure when appropriately indicated in patients with medically refractory cerebral vasospasm as a result of subarachnoid hemorrhage.

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ANGIOPLASTY AND WINGSPAN STENTING FOR INTRACRANIAL ATHEROSCLEROTIC DISEASE

Intracranial atherosclerotic disease is present in 9% of the poulation and the standard of care is medical management conform results of the WASID and SAMMPRIS trials supporting medical management of symptomatic atherosclerosis with antiplatelet agents. However, there remains a subgroup of patients that, despite maximal medical management as supported by the SAMMPRIS protocol, suffer recurrent ischemic events. This was recognized by the FDA in their 2012 publication (http://www.fda.gov/medicaldevices/safety/alertsandnotices/ucm314600.htm) which reads as follows:

> On March 23, 2012, the FDA convened an expert advisory panel to discuss the most current knowledge regarding the safety and effectiveness of the Wingspan Stent System for the treatment of intracranial stenosis, including the results of the recent SAMMPRIS study. Panel members were asked to discuss the comparability of the patient populations involved in clinical studies of the Wingspan Stent System and how study results may impact the safety and effectiveness of the device. The panel members agreed that there was no evidence of benefit for use of the Wingspan system for most patients with TIA or stroke due to intracranial atherosclerotic stenosis when compared to a program of aggressive comprehensive medical management as was administered in the SAMMPRIS study. Some panelists also suggested that for a certain specific set of patients, Wingspan remains an important option.
>
> The FDA analyzed available clinical evidence and concluded that there is evidence from the original HDE study of probable benefit for the use of the Wingspan Stent System for a specific population of patients. ***The FDA determined that Wingspan should remain available for those patients who have failed to respond to, or who are ineligible for, an aggressive and comprehensive program of medical management.*** The FDA will continue to monitor and evaluate adverse events associated with Wingspan and also monitor the results of ongoing follow-up of patients from the SAMMPRIS study. The agency will make available any new information that might affect its use. Consequently, the FDA revised the approval for the use of the Wingspan stent as:

Wingspan is now approved only for patients who are between 22 and 80 years old AND who meet ALL of the following criteria:

-Who have had two or more strokes despite aggressive medical management;
-Whose most recent stroke occurred more than seven days prior to planned treatment with Wingspan;
-Who have 70-99 percent stenosis due to atherosclerosis of the intracranial artery related to the recurrent strokes; and
-Who have made good recovery from previous stroke and have a modified Rankin score of 3 or less prior to Wingspan treatment. The Rankin scale is used to measure the degree of disability in stroke patients. Lower scores indicate less disability.

The Wingspan Stent System should not be used for:

-The treatment of stroke with an onset of symptoms within seven days or less of treatment; or for the treatment of transient ischemic attacks (TIAs).

While cerebrovascular specialists who treat intracranial atherosclerosis will continue to maximize medical management, recognition of this select sub-group of patient group that is at risk for major neurologic deficits because of refractory vasospasm, with possibly devastating consequences, is best left at the discretion of the treating physician. We urge you, therefore, to reconsider this denial of coverage and align with the FDA in supporting endovascular treatment for this select group of patients who fail maximal medical treatment.

TREATMENT OF LARGE AND GIANT INTRACRANIAL ANEURYSMS WITH PIPELINE FLOW DIVERSION DEVICE

One of the main challenges of endovascular treatment of cerebral aneurysms is treatment of patients with wide-necked or fusiform aneurysm morphology. These aneurysms are unique in that aside from their more traditional counterparts, the narrow necked aneurysm, these wider-neck aneurysms are more challenging to treat with endovascular means. Maintaining patency of the parent cerebral artery once coils are deployed is a principal concern in wide-necked aneurysms. Balloon-assisted remodeling, stent-assisted coiling, and the use of aneurysm neck-bridge devices are all adjunctive techniques that have been used in the treatment of wide-necked aneurysms.

In the last 10-15 years, intracranial stents have emerged as an alternative in the management of wide-neck intracranial aneurysms. The stent serves as a scaffold in the parent artery to prevent coil migration, and, secondarily, it may decrease the chance of recanalization of the aneurysm due to redirection or dampening of blood flow into the aneurysm.

Clinical Background Justifying Medical Necessity Criteria

Intracranial aneurysms (IAs) result when weakness in the wall of a cerebral artery causes ballooning or out-pouching of the blood vessel. Most IAs are asymptomatic until they rupture, which can occur suddenly and without warning, leading to cerebral bleeding or subarachnoid hemorrhage (SAH). SAH is a devastating complication with a case-fatality rate of 51%, leaving nearly half of its survivors functionally incapacitated with less than 5% good outcomes.[1, 2]

While a majority of intracranial aneurysms do not require treatment, those unruptured aneurysms that meet certain criteria, or all ruptured aneurysms require treatment. As noted above, there are two primary modalities of treatment of IAs; endovascular treatment and open surgical treatment. At one time, open surgical clipping of IAs was the only available treatment. Endovascular embolization with coils became available in the 1990s and quickly became a valuable alternative. Due to issues in some patients with gaps forming between coils as well as prolapse of coils out of the aneurysm sac, particularly for large and wide-necked IAs, specialized stents such as Neuroform® were introduced in the early 2000s. These stents are used as an adjunctive measure to coiling as a means of retaining the

coils within the aneurysm sac in selected patients, thereby reducing recurrence and potential complications (17).

Coiling and its adjuncts work by occluding the aneurysm sac and this is quite effective for occluding certain types of IAs. However, results over time have indicated that the aneurysm occlusion that is achieved is often incomplete and may lack durability in certain cases, with the possibility of some degree of recanalization taking place. This puts patients at higher risk for continued disease progression, further follow-up and treatment, and possible aneurysm rupture.

Endovascular stents are typically an open cell design, with a physical gap within the stent. While they can be very effective when used in conjunction with endovascular coils, stents themselves cannot be typically used as the sole treatment for IAs as they alone lack the ability to redirect blood flow. Flow-diverting devices represent a paradigm shift in the endovascular treatment philosophy for IAs and act in a two-fold manner:

(1) They divert flow away from the aneurysm sac, thereby inducing thrombosis within the sac and potentially obviating the need for coil embolization; and
(2) They facilitate reconstruction of the parent vessel by providing a scaffold for endothelization. This recreates the full circumference of the parent vessel, while allowing blood flow into branch vessels that may also be covered.

While similar to the traditional intracranial stents in concept, a few technical distinctions should be noted as to the difference between a flow-diverting stent. Conventional intracranial stents serve to re-open vessels that are narrowed or blocked, by atherosclerosis such as Wingspan™. By comparison, specialized stents such as Neuroform™ and Enterprise™ serve as adjuncts to coil embolization by retaining the coils within the aneurysm sac. In contrast to both, parent vessel reconstruction or flow-diverting devices are stand-alones that cure the aneurysm by rebuilding the vessel from which it arose.

In these procedures, a tighter construction and design cylindrical mesh stent is implanted within the parent artery, across the aneurysm neck. The mesh is engineered to provide a high percent of metal surface area when deployed. The result of the procedure is not only exclusion of the aneurysm, but

also reconstruction of the parent vessel from which the aneurysm arose. The degree of metal surface area over the aneurysm neck directs the flow of blood away from the aneurysm. This diminishes the "hammering" effect of pulsating blood within the sac, as seen with coiling, and reduces the stress on the aneurysm wall. The metal surface also serves as scaffolding, triggering regular and even growth of endothelial cells across the neck of the aneurysm. This newly reconstructed vessel wall seals the aneurysm and excludes it from circulation.

Because the devices do not enter the aneurysm sac but rather address the parent vessel, they can be used to treat a variety of challenging types of aneurysms including small aneurysms, shallow aneurysms, fusiform, wide-necked aneurysms and large aneurysms, and indeed represents a paradigm shift in the treatment of challenging intracranial aneurysms.

Currently, the only FDA-approved flow diverter is the Pipeline™ device, which is indicated for the endovascular treatment of adults (22 years of age or older) with large or giant wide-necked IAs in the internal carotid artery (ICA) from the petrous to the superior hypophyseal segments of the internal carotid artery. Published data on the Pipeline™ device used to treat complex large/giant aneurysms show rates of 68-94.4% complete occlusion that remains persistent 2-3 years after the index procedure and 0-13.9% associated morbidity and 0%-6.4% mortality.[3-9] These rates are similar to or better than those for conventional IA treatments of surgery or coiling.[10, 11]

BCBSNC specific comments regarding Pipeline Embolization Device (flow diversion stent)

- There is growing body of clinical evidence referenced in many of the BCBS plans as well as HealthNet which recognizes that Pipeline flow diversion is safe and effective (see Table 1).
- As noted in the BCBSNC policy for stent-assisted coiling, *"For the treatment of intracranial aneurysms, there are no RCTs of stent-assisted coiling with coiling alone. Non-randomized comparative studies report occlusion rates that are similar to coiling alone, and recurrence rates that may be lower than for coiling alone. Results of clinical vetting indicated strong support for treatment of aneurysms that are not amenable to surgery or simple coiling."*
- As recognized in BCBSNC's policy as well as that of other payers, there is a lack of RCTs for flow-diverting stents, such as the Pipeline™ device. There is a strong clinical explanation for a

lack of randomized controlled trials (RCTs): minimally invasive treatments that could form a reasonable concurrent control group are not available.

  - Currently, the most common treatment method for these intracranial aneurysms is stent-assisted coiling. Although stent-assisted coiling is commonly performed, it is also important to note that not all aneurysms (e.g. fusiform), which can be treated with the Pipeline™ device can be treated with stent-assisted coiling.
  - The aneurysm retreatment and recurrence rates associated with stent-assisted coiling demonstrate the need for a more durable treatment. In the scenario of a randomized controlled trial, if a subject is randomized to stent-assisted coiling and the aneurysm recurs or enlarges and requires retreatment, potential retreatment options will be limited. In particular, retreatment with flow diversion therapy is not possible in cases where a stent is already placed in the target IA. The labeling of the Pipeline™ device specifically states that it is contraindicated in patients who have a pre-existing stent in place in the parent artery at the target IA location.
  - Furthermore, stents are not approved by the FDA for use in the treatment of aneurysms and may only be used under the conditions of HDE approval.

- Patients indicated for Pipeline™ meet the current BCBSNC medical necessity criteria.

Clinical Evidence

The necessity for better treatment of these challenging, wide-necked aneurysms has been established by the sobering surgical and, more recent, stent- and balloon-assisted coiling results. The widely quoted International Study of Unruptured Intracranial Aneurysms (ISUIA) established that aneurysms >10 mm size were at critical risk of rupture with those >25 mm in size carrying a 0.17 probability of rupture in the first year after diagnosis in patients with no prior history of subarachnoid hemorrhage. Open surgical treatment consists of direct surgical clipping, parent vessel occlusion or high flow bypass, with mortality rates of 5-22%. Surgical treatment has therefore generally been abandoned in favor of endovascular treatment in many cases.

Coiling alone carries a high rate of incomplete occlusion after embolization for certain types of challenging to treat aneurysms. UCLA reported occlusion rates of only 40.4% (80/198) of large and 26.0% (19/73) of giant aneurysms in their 11 years of experience.[12] The significance of incomplete occlusion of cerebral aneurysms was identified in the CARAT study.[13] In this study 1001 patients were followed for a mean of 4.0 years and the degree of aneurysm occlusion after treatment was strongly associated with risk of re-rupture: overall risk: 1.1% for complete occlusion of the aneurysm, 2.9% for 91-99% occlusion, 5.9% for 70-90% and ***17.6% for <70% occlusion***. *It is the latter* statistic for which the flow diverting stents were designed. CARAT concluded that *"the degree of aneurysm occlusion is a strong predictor of risk of subsequent rupture… and justifies attempts to completely occlude aneurysms."* As demonstrated by the CARAT study and corroborated by several similar studies with recanalization rates up to 100% (need citation), the need for better occlusion rates is the core reason that newer techniques like flow diversion were developed.

First generation bridging type of stents (Neuroform ®, Enterprise ®) were designed to improve long term durability of endovascular treatment of certain aneurysms. Series that reported outcomes of large and giant aneurysms treated with stent-assisted coiling attained a higher, though still imperfect, occlusion rate with recanalization between 7 to 26%. [14-18]

Flow-diverting stents (Pipeline®) have shown more promise with certain types of more challenging aneurysm such as aneurysms. The first prospective study, the Pipeline Embolization Device for the Intracranial Treatment of Aneurysms Trial, was conducted at 4 centers treating wide-necked or aneurysms that had failed a previous procedure.[4] In this study, complete occlusion was attained in 93.3% and 96.7% at 180 days and 2 years respectively. Following these excellent outcomes, the Pipeline for Uncoilable or Failed aneurysm study, the 'PUFs' trial was conducted, which resulted in FDA approval.[19] In reviewing the design for this trial, the FDA deemed that a **randomized, controlled trial** ***was not required due to known poor outcomes for the target population and that adequate data existed in the literature to serve as historical controls.*** As neither coiling nor surgery are appropriate for some large and giant aneurysms, stent-assisted coiling ("HDE" status) had only demonstrated "probable benefit" and could not serve as control. Lastly, observation was unethical due to the high rate of rupture in these patients, many of whom were symptomatic. Of the devices used, 97.8% were delivered successfully. The primary endpoint of complete aneurysm occlusion without

major parent vessel stenosis was attained in 82% at 180 days and 86% at 1 year. The primary safety endpoint (major ipsilateral stroke or neurological death, target rate of <20% was attained (rate: 5.6%). In conclusion, the trial demonstrated that Pipeline flow diversion device was effective, safe and performed well in the treatment of these large, challenging aneurysms.

Many other studies have followed, leading to overwhelming body of evidence to support the superior efficacy and safety of this device over the previously available surgical and endovascular techniques. These are detailed below, as found in other BCBS policies.

Below are the complete references from other Blues Policies that are omitted in BCBSNC policy:

Nonrandomized comparative studies. In 2013, Chalouhi et al., reported outcomes from patients with unruptured, large or giant aneurysms treated with the Pipeline device enrolled in a registry compared with those treated with endovascular coiling.[20] They identified a total of 229 patients enrolled during their data collection period from 2004-2013, 54 treated with the Pipeline device and 175 with coiling. Patients treated with the Pipeline device were significantly older and had significantly larger aneurysms that were more likely to be fusiform. Because of this, the authors excluded patients with fusiform or anterior communicating artery aneurysms and conducted their analysis in 160 patients (40 Pipeline and 120 coil patients) who were matched in a 1:3 ratio on the basis of patient age and aneurysm size. Aneurysm neck size, overall size, and anterior versus posterior circulation location were similar between the groups. Of the patients treated with the Pipeline device, 4 patients (10%) also required adjunctive coil placement. Of the patients treated with endovascular coiling, 67 (56%) were treated with coiling along, while 52 (43%) were treated with stent-assisted coiling and 1 (1%) with balloon-assisted coiling. Primary outcomes included obliteration of the aneurysm on follow up imaging and clinical outcomes, measured by modified Rankin scale score of 0-2 (vs 3-6). At the time of latest follow up, a higher proportion of aneurysms treated with the Pipeline device compared with those treated with coiling achieved complete obliteration (30/35 [86%] vs. 37/09 [41%] $p<0.001$). However, angiographic follow up was available for a greater proportion of patients treated with the Pipeline (35/40 [87.5%]) than those treated with coiling 90/120 [75%]), and the median angiographic follow up time differed significantly between the groups (7 months in the Pipeline group and 12 months in the coil group, $p<0.001$). In terms of clinical outcomes, similar proportions of the Pipeline and coil groups did

have a modified Rankin Scale score 0-2 (35/38 [92%] in the Pipeline group vs. 97/103 [94%], p=0.8). Similar to the angiographic follow up results, the median clinical follow up time differed significantly between the groups. Treatment type was not significantly associated with rates of procedure-related complications. While this study directly compares patients treated with the Pipeline endovascular device and those treated with coiling, it is limited by its nonrandomized, retrospective design. In particular, patients treated with coiling were treated in an earlier period (2004-2011) than those treated with the Pipeline device (2011-2012); this may have systematically biased the study in favor of the Pipeline device because aspects of neurointerventional care other than the device used may have differed over time.

Single-arm series. Multiple non-comparative studies that reported the outcomes from flow-diverting stent-assisted treatment of intracranial aneurysms have been published since the introduction of the Pipeline™ endovascular device. These studies have been summarized in several systematic reviews and meta-analysis. The largest meta-analysis by Brinjikji et al., published in 2013, included 1451 patients with 1654 aneurysms reported in a total of 29 studies published through 2012.[21] The authors evaluated aneurysmal occlusion rates at 6 months, and procedure-related morbidity, mortality, and complications across studies. They found a high rate of complete aneurysmal occlusion (76% [95% CI, 70%-81%]), but also a high rate of procedure-related morbidity and mortality [5% [95% CI, 4%-7%] and 4% [95% CI, 3%-6%], respectively.

Also in 2013, Arrese et al. reported results of a meta-analysis that used somewhat more restrictive inclusion criteria included 897 patients with 1018 aneurysms reported in a total of 15 studies.[22] All but 2 of the studies that they included were included in the Brinjikji meta-analysis. The authors determined rates of complete or nearly complete occlusion of the treated aneurysm with a patent parent artery and early procedure-related mortality and neurological morbidity. Similar to the Brinjikji meta-analysis, this study found a high rate of procedure-related morbidity and mortality (2.8% [95% CI, 1.7%-3.8%] and 7.3% [95% CI, 5.7%-9%], respectively. The authors assessed for publication bias using funnel plots and the Egger's test to assess whether the study estimate size is related to the size of the study, and find that $p<0.001$ for the Egger's test for both early and late morbidity and aneurysmal occlusion, suggestive of publication bias.

Both meta-analyses mentioned above included patients treated with either the Pipeline or Silk flow diversion devices. However, only the meta-analysis by Arrese et al. included a subgroup analysis comparing the Pipeline device with the Silk device which is currently being tested for FDA approval in the US. The studies using SILK device had a mean occlusion rate of 68% (95% CI 62-74), compared to a mean occlusion rate of 88% (95% CI 84-92) with the Pipeline device, which is a significant statistical difference (test for the comparison of two proportions, p <0.01).

Since the publication of these two contemporary meta-analyses demonstrating efficacy and safety of the Pipeline™ endovascular device, several additional non-comparative studies evaluating flow-diverting stents in the treatment of aneurysms have been published. Representative studies are summarized in the table below.

Table 1. Noncomparative Studies for Flow-Diverting Stent-Assisted Endovascular Treatment of Aneurysms

Study	Study Type	Patient Population	Intervention	Primary Outcome
Kan et al., 2013[7]	Prospective case series (registry)	56 patients with intracranial aneurysm treated at 7 institutions	Pipeline Embolization Device placement	6/123 devices incompletely deployed Among 19 patients with 6 month follow up, 68% (13 patients) had complete aneurysm occlusion 4 fatal post-procedural hemorrhages occurred.
Lin et al., 2013[23]	Retrospective case series	41 patients with small (<10 mm) internal carotid artery aneurysm at a single institution	Pipeline Embolization Device placement	80% of patients had complete or near-complete aneurysm occlusion. One patient (2.3%) had a major periprocedural complication (death)
Malatesta et al., 2013[24]	Retrospective case series	28 patients with intracranial aneurysm at a single institution	Flow-diverting stent placement (Pipeline Embolization Device or SILK artery reconstruction device [Balt Extrusion, Montmorency, France])	89% of aneurysms had complete occlusion at 12 months One death occurred
Piano et al., 2013[25]	Retrospective case series	101 patients with intracranial aneurysm at a single institution	Flow-diverting stent placement (Pipeline Embolization Device or SILK device), with or without endovascular coiling	86% of aneurysms evaluated at 6 month follow up showed complete occlusion
Toma et al., 2013[26]	Retrospective case series	84 patients with intracranial aneurysm at a single institution	Flow-diverting stent placement	61% of aneurysms had resolved at 12 months 9.5% of patients had a new, permanent neurologic deficit and 5.9% of patients had procedure-related mortality
Yavuz et al., 2013[27]	Retrospective case series	25 patients with middle carotid artery aneurysm at the carotid bifurcation at a single institution	Pipeline Embolization Device placement	84% of patients had complete aneurysm occlusion

Cost analysis of the Pipeline™ endovascular device

Two studies have directly compared the cost of treating intracranial aneurysms with the Pipeline flow diversion device as compared to stent-assisted coiling. The first study by Colby et al. reviewed sixty consecutive patients, 30 with Pipeline and 30 with stent-assisted coiling.[28] The mean aneurysm size was 9.8mm and 7.3mm, respectively. The costs of catheters and wires were identical for both groups. The cost of implants, however, was significantly lower in the Pipeline group: $13,175 (± $726) vs $19,069 (± $2015), despite the Pipeline group's larger aneurysm size. In addition, the total procedure cost was significantly lower for the Pipeline vs the second group ($16,445 vs $22,145). This resulted in a net 27.1% reduction in the cost per millimeter of aneurysm size treated in the Pipeline group vs. the stent-assisted coiling group.

Colby et al. goes on further to note "The added potential cost benefit of embolization with the PED (Pipeline™ endovascular device) comes from its efficacy and durability of treatment. Studies have demonstrated complete angiographic occlusion of aneurysms treated with the PED in over 90% of cases at 6 months, with no reports of recurrence.[8, 28] Although longer-term data is required to further validate these findings, these data are both promising and dramatically different than the recurrence rates of up to approximately 35% for aneurysms coiling without stents [11, 28] and rates of approximately 10% to 23% for stent-assisted coiling.[16, 17, 28, 29] Decreased recurrence rates should translate to long-term cost savings for patients treated with the PED."

A study by Chalouhi et al. performed a cost comparison between the 30 aneurysms treated with Pipeline flow diversion and a theoretical model in which the costs were calculated for coiling alone (no stent-assistance, therefore less cost) to a packing density of 25%, an accepted degree of coil compactness.[30] The overall procedure cost was lower with Pipeline flow diversion than with coiling alone: (mean $23,911 vs $30,522). In a follow-up study published recently, the authors established that a single Pipeline device (as opposed to multiple devices) is sufficient for the treatment of most intracranial aneurysms.[31] Considering the high recanalization rate of large and giant aneurysms with conventional endovascular techniques, repeat coiling may result in further increase in overall cost of treatment, making the investment in the Pipeline embolization device further cost effective.

Radiation and Intravenous Contrast Exposure with the Pipeline™ endovascular device

As occlusion of intracranial aneurysms with coiling constitutes a step-wise obliteration with multiple interim contrast injections (for confirmation of extent of obliteration and maintenance of safety), radiation exposure to the patients (and the surgical team) remains a serious concern. This is potentially amplified in large and giant aneurysms that require many coils (more radiation and contrast per procedure) and often staged procedures for a satisfactory result. Should these recur, the radiation exposure may result in a cumulative radiation exposure that is higher than desired or intended.

Recent evaluation of these parameters in 55 patients treated with either Pipeline device vs traditional coiling showed a mean fluoroscopy time of 56.1 vs 85.9 minutes, with a 35% decrease with Pipeline. This resulted in a radiation dose of 2840 (± 213) mGy for the Pipeline device vs. 4010 (± 708) mGy in the traditional coiling group.[32] Therefore, patients treated with a Pipeline were exposed to 29% less radiation than those treated with conventional coiling techniques. In addition, 37% less contrast was used in the flow diversion group, potentially decreasing risk for patients.

Other Coverage Policies

Payers with a written coverage policy for aneurysm treatment consistently state that percutaneous intracranial artery stent placement with or without angioplasty is considered medically necessary as part of the treatment of individuals with an intracranial aneurysm when ALL of the following criteria are met:

1) Surgical treatment is not appropriate or attempted surgery was unsuccessful and
2) Standard endovascular techniques (coiling) are inadequate to achieve complete isolation of the aneurysm because of anatomic considerations which include, but are not limited to:
    a. wide-neck aneurysm (4 mm or more); or
    b. sack-to-neck ratio less than 2:1.

In summary, we respectfully request that you reconsider Pipeline™ Embolization device as "investigational" and allow BCBS NC members access to this treatment option for the following reasons:

- Patients indicated that Pipeline™ meets the current BCBSNC medical necessity criteria – aneurysms that are not amenable to surgery or simple coiling
- There is a growing body of clinical evidence referenced in many of the Blues plans, as well at HealthNet, which recognizes that Pipeline is safe and effective
- Published data on the Pipeline™ device used to treat complex large/giant aneurysms show rates of 68-94.4% complete occlusion which persists at least 2-3 years after the index procedure with 0-13.9% associated morbidity and 0%-6.4% mortality. These rates are similar to or better than those for conventional intracranial aneurysm treatment.
- There is no reasonable concurrent control group to conduct a randomized controlled trial.
- There is increasing evidence that treatment with Pipeline is more cost effective than possible alternative procedures
- Patients treated with Pipeline have reduced exposure to radiation and contrast as compared to coiling

The following Blues plans reference Pipeline and do NOT state that Pipeline is investigational:

Payer	Title	Policy
Anthem/Wellpoint	Carotid, Vertebral and Intracranial Artery Angioplasty with or without Stent Placement https://www.unitedhealthcareonline.com/b2c/CmaAction.do?viewKey=PreLoginMain&forwardToken=PreLoginMain	SURG.00001
BCBS Federal	Endovascular Procedures for Intracranial Arterial Disease (Atherosclerosis and Aneurysms) http://www.fepblue.org/benefitplans/medical-policies.jsp	2.01.54
BCBS MA	Endovascular Procedures (Angioplasty and/or Stenting) for Intracranial Arterial Disease (Atherosclerosis and Aneurysms) https://www.bluecrossma.com/common/en_US/medical_policies/medcat.htm	323
BCBS MI	Endovascular Procedures for Intracranial Arterial Disease http://www.bcbsm.com/providers.html	
BCBS AL	Endovascular Procedures for Intracranial Arterial Disease (Atherosclerosis and Aneurysms) https://www.bcbsal.org/web/medical-policies1	263
Wellmark	Percutaneous Intracranial Angioplasty and Stenting http://www.wellmark.com/Provider/index.aspx	07.01.32
Horizon BCBS NJ	Endovascular Procedures (Angioplasty and/or Stenting) for Intracranial Arterial Disease (Atherosclerosis and Aneurysms) https://services5.horizon-bcbsnj.com/eprise/main/horizon/tsnj/tsweb/members.html	123
BCBS SC	Endovascular Procedures for Intracranial Arterial Disease (Atherosclerosis and Aneurysms) http://www.cam-policies.com/internet/cmpd/cmp/mdclplcy.nsf/DispContent/E0275439E60F76418525717000661FD8?opendocument	CAM 20154

The following plans explicitly cover Pipeline:

Payer	Title	Position Statement	Comments
HealthNet	Transcatheter Placement of Intracranial Stent NMP 527 https://www.healthnet.com/portal/provider/home.do	Health Net considers transcatheter placement of an intracranial stent medically necessary as part of the treatment of individuals with a cerebral aneurysm when all of the following criteria are met: 1. surgical treatment is not appropriate or attempted surgery was unsuccessful and 2. standard endovascular techniques are inadequate to achieve complete isolation of the aneurysm because of anatomic considerations which include, but are not limited to: wide-neck aneurysm (4 mm or more) or sack or dome-to-neck ratio less than 2:1.	The concept of functional reconstruction with the use of flow diverters, has recently been introduced. In addition, these types of special stents do not require coil embolization, because they elicit hemodynamic changes that produce aneurysm thrombosis between 3 and 10 days (i.e. Merlin, Silk, Pipeline embolization devices). They are especially useful for very small, giant, wide-necked, or otherwise difficult to treat aneuryms and can be used with intramural coil placement.
The Lifetime Healthcare Companies (Excellus and Univera)	Endovascular Repair (Coil Embolization) of Intracranial Aneurysms Policy Number: 7.01.81 https://www.excellusbcbs.com/wps/portal/xl/prv	Endovascular repair of wide-necked intracranial aneurysms using stent assisted embolic coiling is considered a medically appropriate treatment for otherwise inoperable aneurysms only when performed in an institution with a multidisciplinary neurosurgical team.	References Pipeline and PUFS trial.

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MECHANICAL THROMBECTOMY FOR TREATMENT OF LARGE VESSELS OCCLUSIONS IN ACUTE STROKE

Background: Acute Ischemic Stroke

Acute ischemic strokes account for approximately 795,000 strokes in the US annually. [1] As many as 87% of all strokes are ischemic, meaning the oxygen rich blood is blocked from entering the cerebrovascular circulation by clot or emboli. [1] Treatment for ischemic stroke is limited; IV t-PA given within 3 hours of symptom onset is currently the only FDA approved treatment for AIS. More recent studies have shown that although IV t-PA is only approved for use within 3 hours of symptom onset, current peer reviewed data supports the use of IV t-PA for up to 4.5 hours from symptom onset. [2-7] Data suggests that IV t-PA improves the outcome of one in three patients when treated within the first 3 hours and one in six patients when treated between 3 and 4.5 hours. No net benefit has been demonstrated beyond 4.5 hours. [8]

Stroke care in the United States varies, however in most centers in the United States, less than 20% of patients arriving at a stroke center are eligible for IV t-PA, and even then, most centers only administer IV t-PA in approximately 5% of the stroke patients. Complicating the ischemic stroke management, it is well documented in the scientific literature that clots in the large vessels of the brain (such as the middle cerebral artery) fail to respond to lytic therapy. Approximately 35-40% of all patients experiencing an acute ischemic stroke typically suffer a large vessel occlusion within the ICA, MCA and vertebrobasilar regions. [9-13] Because of the territories that are supplied by these larger intracranial vessels, these strokes are most often disabling. The natural history of ischemic stroke is well understood from the IV t-PA trials, and without tPA, for which most patients are ineligible as discussed above, those patients with a NIHSS >10 have less than 25% chance of a good clinical outcome after an acute ischemic stroke [19] and a high rate of death, especially with large vessel occlusions. Basilar artery occlusions were associated with a 50% mortality, internal carotid occlusions with 35% mortality, and MCA occlusions with 24% mortality. [10]

The limited thrombolytic effect of IV t-PA has led clinicians to try a different approach to stroke treatment:. Mechanical thrombectomy is an endovascular treatment designed to reopen occluded vessels by physically extracting occlusive thrombi from the cerebral vasculature in a timely fashion.

Revascularization is the goal of the mechanical thrombectomy procedure which re-opens the occluded vessel and establishes oxygen rich blood flow to the ischemic area of the brain. By mechanically removing the clot through endovascular means, blood is restored to the penumbra, and the size of the stroke, and its effects on the patient, can be reduced. [14]

Mechanical thrombectomy has been successfully used by stroke interventionalists in ischemic stroke patients who have failed pharmacologic therapy, as demonstrated by two randomized controlled studies , SWIFT and TREVO 2. These studies included patients in whom IV t-PA was contraindicated, or those who failed to improve with IV t-PA. The mean baseline NIHSS in both these trials was 18, indicating a large vessel occlusion, which as noted above is a subgroup of ischemic strokes that respond poorly to thrombolytics and carry a high morbidity. Both SWIFT and TREVO 2 found that 58% and 53%, of the patients, respectively, within these studies met the composite favorable neurological outcome (defined as mRS 0-2, NIHSS improvement of 10 points or more, or a return to baseline mRS) and 36% and 40% of the patients achieved good functional outcomes (mRS 0-2) at 90 days post treatment. [15, 16, 17] Additionally, the safety profile of these patients is satisfactory; notably, 90-day mortality was recorded in 17.2% of the patients (within Solitaire™ FR arm) of the SWIFT clinical study. Another prospective Solitaire™ FR device study (STAR) reports a similar long-term good functional outcome rate of 58% (mRS 0-2 at 90 days) and a low mortality rate of 7%. [18]

Limitations of Currently Approved Therapy

Although IV t-PA's efficacy has been proven and established as the initial, standard treatment for acute ischemic stroke patients, widespread use of IV t-PA is constrained because of the following limitations:

- Contraindications and co-morbidities: Patients are contraindicated to receive IV t-PA therapy for numerous reasons, with the most common being delayed presentation to the ER after symptom onset (i.e. beyond the 4.5 hour window after the onset of symptoms). A 2006 study revealed about 77% of ischemic stroke patients arrived at the ER beyond indicated treatment window. [20] Additionally, patients on anticoagulants cannot receive IV t-PA as it increases the risk of hemorrhage. Other comorbidities such as recent surgery or trauma also preclude IV t-PA therapy.

- High percentage of non-responders to IV t-PA therapy: There is a high variability in thrombolysis in the proportion of patients who achieve therapeutic benefit of IV t-PA therapy. In the NINDS[1] and ECASS III[2] studies, the percentage of patients with an *unfavorable* outcome (mRS 3-6) ranged from 48-57%. Factors such as large vessel occlusion (see below), systolic hypertension, early ischemic changes on CT and increased time to treatment are found to predict poor outcome with IV t-PA.

- Large vessel occlusions: A primary reason for non-responders to IV t-PA therapy is proximal large vessel occlusion; patients with clots in the internal carotid, middle cerebral, anterior cerebral or vertebrobasilar arteries. [9 - 11] For patients in whom the underlying etiology for ischemic stroke is proximal large vessel occlusion (35-40% of all ischemic stroke cases), IV t-PA's ability to achieve recanalization is limited due to the large thrombus burden and inability for IV t-PA to penetrate the clot and achieve thrombolysis. [9, 12, 13,21, 22] These patients do poorly, with a with a 4.5-fold increased odds of death and a 3-fold reduction in odds of good outcome (mRS $\leq$2). (Table 1, below). [10, 21, 23, 25, 26, 27] This group of patients typically present with a higher NIHSS score (NIHSS $\geq$ 10), as these strokes typically cover a larger area of the brain, with more symptoms, increasing care and cost of the patient. [10]. Given the large number of patients with large vessel occlusion, the poor response to IV t-PA, and the devastating effects of these strokes, mechanical thrombectomy is necessary as a viable treatment option.

[1] National Institute of Neurological Disorders and Stroke
[2] European Cooperative Acute Stroke Study

Table 1: Recanalization, Morbidity and Mortality Outcomes in Large Vessel Occlusions				
Article	**Target vessel(s)**	**Recanalization**	**Morbidity**	**Mortality**
Jansen et al., AJNR 1995[21]	ICA-T	12.5%	31%[28]	57%
Brandt et al., Stroke 1996[23]	BA	51%	12%[29]	46% in recan 92% in nonrecan
Hacke et al., Arch neurol 1996[25]	MCA	NR	NR	78%
Watanabe et al., Neurol Med Chir 2011[26]	ICA-T	50%[31]	50%[30]	40%
Dabus et al., Tech Vasc Interv Rad 2012[27] (Review article)	ICA-T, BA	NR	NR	ICA-T: 41-75% BA: 37-87%
1: Moderate to severe neurologic deficit 2: Rankin scale 4-5 3: Rankin scale 3-5 4: TICI 2				

Evolution of alternative treatments: Intra-Arterial (IA) Therapy

While IV tPA can be used for many patients as a front-line treatment option as noted above, non-responders to this treatment modality such as those patients with large vessel occlusions have few options. Mechanical *thrombolysis was the first interventional therapy*, in which a clot is broken up by intra-arterial tPA and/or mechanical manipulation by a guide wire. This differs significantly from the current treatment of mechanical *thrombectomy*,, in which the clot is removed with a specialized device called a *stentriever*. This difference is important, because in mechanical thrombolysis, physical disruption of the clot causes the clot fragments to shower distally, and while a large vessel stroke may be avoided, multiple small infarctions may be created instead.. This difference is essential when evaluating the recent randomized controlled studies comparing IV tPA to mechanical intervention, as 2/3 of those patients received mechanical *thrombolysis* rather than mechanical *thrombectomy*.

Endovascular mechanical thrombectomy devices, approved for use within 8 hours of stroke symptom onset, are designed to directly remove thrombus occluding the blood vessel and thus restore patency of the occluded vessels. In the United States, currently approved mechanical thrombectomy devices include the Merci™* Retriever (Stryker/Concentric Medical, Inc.), Penumbra™* System (Penumbra, Inc.), Solitaire FR device (Covidien) and Trevo™* Pro Retrieval System (Stryker/Concentric Medical, Inc.). Clinical evidence has demonstrated that mechanical thrombectomy devices are capable of

restoring blood flow, particularly in large vessel occlusions, both within and beyond 4.5 hours from stroke symptom onset, albeit with different efficacy depending on the device used. Data from respective clinical studies indicate that *these devices provide an important therapeutic alternative for this critical population, where no other approved therapy exist, and can result in excellent outcomess* (**Table 2**, below). [32, 33]

Table 2: Efficacy and Safety Outcomes of IA Thrombolysis/Mechanical Thrombectomy Trials

THERAPY TYPE	THROMBOLYSIS	MECHANICAL THROMBECTOMY						
	Pro-urokinase	Covidien / ev3			STRYKER / Concentric Medical			Penumbra
Clinical Trials	PROACT 2 [34] (r-proUK+Hep only)	SWIFT Study (Rand SFR only)	Retrospective Solitaire FR Study	STAR [18] Solitaire FR Study	TREVO™ * Study	TREVO 2™* Study	Multi MERCI Trial	Penumbra Pivotal Trial
Symptom onset to treatment	<6 hours	*<8 hours*	*<8 hours*	*<8 hours*	*< 8 hours*	*<8 hours*	*<8 hours*	*<8 hours*
N	121	58	141	202	60	88	131	125
Baseline NIHSS	17 (5-27)	18 (9-28)	18 (1-32)	17	18	19	19	17.6±5.2
Partial or Better Successful Recanalization as defined per protocol	66%	61% [2, 28]	86% [3, 29]	84.2% [7]	78.3% [8]	86% [8]	55% [4, 30]	82% [5, 31]
Complete Successful Recanalization (TIMI/TICI 3) as defined per protocol	20%	50%	37%	58%	UNK	14%	23%	23%
Functional independence (mRS ≤2) at 90 days	40%	36%	55%	57.9%	55%	40%	36%	25%
Mortality Rate at 90 days	25%	17%	20% [5, 35]	6.9%	20%	33%	34%	33%
Symptomatic ICH%	10%	2%	5.5%	1.5%	5%	7%	10%	11%

1: TIMI 2-3 flow on all treatable vessels without use of rescue therapy or symptomatic ICH as assessed by blinded core lab.
2: TICI 2b-3 flow assessed by independent core lab.
3: TIMI 2-3 flow on all treatable vessels.
4: TIMI 2-3 flow at the site of primary occlusion. Final determination made by core lab.
5: Includes 3 subjects who were lost to follow-up. These subjects were assigned the worst outcome at 90 days (classified as deaths).
6: TICI 2b-3flow assessed by independent core lab within 3 passes
7: TICI $\geq$ 2

Consideration of the IMS III, MR RESCUE and SYNTHESIS Thrombectomy Trials

There have been three trials that have recently been published that attempted to examine the value of mechanical thrombectomy (clot removal) in cases where IVtPA failed. The trials included the Interventional Management of Stroke (IMS III), Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE), and SYNTHESIS trials, all of which prompted skepticism in the lay press about the clinical value of mechanical thrombectomy for the treatment of ischemic stroke. However after thourough review, endovascular and stroke experts have clearly concluded that these trials were fundamentally flawed and not consistent with accepted US stroke care. *These trials did in fact show expected improvement in the patient subset with large vessel occlusions* (where the value of mechanical thrombectomy lies), and **demonstrated non-inferiority** to the small subset of stroke patients presenting in <3 hrs after stoke, in whom tPA is more likely to show its benefit rendering the conclusion that mechanical thrombectomy is not beneficial which was premature and inaccurate. So while the individual conclusions of the trials themselves were flawed, and often not consistent with US stroke care modern practice standards, there were some elements (such as the large vessel occlusion patients subset) that do show promise with thrombectomy.

These trials provide compelling support for preserving the best elements of endovascular stroke care; review of the data from these three studies demonstrates:

- An absence of competing therapeutic alternatives for non-iv TPA eligible patients.
- The importance of pre-procedural arterial imaging such as computed tomography angiogram or conventional angiogram to identify and distinguish strokes due to Large-Vessel Occlusions.
- A statistically significant clinical advantage of endovascular therapy in patients with large vessel occlusions confirmed by pre-procedural imaging,
- The critical importance of process efficiency to minimize delays in care as emphasized by the Joint Commission,
- Dramatic improvements in the technical performance and safety profile of modern endovascular devices that has occurred in the very recent past.

It is important to ensure that the narrow cohorts evaluated in these studies not become a broad basis for the denial of endovascular care access to all stroke patients, especially given some significant design flaws of the afore mentioned studies that will be discussed. Prior to reviewing the trials investigating

IV versus mechanical thrombectomy (below), one might consider SWIFT and TREVO, trials evaluating third generation (current) intraarterial thrombectomy devices to gain perspective on what endovascular experts would consider acceptable rates of recanalization and outcomes of mechanical thrombectomy.

Modern Stentriever technologies (Solitaire FR and TREVO) achieved complete or near-complete (TICI 2b and 3)[3] revascularization at much higher rates and with improved safety profiles compared to first generation technologies (that were used in the three failed trials). The SWIFT Trial demonstrated a statistically significant difference in mortality, recanalization (TIMI 2/3) and good neurological outcome (mRS 2 or more, or 10 point improvement in NIHSS). Similarly, TREVO EU showed across 60 patients with confirmed large vessel occlusion and a mean NIHSS of 18, that the TREVO Stentriever device achieved a 78.3% recanalization (TICI 2b or better) and 55% of patients enjoyed 90-day functional independence (mRS < 2).

In sharp contrast, IMS III, MR RESCUE and SYNTHESIS did not evaluate modern devices in 2/3 of patients, instead using thrombolysis and first generation devices for this vast majority. Only 5 of 434 patients received Solitaire FR[4] in IMS III and in SYNTHESIS, only 56 of 165 endovascular therapy patients even received mechanical treatment. In MR RESCUE, the preponderance of endovascular treatment was MERCI (a first generation device with much lower efficacy); these endovascular treatment arms therefore do NOT reflect modern thrombectomy practice.

[3] TCI 2b and 3 is the modern 'gold standard' used for evaluating whether a revascularization therapy has been successful. It represents the physical opening of the vessel. 2a is a revascularization that represents a partial opening that is not currently accepted as adequate.
[4] Solitaire FR is a third generation mechanical thrombectomy device.

Thrombectomy Trial Summaries

As noted above, there have been 5 major trials examining the value of thombectomy trials. The first three (IMS III, MR RESCUE and SYNTHESIS) **failed to incorporate modern US endovascular practices in their study design or execution, although subset analysis done where possible examining the more limited parameters of what is typically regarded as the accepted application of mechanical thombectomy, does show successful clinical outcomes.**

1: IMS III

The Interventional Management of Stroke (IMS III) Trial was a randomized, open-label multi-center study to compare a combined intravenous (IV) and intra-arterial (IA) treatment approach to the current standard FDA approved treatment approach of giving IV rt-PA alteplase, Activase®/ Actilyse® alone. Both approaches required treatment initiation within 3 hours of stroke onset. After randomization of 656 participants, the (IA) endovascular group and IV tPA cohorts experienced similar rates of functional independence (mRS 0-2) (40.8% versus 38.7%) and mortality (19.1% and 21.6%, P=0.52) at 3-month follow-up. Sub-group analysis based on NIHSS severity (NIHSS 8-19 and NIHSS > 20) showed greater therapeutic benefit for endovascular therapy, but did not achieve statistical significance. Rates of symptomatic intracerebral hemorrhage were additionally comparable (6.2% and 5.9%, P=0.83).

Limitations to IMS III include the following:

1. The majority of the patients in the IV plus IA treatment arm did not receive standard FDA–approved IV tPA treatment, but rather a nonstandard two-thirds IV dose.
2. The IA dose of tPA could be as much as the remaining third of the standard systemic IV tPA dose (up to 30 mg IA tPA), for which efficacy is unproven.
3. Approximately two thirds of patients were treated with tPA alone in the endovascular group. Only 5 of 434 patients in the IA treatment arm were treated with a stentriever, *eliminating this as a study of thrombectomy*. This explains the significantly lower rates of recanalization compared to other trials.
4. Presentation within 3 hours of symptoms represents only 5-10% of strokes, so these results cannot be extrapolated to the majority of our patient population. There is likely a larger therapeutic window for mechanical thrombectomy patients who present outside of the traditional window with large vessel occlusion.

5. By definition, thrombectomy cannot be performed unless there is a large vessel thrombus. The IMS III trial selected patients by NIHSS values, expecting and finding that 20% of patients did not have a large vessel occlusion at catheter angiography. These patients did not receive endovascular therapy but were still included in the intent-to-treat outcomes analysis.

Summary: IMS III

When comparing those patients who would actually be treated with the modern standard of endovascular revascularization (ie, those who had a large vessel occlusion), IA endovascular treatment provided patients with statistically significant benefit over IV tPA alone [mRS score of 0-1 (almost complete neurologic recovery) were 35% for IA treatment and 19.8% for IV treatment]. There is a clear benefit of endovascular IA over IV treatment, which represents a different much different finding from the published IMS III conclusion that IA therapy provides no benefit over IV therapy.

2: MR RESCUE

The Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) Trial was a multi-center, randomized trial comparing standard medical care to embolectomy in patients presenting within 8 hours with a large-vessel anterior circulation strokes. All patients received pre-procedural parenchymal imaging by CT or MRI to assess penumbral[5] profile. Patients treated with IV t-PA were only enrolled if arterial imaging demonstrated persistence of a large-vessel occlusion. Of 118 enrolled patients, Rankin scores did not differ between embolectomy and standard medical care (3.9 vs. 3.9, P = 0.99), regardless of penumbral pattern (mean score, 3.9 vs. 3.4; P = 0.23).

Importantly, patients with reperfusion or revascularization did demonstrate mean improvements in 3-month mRS (3.2 [2.6-3.8] versus 4.1 [3.7-4.5], P=0.04) and median absolute infarct growth (9.0 versus 72.5 mL, P<0.001). Moreover, MR RESCUE only included first generation Merci and Penumbra endovascular technologies. *Partial* or complete reperfusion was defined by Thrombolysis in Cerebral Infarction (TICI) Scale 2a-3 results (2a represents a lower degree of recanalization); modern stentriever

[5] The penumbra is defined as the region that often surrounds the area of completed stroke, and without restoration of blood flow to this area (by medical or mechanical means), this area will often go on to stroke. It is this area that is the target of pharmacologic and/or mechanical treatment.

trials define adequate recanalization as a TICI 2b or 3 result (complete or near-complete), a significant disparity with regards to angiographic reperfusion.

Limitations to MR RESCUE study include the following:

1. The trial failed to distinguish groups with or without penumbra. Penumbra was defined as an infarct core less than 90 cm^3 and core/total ischemic tissue volume less than 70% (ie, mismatch ≥ 30%). The study shows that the NO-penumbra group actually had a median mismatch of 50% (table 1 within the study). There was no separation based on the presence or absence of penumbra: the groups were actually separated on the basis of core infarct size. Without defining a penumbra, one cannot be certain if the patient may or may not have the potential for improvement with therapy.
2. Revascularization was assessed at 7 days, a clinically irrelevant time frame as it must occur within minutes to hours to provide benefit. Additionally, natural thrombolysis in a vessel may have occurred, despite the completed infarct having occurred.
3. TICI 2a flow was achieved in 40% of cases, but only 27% reached TICI 2b or 3 flow outlining limitations in the techniques and devices used in this study as markedly improved recanalization rates were evidenced in the SWIFT and TREVO trials previously discussed.
4. Good outcomes were reported in only 21% of patients treated with penumbra and embolectomy. This is half the expected rate based on comparisons with other IA studies, including IMS III and SYNTHESIS Expansion which suggests that there may have been patient selection, technical or other undefined issues which may have swayed the data.
5. In the penumbra groups, patients treated with embolectomy had more infarct growth than seen with standard of care (27 cm^3 vs 7 cm^3). For patients receiving standard of care, there was almost no infarct growth in the penumbra group (7 cm^3) but extensive infarct growth in the no-penumbra group (84 cm^3). These results are counterintuitive and suggest that the conclusion of no embolectomy benefit is unfounded.

Summary of MR RESCUE trial:

The study has several significant limitations as noted above. Perhaps most importantly, the size of penumbra, and therefore the size of the potential salvageable area that is at risk for infarct (but not yet infarcted at the time of the treatment (the area of mismatch)) was not accounted for in this study. Instead, the size of the core infarct alone was the determining factor upon which group these patients

were categorized. Without knowing the true penumbra, treatment outcomes will be varied considerably for those that have a very small penumbra (little mismatch between completed infarct and the area at risk) as compared to those that have a large penumbra (a significant difference (mismatch) between completed infarct and the area at risk for further stroke, but said stroke is not yet occurred).

3. SYNTHESIS

The Intra-Arterial versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS) Trial was a multi-center Italian trial that randomized 362 patients presenting with an acute ischemic stroke to IV t-PA within 4.5 hours of onset versus intra-arterial therapy within 6 hours of onset. No pre-procedural imaging was obtained to confirm large vessel occlusion. Moreover, only 165 of the 181 patients randomized to intra-arterial therapy received an endovascular procedure. Due to endovascular treatment differences between the study centers and the United States, 109 patients received endovascular treatment with pharmacologic agents and wire manipulation; only 56 patients received mechanical thrombectomy procedures in the endovascular therapy arm. The efficacy of these alternative intra-arterial therapy was not reported in terms of post-procedural TICI and time to reperfusion.

These factors show that the SYNTHESIS study population and management *does not* reflect the standards of management within the United States. While the SYNTHESIS Trial failed to demonstrate a 3-month clinical benefit by mRS for this unconventional endovascular therapy, despite withholding IV tPA (a failure to comply with a Class 1 indication) and delivering IA tPA in patients without occlusion, endovascular still therapy had no increase in death or symptomatic ICH. Despite this, SYNTHESIS thereby affirms the safety of endovascular therapy.

Limitations to the Synthesis study include the following:

1. There was no confirmation of large vessel clot in the IV therapy group. If there was no large vessel clot seen on cerebral angiography in the IA group, IA tPA was given anyway. This does not conform to the standard of care in the United States.
2. Only one third of patients were treated with a mechanical device and only one sixth were treated with a stentriever (a thrombectomy device). *Therefore, despite its intent, this was ultimately a trial of systemic-dose tPA administered IV versus IA.*

3. There was no exclusion based on a low NIHSS score. Patients with a lower NIHSS score are expected to do well regardless of type of treatment and tend to do very well with IV tPA alone or even placebo, as demonstrated in the European Cooperative Acute Stroke Study III.
4. TICI revascularization scores were not reported. Poor revascularization could be caused by ineffective results of very large amounts of tPA via IA administration.
5. Failure to give standard doses of IV tPA to appropriate candidates.

Summary of SYNTHESIS:
This study did not define the population most at risk – those with large vessel occlusions and the group most likely to benefit from mechanical thrombectomy. Further it did not exclude for low NIHSS scores which clouds the data considerably, as the natural history of low NIHSS patients will typically have a vastly improved outcome (as compared to more severely affected patients) regardless of treatment administered. Finally, the vast minority of patients received actual mechanical thrombectomy with modern stroke devices.

Technical Performance of Endovascular Therapy: The Modern Standards of Safety and Reperfusion

The literature supports endovascular mechanical thrombectomy to be a safe treatment for stroke with improved recanalization rates with modern devices (as evidenced in SWIFT and TREVO). IMS III, despite its shortcomings, showed death and symptomatic intracerebral hemorrhage rates to be comparable among the two study groups and demonstrates the safety of endovascular therapy in the setting of tPA .

IMS III also demonstrated the strong concordance between adequacy of reperfusion (opening the vessel by removing the clot) and 3-month clinical outcome. Patients who obtained TICI 2b or 3 results (complete or near-complete restoration of blood flow) were statistically more likely to be functionally independent (mRS 0-2) at 3 months. Again, modern standards are measured by the TREVO study, showing 77% recanalization.

The compilation of data supports mechanical thrombectomy, and when applied to the large population of stroke patients presenting with large vessel occlusion and those ineligible for IV t-PA (as many as 80-95% of all stroke patients), mechanical thrombectomy is safe and effective, and often the *only available* treatment to prevent long-standing loss of function and dependence.

The National Institute for Health and Care Excellence (NICE) published *Mechanical Clot Retrieval for Treating Acute Ischaemic Stroke*, Interventional Procedure Guidance 458 (July 2013), recognizing the poor prognosis of many patients with stroke. As such, NICE allows mechanical thrombectomy usage under strict clinical governance where IV thrombolysis is unsuitable or has failed. [53]

Following the NICE decision highlighting the advantages of mechanical thrombectomy, evidence continues to mount in the literature to support this. Walcott, et al., performed a metaanalysis showing a total of 576 patients treated with either the Trevo (n=221) or Solitaire (n=355) devices. Baseline NIHSS scores were 18.5 and 17.9, respectively, and time to recanalization on average 53.9 ± 23.6 minutes and 59.0 ± 8.0 minutes. Revascularization (83%, 82%), mortality (31%, 14%), hemorrhage (8%, 6%), device complications (5%, 6%), and good patient outcomes (51%, 47%) were found with

the Trevo and Solitaire devices, respectively. Analysis revealed excellent clinical outcomes for retrievable stent technology, which could be attributable to both high rates of revascularization with a relatively short time to perfusion restoration.

Further supporting the use of modern mechanical thrombectomy beyond TREVO and SWIFT, Mortimer, et al, reveiewed multiple observational studies demonstrating consistently high rates of large vessel occlusion recanalization; TICI 2b/3 in 65-95% and good clinical outcomes (mRS 0-2) in 55% (42.5-77%).

Additional support of third generation mechanical thrombecotmy, Lefevre, et. al, evaluated 62 patients who underwent mechanical thrombectomy with the Solitaire FR device with or without intravenous thrombolysis. Mean NIHSS score on admission was 19.8. Recanalization was successful (TICI score 2b or 3) in 23 of 26 (88.5%) patients with posterior circulation occlusion and in 23 of 36 (63.9%) patients with anterior circulation occlusion. MRS was 0-2 in 25 of 62 patients (40.3%).

Hann, et al, compared 31 patients treated with the Solitaire and 20 comparable patients treated with Merci or Penumbra systems. Compared with the Merci/Penumbra group, the Solitaire group showed a statistically significant improvement in favorable outcomes (mRS $\leq$ 2) (69% versus 35%, P = 0.03) and symptomatic ICH rate (0 versus 15%, P = 0.05), with a trend towards higher recanalization rates (93.5% versus 75%, P = 0.096) and shorter length of procedure (58.5 min versus 70.8 min, P = 0.08). Radiographic comparison also showed a significantly larger area of salvage in the Solitaire group (81.9% versus 71.9%, P = 0.05).

Summary

Similar to the position of the Society of Interventional Radiology and the AANS/CNS Joint Cerebrovascular section, we have provided a thoughtful review and analysis of the successes, challenges and controversies of stroke treatment when IV tPA has failed. The following represents a concise synopsis of these findings:

1. IA stroke revascularization is beneficial to patients in whom IV tPA fails or who are not eligible for IV tPA.
2. Patients with a large vessel occlusion who are treated with mechanical thrombectyomy have improved outcomes compared those treated with IV tPA alone.

3. Second-generation mechanical thrombectomy devices show a considerable improvement as compared to first generation devices, and are most effective therapy for large vessel occlusions.
4. Participation in research is critically important, but reimbursement for IA stroke revascularization should not be restricted to clinical trials.
5. All mechanical thrombectomy cases should be contributed to a trial or national registry, including 90-day clinical outcomes.

As stated earlier, when patients fail or are not candidates for IV t-PA, there have no other alternative to address their acute stroke. Therefore, based on the published evidence, endovascular mechanical thrombectomy of angiographically documented intracranial arterial occlusions has demonstrated sufficient safety and efficacy to consider the procedure reasonable and medically necessary for a select group of acute ischemic stroke patients with profound neurological deficits who have failed or are not candidates for thrombolysis.

In summary, we urge you to consider the conclusions drawn from these trials with caution and refer to the recent update of the *Guidelines for Early Management of Patients with Acute Ischemic Stroke* in revising the proposed BCBSNC policy change:

The American Heart Association and American Stroke Association (AHA/ASA), supported by the American Academy of Neurology and endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons, updated the *Guidelines for Early Management of Patients with Acute Ischemic Stroke* (Jauch, 2013). [52] Below are the new or revised recommendations specific to mechanical thrombectomy which we support, and are hopeful that BCBSNC will adopt:

- When mechanical thrombectomy is pursued, stent retrievers such as Solitaire FR and Trevo devices are generally preferred to coil retrievers such as the Merci device.
- The Merci, Penumbra System, Solitaire FR, and Trevo thrombectomy devices can be useful in achieving recanalization alone or in combination with pharmacological fibrinolysis in carefully selected patients.
- Intra-arterial fibrinolysis or mechanical thrombectomy is reasonable in patients who have contraindications to the use of intravenous fibrinolysis.
- Rescue intra-arterial fibrinolysis or mechanical thrombectomy may be reasonable approaches to recanalization in patients with large-artery occlusion who have not responded to intravenous fibrinolysis.

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