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Endovascular Grafts for Abdominal Aortic Aneurysms

Policy # 00035
Original Effective Date: 01/27/2003
Current Effective Date: 07/16/2014

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

Note: Endovascular Stent Grafts for Thoracic Aortic Aneurysms or Dissections is addressed separately in medical policy 00181.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider endoprostheses as a treatment of abdominal aortic aneurysms (AAAs) to be **eligible for coverage**.

Patient Selection Criteria
Coverage eligibility for the use of endoprostheses will be considered when all of the following criteria are met:

- The device is U.S. Food and Drug Administration (FDA) approved and is used according to the U.S. Food and Drug Administration (FDA) labeling.
- As a treatment of abdominal aortic aneurysms (AAAs) in any of the following clinical situations:
    - An aneurysmal diameter greater than 5cm; or
    - An aneurysmal diameter of 4-5cm that has increased in size by 0.5cm in the last 6 months; or
    - An aneurysmal diameter that measures twice the size of the normal infrarenal aorta; or
    - A ruptured abdominal aortic aneurysm (AAA).

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

The use of endoprostheses approved by the U.S. Food and Drug Administration (FDA) as a treatment of abdominal aortic aneurysms (AAAs) is considered **investigational*** for the following clinical situations:

- Treatment of smaller aneurysms that do not meet the current recommended threshold for surgery
- Treatment of aneurysms that do meet the recommended threshold for surgery in patients who are ineligible for open repair due to physical limitations or other factors

The use of endoprostheses when patient selection criteria are not met is considered **investigational.***

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Background/Overview

Endovascular grafts are minimally invasive alternatives to open surgical repair for treatment of AAAs. Open surgical repair of AAAs has high morbidity and mortality, and endovascular grafts have the potential to reduce the operative risk associated with AAA repair.

The conventional management of a clinically significant AAA consists of surgical excision with placement of a sutured woven graft. Surgical excision is associated with a perioperative mortality rate of 4%, which may rise to 10% in symptomatic patients. Due to this high mortality rate, endovascular prostheses have been investigated as a minimally invasive, catheter-based alternative to open surgical excision of AAAs. These devices are deployed across the aneurysm such that the aneurysm is effectively "excluded" from the circulation, with subsequent restoration of normal blood flow.

There are several types of grafts currently under investigation—straight grafts, in which both ends are anchored to the infrarenal aorta, and bifurcated grafts, in which the proximal end is anchored to the infrarenal aorta, and the distal ends are anchored to the iliac arteries. Recently, fenestrated grafts have also been investigated. These grafts are designed with openings in the wall that can be placed across the renal or celiac arteries while still protecting vessel patency through these critical arteries. In addition, extensions can be placed from inside the main endograft body into the visceral arteries to create a hemostatic seal.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration
In 1999, the FDA approved t2 endovascular grafts for use in the abdominal aorta: the EVT Abdominal Aortic Endovascular Grafting System (Guidant Endovascular Technologies) and the AneuRx®‡ Prosthesis System (now called AneuRx AAAdvantage Stent Graft - Medtronic Vascular Inc.). In the Guidant system, the endograft is placed in the aorta and expanded using balloon dilation. The graft is anchored to the vessel wall using sutureless hooks at its superior and inferior ends. The AneuRx system consists of a woven polyester interior surface with a self-expanding nitinol exoskeleton. The radial force of the expanding stent embeds the exoskeleton into the aneurysm wall and thus constitutes the attachment mechanism. In April 2002, FDA approved an additional Guidant device, the Ancure®‡ Aortoiliac System. The Ancure device consists of a woven polyester graft that is housed within a long flexible delivery tube (catheter) for use in patients whose anatomy is not suited for the use of the single tube or bifurcated endograft device. This version is identical to the earlier Guidant Endovascular Grafting System except that the aortoiliac Ancure grafts have suture loops on the superior and inferior attachment systems. Several other grafts have been subsequently approved, including the Gore®‡ Excluder®‡ (2002), the Zenith®‡ AAA Endovascular Graft (2003 – now called Zenith Flex AAA Endovascular Graft), the Endologix Powerlink®‡ (2004), the Medtronic Talent®‡ Abdominal Stent Graft System (2008), the Medtronic Vascular Endurant®‡ II AAA Stent Graft System (2010), and the Aorfix™‡ AAA Flexible Stent Graft System (2013, Lombard Medical, PLC). In 2012, the Ovation™‡ Abdominal Stent Graft System (TriVascular Inc.), a lower-profile stent graft that uses a postimplantation polymer deployment system to seal the device to the aorta, was approved for endovascular repair of AAAs with suitable anatomy.

The Zenith®‡ Fenestrated AAA Endovascular Graft, a graft that extends across the visceral arteries, was approved by FDA with the adjunctive Zenith Alignment Stent in April 2012. The device is approved for

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endovascular treatment of aortic or aortoiliac aneurysms that are suitable for endovascular repair with the following:

- "Adequate iliac/femoral access compatible with required introduction systems
- Nonaneurysmal infrarenal aortic segment (neck) proximal to the aneurysms with:
  - Length 4 mm and unsuitable for a nonfenestrated graft
  - Diameter <31 mm and 19 mm
  - Angle <45 degrees relative to long axis of aneurysm
  - Angle <45 degrees relative to axis of suprarenal aorta
- Ipsilateral iliac artery fixation site >30 mm in length and between 9 - 21 mm in diameter
- Contralateral iliac artery distal fixation site >30 mm in length and between 7 - 21 mm in diameter."

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD).

Rationale/Source

The main potential advantage of endovascular grafts for AAA is in offering a less invasive and risky approach to the repair of abdominal aneurysms. This approach has the potential to reduce the relatively high perioperative morbidity and mortality associated with open AAA repair.

The use of endovascular grafts also has potential disadvantages. In particular, there are concerns regarding the durability of the anchoring system, aneurysm expansion, and other late complications related to the prosthetic graft. Aneurysm expansion may result from perivascular leaks, also known as endoleaks, which are a unique complication of endoprostheses. Perivascular leaks may result from an incompetent seal at one of the graft attachment sites, blood flow in aneurysm tributaries (these tributaries are ligated during open surgery), or perforation of graft fabric.

This policy is also supported by a 2001 Technology Assessment Evaluation (TEC) Assessment.

Literature Review

EVAR as an alternative to open repair for elective treatment of AAAs

A number of moderate- to large-sized randomized, controlled trials (RCTs) have been completed comparing endovascular aneurysm repair (EVAR) with open surgical repair, and these studies comprise the main body of literature on the comparative efficacy of the two procedures. Early reports of outcomes from these trials demonstrated that the perioperative morbidity and mortality of an endovascular approach were reduced compared to open surgical repair. These results were consistent with prior large observational studies. However, the midterm results of these studies suggest that the short-term improvements are not associated with a long-term benefit compared to an open approach. These studies are reviewed below:

Open versus Endovascular Repair (OVER) Trial

Long-term results of the OVER trial were published by Lederle et al. in 2012. In this trial, 881 patients with asymptomatic AAAs from multiple Veterans Administration medical centers were randomized to EVAR versus open repair and followed up for a mean of 5.2 years. An early survival advantage was reported for EVAR of up to 3 years, but at final follow-up, mortality was similar between groups (hazard ratio [HR]: 0.97,

95% confidence interval [CI]: 0.77-1.22, p=0.81). On subgroup analysis, differences in mortality were noted according to age. For patients younger than 70 years, mortality was increased in the EVAR group (HR: 1.31, 95% CI: 0.99-1.73), while for patients older than 70 years, mortality was reduced in the EVAR group (HR: 0.65, 95% CI: 0.43-0.98).

Dutch Randomized Endovascular Aneurysm Management (DREAM) Trial
This trial enrolled 351 patients who were randomized to either endovascular or open repair. The incidence of aneurysm-related death (i.e., within 30 days) was 4.6% in the open repair group and 1.2% in the endovascular repair group. However, after 2 years, the cumulative survival rates were 89.6% for open repair and 89.7% for endovascular repair, due to a higher incidence of late death in the endovascular group. The authors suggest that an open approach may precipitate the mortality of frail patients who were most likely to die in the coming year and that the advantage of an endovascular approach may primarily be to delay death. Alternatively, the late mortality of endovascular repair may relate to its inferior ability to prevent rupture or prevent additional complications, compared to an open approach. If this is true, longer term follow-up is important to determine if the endovascular approach has an inferior outcome over the long term.

Longer term follow-up from this study was reported in 2010. After 6 years of follow-up, the survival rates were similar between the EVAR and open repair groups (68.9% vs. 69.9%, respectively; 95% CI: -8.8 to 10.8; p=0.97). Re-interventions were more common in the EVAR group. Freedom from reinterventions was 70.4% for EVAR compared to 81.9% for open repair (95% CI: 2.0 to 21.0; p=0.03).

Endovascular Aneurysm Repair versus Open Repair in Patients with Abdominal Aortic Aneurysm (EVAR 1) Trial
A larger trial, EVAR 1, enrolled 1,082 patients 60 years or older with abdominal aneurysms at least 5.5 cm in diameter and randomized them to either elective open or endovascular repair. Similar to the DREAM trial, endovascular repair was associated with an improvement in aneurysm-related survival (4.7% open vs. 1.7% at 30 days), but no advantage with respect to all-cause mortality and quality-of-life measures. For example, within 4 years of follow-up, endoscopic repair was associated with a complication rate of 41% compared to only 9% in the surgically treated group. Due to the higher incidence of late complications in those undergoing endovascular repairs, ongoing surveillance is required.

Longer term follow-up from this trial was reported by the EVAR Investigators in 2010. This publication included a total of 1,252 patients with aneurysms 5.5 cm or larger randomized to EVAR or open repair. After 8 years of follow-up, there was no difference in survival between the groups (HR: 1.03; 95% CI: 0.86-1.23). This evidence suggests that the early survival advantage of EVAR is lost over time due to late endograft ruptures, some of which are fatal.

Another follow-up publication from the EVAR-1 trial focused on cardiovascular morbidity and mortality at 5 years post-treatment. The EVAR group had a lower total cardiovascular event rate at all follow-up time points, but the difference over the course of the study did not reach statistical significance (HR: 0.83, 95% CI: 0.62-1.10). During the period of 6-24 months post-surgery, the EVAR group had a higher rate of cardiovascular events (HR: 1.44, 95% CI: 0.79-2.62), which attenuated the early benefit of EVAR and led to

convergence of events between the two procedures. Cardiovascular mortality over the course of the trial was similar between the groups (HR: 1.06, 95% CI: 0.83-1.36).

ACE Trial
This trial compared EVAR to open surgical repair in patients who were low-to-moderate surgical risk. A total of 306 patients were randomized from 25 clinical centers in France. Inclusion criteria included a Society of Vascular Surgery comorbidity score of 0-2 and suitable anatomy for EVAR without high-risk features. There were 17 crossovers from open surgery to EVAR (11%) and 4 crossovers from EVAR to open surgery (3%). Median follow-up was 3 years.

Perioperative mortality was 1.3% for the EVAR group and 0.6% for the open surgery group (p=0.12). Survival at one year was 95.2% for EVAR and 96.5% for open surgery (p=0.24). At 3 years, survival remained similar at 86.3% for EVAR and 86.7% for open surgery. Major adverse cardiovascular events were present in 6.7% of EVAR patients compared to 4.0% of open surgery, a difference that was also not significant. Re-interventions were more common in the EVAR group compared to open surgery (16% vs. 2.7%, p<0.0001).

Endoleaks were identified on follow-up computed tomography (CT) scanning in 27% of EVAR patients (41/150). There were a total of 10 types I endoleaks; 5 were treated by endoluminal procedures, 2 were treated with open surgery, and 3 were treated by observation. There were a total of 31 type II endoleaks; 8 of these were treated with coil embolization and 23 were left untreated.

Systematic Reviews
Agency for Healthcare Research and Quality (AHRQ) published an Evidence-based Practice Center report comparing endovascular and open surgical repair for AAA. Based primarily on the DREAM and EVAR studies discussed here, the report concludes that for aneurysms larger than 5.5 cm, endovascular intervention improves perioperative outcomes compared with open surgical repair, but it has not been shown to improve long-term survival or health status compared with open surgery. The U.K.'s National Institute for Health and Clinical Excellence (NICE) also updated their guidance following a 2005 systematic review of the safety and efficacy of elective endovascular repair. The guidance states, "Current evidence on the efficacy and short-term safety of stent graft placement in AAA appears adequate to support the use of this procedure."

A systematic review of RCTs was published in 2012 by Dangas et al. This review included 6 trials involving a total of 2,899 patients. Combined analysis revealed a lower 30-day mortality rate for the EVAR group (relative risk [RR]: 0.35, 95% CI: 0.19-0.64). At the longest follow-up, there was no difference in overall mortality (RR: 0.99, 95% CI: 0.85-1.15), or in AAA-related mortality (RR: 1.58, 95% CI: 0.20-12.74). There were more reinterventions in the EVAR group at both short-term and long-term follow-up. The RR for reinterventions at the longest follow-up was 2.24 (95% CI: 1.58-4.08).

A 2014 Cochrane review assessed the evidence on the effectiveness of EVAR compared with open surgery for patients considered fit for surgery. The authors identified 4 trials considered high quality that compared EVAR with open repair (ACE, DREAM, OVER, EVAR 1 trials described above; N=2790 patients). In a

pooled analysis, short-term mortality (30-day or in-hospital mortality) was significantly lower in patients treated with EVAR (1.4% vs 4.2%; odds ratio [OR], 0.33; 95% CI, 0.2 to 0.55; p<0.001). There were no significant differences in mortality between EVAR and open repair groups at intermediate-term follow-up.

Stather et al conducted a systematic review and meta-analysis of studies of EVAR compared with open surgical repair for AAA with the goal of evaluating longer-term outcomes. The authors included RCTs and validated age-sex matched nonrandomized cohort studies of AAAs that met the following characteristics: compared EVAR with open surgery; contained more than 200 patients for RCTs or more than 2000 patients for cohort studies; and reported on 30-day and longer-term mortality. The final analysis included 11 studies: 9 articles that reported the outcomes from 4 RCTs at different follow-up time points, and 2 nonrandomized studies. The RCTs included 1393 patients who underwent EVAR and 1390 who underwent open surgical repair. The nonrandomized studies included age- and sex-matched cohorts of 23,685 patients who had EVAR and 25,752 who had open repair. Overall, the short-term (30-day or in-hospital) mortality was lower in the EVAR groups (OR=0.36; 95% CI, 0.21 to 0.61). However, at longer term follow up, there were no significant mortality differences between groups (2-year all-cause mortality OR=0.87; 95% CI, 0.72 to 1.06; ≥4-year all-cause mortality OR=1.11; 95% CI, 0.91 to 1.35). Rates of reintervention were significantly higher in patients treated with EVAR (OR=2.08; 95% CI, 1.27 to 3.39). Similarly, rates of aneurysm rupture were higher in patients treated with EVAR (OR=5.94; 95% CI, 2.33 to 15.14). However, the this result may have been driven by a higher rate of rupture in the EVAR 1 trial than the other RCTs and the nonrandomized trials, which may have reflected surgeon inexperience, along with the fact that the OVER trial used a significant proportion of the Medtronic AneurX devices, which were associated with worsened survival rates.

Quadura et al conducted a systematic review and meta-analysis of RCTs comparing EVAR to open surgery for elective AAA repair for patients who were good surgical candidates. The authors included the DREAM, ACE, EVAR 1, and OVER studies previously discussed. Overall, the 30-day mortality rate was significantly higher in the open repair groups than the EVAR groups (3.2% vs 1.2%; RR=2.81; 95% CI, 1.61 to 4.94). There was no statistically significant difference in long term (at all-cause mortality rates between the open and EVAR repair groups (RR=0.95; 95% CI, 0.84 to 1.10). Reintervention rates were lower in the open repair group than the EVAR group (9.3% vs 18.9%; RR=0.49; 95% CI, 0.40 to 0.60), but there was significant between-study variability (92%), which limits the validity of the pooled RR for reintervention rates.

Numerous nonrandomized studies have been performed, including the studies that were originally the basis of FDA approval for endovascular grants. However, these studies add little additional evidence to the RCTs that have been published. A systematic review of nonrandomized studies that compared EVAR versus open surgery in elderly patients, 80 years or older, was published in 2011. This analysis included observational studies of elderly patients who had undergone EVAR and compared results with observational studies of elderly patients undergoing open repair. Pooled analysis revealed that operative mortality was lower in the EVAR group (2.3%) compared with the open surgery group (8.6%) and that EVAR also had lower rates of postoperative cardiac, pulmonary and renal complications. Survival at 3 years did not differ between patients undergoing EVAR and open repair (RR=1.10; 95% CI, 0.77 to 1.57).

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Section Summary
Evidence from several RCTs supports EVAR as a reasonable alternative to open surgical repair for aneurysms greater than 5.5 cm, or for aneurysms that have high-risk features such as rapid growth. In unselected patients with AAAs appropriate for surgery, EVAR is associated with lower perioperative morbidity and mortality. However, EVAR is associated with a higher rate of longer term complications, including endoleaks and the need for reinterventions. Longer term mortality is similar between EVAR and open surgery at 5 to 8 years of follow-up. For patients who are low risk for open surgery, 1 RCT reports low perioperative morbidity and mortality for both EVAR and open surgery, with no difference between the 2 procedures. Thus, the advantage for EVAR in reduced perioperative morbidity and mortality may not be present for patients who are low risk for surgery.

EVAR as an alternative to open repair for ruptured aneurysms
Emergency EVAR (eEVAR) for ruptured AAAs is being studied as a potential method to decrease the high mortality rate associated with open surgical repair. RCTs are difficult in this area due to the emergent or semi-emergent nature of treatment for ruptured aneurysms. As a result, until 2013, the most relevant evidence on this question is from nonrandomized, comparative studies of EVAR versus open surgery. However, there is a high risk for selection bias in uncontrolled studies. Aneurysms that meet the anatomic criteria for EVAR tend to be smaller and less complex than aneurysms that do not meet criteria for EVAR, resulting in the highest risk patients being preferentially treated with open surgery. Some studies have attempted to identify the degree to which selection bias may contribute to apparent favorable outcomes in endovascular EVAR repair by comparing outcomes for patients who underwent open repair in patients who met eligibility for EVAR compared with those who did not. In a study by Krenzien et al, those who were suitable for EVAR had a significantly lower prevalence of in-hospital deaths compared with patients unsuitable for EVAR (25% vs 53%, p=0.02). In contrast, in an observational cohort of 279 patients who underwent open repair of suspected ruptured AAA who were enrolled in parallel to the Amsterdam Acute Aneurysm Trial previously described, 30-day morbidity was not lower among the 71 patients who met criteria for EVAR compared with the 208 patients who did not meet criteria for EVAR (38% vs 30%, p=0.23). Because of the possibility of selection bias, several nonrandomized studies have used patient matching or other methods to reduce selection bias.

Two RCTs were published in 2013 that compare short-term results following endovascular versus open repair for ruptured aneurysms, but longer term follow up is still pending.

RCTs of EVAR compared with open repair for ruptured AAA
In 2013, the IMPROVE investigators reported 30-day follow up results for The Immediate Management of Patients with Rupture: Open Versus Endovascular Repair (IMPROVE) trial. This study randomized 623 patients at 30 centers (29 in the UK, 1 in Canada) with a clinical diagnosis of a ruptured AAA to either an endovascular strategy of immediate CT and eEVAR, with open repair for patients anatomically unsuitable for EVAR (endovascular strategy group), or to the standard treatment of emergency open repair (open repair group). Patients were excluded if they had a previous aneurysm repair, rupture of an isolated internal iliac aneurysm, aorto-caval or aorto-enteric fistulae, recent anatomic assessment of the aorta (for example, awaiting elective EVAR), a diagnosis of connective tissue disorder, or if intervention was considered futile. The study protocol permitted inclusion of hemodynamically unstable patients. Ten patients who were

randomized were excluded from data analysis due to breach of inclusion criteria. Three hundred sixteen patients were randomized to EVAR, 275 (87%) of whom had a confirmed diagnosis of ruptured AAA and 174 (64%) were considered anatomically suitable for EVAR. EVAR was attempted in 154 patients, 4 of whom were converted to open repair. Open repair was attempted in 112 other patients (84 anatomically unsuitable for EVAR, 28 crossovers). Sixteen patients died before repair, and 1 patient refused repair and was discharged. Two hundred seventy nine patients were randomized to open repair, 261 (88%) of whom had a confirmed diagnosis of ruptured AAA. Of the open repair randomization group, open repair was attempted in 220 patients (80%), EVAR was attempted in 36 patients (13%), and 19 patients died before repair.

For the study's primary outcome, overall 30-day mortality was 35.4% (112/316) in the EVAR group and 37.4% (111/297) in the open repair group (unadjusted OR=0.92; 95% CI, 0.66 to 1.28; p=0.62). After adjustment for age, sex, and Hardman index, a prognostic score for mortality after ruptured AAA, there were no significant differences on overall 30-day mortality (adjusted OR=0.94; 95% CI, 0.67 to 1.33; p=0.73). Compared with men, women demonstrated a greater benefit from EVAR than men (adjusted OR=0.44 vs 1.18, p=0.019 for interaction). There was a trend for lower mortality in the EVAR group for patients with higher Hardman index and age. Patients in the EVAR group were more likely to be discharged directly to home than those in the open repair group (94% vs 77%; p<0.001).

Also in 2013, Reimerink et al reported results of the Amsterdam Acute Aneurysm trial, a regional multicenter randomized trial to compare EVAR to open repair in the treatment of ruptured AAA. In this trial, patients were recruited from the set of all patients who presented with suspected ruptured AAA at 1 of 3 trial centers. The other 7 regional hospitals agreed to transfer patients with suspected ruptured AAA to one of the trial centers, if possible. After initial resuscitation, the diagnosis of a ruptured aneurysm was confirmed or rejected based on abdominal ultrasound and/or computed tomographic angiography. Patients who were considered suitable for both EVAR and open repair by the treating vascular surgeon were randomized to either EVAR or open repair. Five hundred twenty patients were diagnosed with ruptured AAA in the trial region; of those, 365 patients were excluded (240 for unfavorable anatomy, 71 with lack of evaluation by computed tomographic angiography, and 54 who were not referred to a trial center). One hundred fifty-five patients were considered to have favorable anatomy; 39 of those were excluded (16 were considered unfit for open repair, 11 for "logistics," 7 with severe hemodynamic instability after computed tomographic angiography, and 5 who refused surgery). One hundred sixteen patients were randomized, 57 of whom were allocated to the EVAR group and 59 to the open repair group. Ten patients in the EVAR group underwent open repair, and there was 1 perioperative death. In the open repair group, there were 3 diagnoses other than ruptured AAA at surgery and 4 perioperative deaths.

For the study's primary outcome, rates of a composite end point of death and severe complications at 30 days were 42% (24/57) in the EVAR group compared with 47% (28/59) in the open repair group (absolute risk reduction [ARR], 5.4%; 95% CI, -13% to 23%). The 30-day mortality was 21% (12/57) in the EVAR group compared with 25% (15/59) in the open repair group (ARR=4.4%; 95% CI, -11% to 20%). The 2 groups had similar median hospital stay and likelihood of intensive care unit (ICU) admission. The authors noted that patients in the open repair group had a much lower 30-day mortality rate than was anticipated in the trial's design (25% compared with results from a prior meta-analysis demonstrating a mortality rate of

48.5% in subjects undergoing open repair of ruptured AAA). As such, the trial may have been underpowered to detect a difference between the groups. In addition, the trial had a high rate of exclusion of patients with ruptured aortic aneurysm, most commonly because of unfavorable infrarenal aortic neck anatomy with absent or very short necks and very wide necks.

Nonrandomized, comparative studies using methods to reduce selection bias
In 2014, Edwards et al published an evaluation of outcomes after EVAR or open repair for ruptured AAAs among traditional Medicare beneficiaries discharged from a U.S. hospital from 2001 to 2008. Overall, 10,998 patients underwent ruptured AAA repair, 1126 by EVAR and 9872 by open repair. The population analyzed in this study included 1099 patient pairs who were propensity-score matched based for baseline demographics, comorbid conditions, admission source, and hospital volume of ruptured AAA repair. Short-term mortality was significantly better in the EVAR group (33.8% vs 47.7%, $p<0.001$). The survival benefit persisted until 4 years before surgery. However, at 36 months before surgery, EVAR patients were more likely to have had AAA-related reinterventions than open repair patients (10.9% vs 1.5%, $p<0.001$). Strengths of this study include a large sample size, the availability of longer-term follow up data, and the use of propensity-score matching to reduce biased based on observed variables. However, the study is subject to bias if unobserved variables are associated with the decision to perform open repair. In particular, patients with hemodynamic instability may be more likely to undergo open repair, which would bias results in favor of EVAR.

In 2012, Saqib et al. published a retrospective comparison of EVAR versus open surgery from a single institution using propensity score matching. Out of a sample of 312 patients undergoing repair for a ruptured aneurysm, 37 cases of EVAR were matched with 111 cases of open surgery. Operative mortality rates were numerically lower in the EVAR group, but did not reach statistical significance (22% vs. 32%, $p=0.40$). Similarly, complications were somewhat lower in the EVAR group, but the difference was not statistically significant (54% vs. 66%, $p=0.23$). Overall survival at 1 year (50% vs. 54%), 2 years (50% vs. 52%), and 3 years (42% vs. 47%) was similar between the EVAR and open surgery groups ($p=0.66$ for overall trend).

A different approach to the problem of selection bias was taken by an industry-sponsored study that enrolled 100 consecutive patients across 10 institutions to determine the percentage of patients for whom eEVAR was applicable and to compare mortality and morbidity between the 2 groups. Open surgical repair was performed in 51 patients; in 80% of cases, this was due to a configuration of the neck that was unfavorable for endovascular repair. Patients with severe hemodynamic instability also received open surgical repair. This study found no difference between the 2 groups in either in-hospital (35% to 39%, respectively) or 3-month mortality (40% in the eEVAR group and 42% in the open repair group). Blood loss, time in intensive care, and the duration of mechanical ventilation were lower in patients treated by eEVAR than in those treated by open surgery. Identical mortality rates (53%) were also found in a pilot study with 32 patients randomized to eEVAR or open surgical repair by intention-to-treat analysis. In addition, endovascular repair requires long-term monitoring and possible re-intervention due to endoleaks, graft migration, and aneurysm enlargement. Paraplegia resulting from spinal cord ischemia during eEVAR has also been reported.

One study attempted to address the issue of selection bias by assessing the overall mortality rate in a unit where eEVAR has become the treatment of choice and comparing it with the overall mortality rate of historical controls treated with open surgical repair. For a 2-year period between 2002 and 2004, patients received eEVAR unless they presented with shock or cardiac arrest during transportation to the hospital or if the CT scan indicated an unfavorable anatomic configuration of the aortic neck (short, conical, or wide). Fifty-one patients (17 eEVAR and 34 open repair) were treated during the study period; they were compared with a group of 41 patients treated in the previous 2-year period in the same unit and by the same vascular surgeons. The study found a decrease in length of stay in intensive care (5.5 vs. 0 days, respectively) and a trend toward a decrease in mortality (59% vs. 39%, respectively; p=0.065) with eEVAR. However, the study also found that patients who were considered too unstable for eEVAR had a 77% mortality rate, while those who were considered unsuitable for eEVAR due to unsuitable aortic neck anatomy had a 19% mortality rate. These results suggest that the favorable mortality rates found in uncontrolled eEVAR studies are due to selection bias.

Non-randomized, comparative studies with unmatched samples
Using a Nationwide Inpatient Sample, McPhee and colleagues found that rates of endovascular treatment of ruptured AAAs increased from 6% in 2001 to 19% in 2006. They found that EVAR had a lower overall in-hospital mortality rate than open repair (32% vs. 41%, respectively) and that the effect was amplified when stratified by institutional volume. Based on analysis of data from Medicare beneficiaries, Egorova and colleagues found that EVAR repair of ruptured AAAs had a protective effect (HR: 0.86, p=0.0061) on long-term survival controlling for comorbidities, demographics, and volume. Another similar study was an analysis of hospital discharge databases for California, Florida, New Jersey, and New York. Perioperative mortality rates were lower for patients treated with eEVAR compared to open surgical repair.

Two nonrandomized, comparative studies using prospectively collected data were reported in 2012. Mehta et al. compared 120 patients who underwent EVAR with 163 patients who underwent open surgery. Thirty-day mortality was lower in the EVAR group (24.2% vs. 44.2%, p<.005). The survival advantage for EVAR was maintained up to 5 years post-treatment. Approximately one-fourth of EVAR patients required secondary interventions over this time period. In a smaller study, Noorani et al. compared 52 patients receiving EVAR with 50 patients undergoing open repair from one institution. In-hospital mortality was 12% (6/52) for EVAR and 32% (16/50) for open surgery. Over a two-year period of follow-up, the risk of mortality for the open surgery group was approximately twice that of the EVAR group (HR: 2.2, 95% CI: 1.1-4.6, p=0.01).

A number of publications report on retrospective comparisons of unmatched patients. For example, Ten Bosch et al. performed a retrospective comparison from 1 institution of 25 patients who underwent EVAR with 79 patients who underwent open repair. EVAR was performed if the EVAR-trained vascular surgeon was on call and the patient was suitable for EVAR; otherwise open repair was performed. Perioperative mortality was 4.0% in the EVAR group compared to 6.1% in the open repair group (p>0.99). At 30 days, mortality was lower for the EVAR group (20.0% vs. 45.5%, respectively; p=0.04), and this survival advantage was maintained at 6 months (28% vs. 54.5%, respectively; p=0.04). Median length of stay was also lower with EVAR (9.5 days vs. 17.0 days, respectively, p=0.03). Another study that retrospectively compared early postoperative outcomes in patients with ruptured AAAs who underwent EVAR or open

repair was performed in one hospital in the Netherlands. There were a total of 56 patients treated over a 2-year period, 15 by EVAR and 41 by open surgery. Thirty-day mortality was 26% in the EVAR group compared to 46% in the open surgery group. The overall complication rate was not different between groups.

Systematic reviews of EVAR compared with open repair for ruptured AAA
Qin et al reported results of a systematic review and meta-analysis of emergent EVAR compared with open repair for ruptured AAAs that included 2 RCTs, 5 prospective comparative studies, and 11 retrospective comparative studies. The authors included English-language studies that evaluated outcomes between emergent open and endovascular ruptured AAA repair, with the intervention at the time of the emergency. In a pooled analysis, for the primary outcome of perioperative mortality, the patients who underwent EVAR had significantly lower mortality rates than those who underwent open repair (pooled OR=0.62; 95% CI, 0.58 to 0.67; p<0.001). There was significant heterogeneity in the studies.

In another systematic review and meta-analysis of emergent EVAR compared with open repair for ruptured AAAs that had less stringent inclusion criteria, Antoniou et al evaluated 41 studies, including all types of comparative studies (prospective or retrospective observational studies or RCTs). Two RCTs were included. The meta-analysis included a total of 59,941 patients, 8201 who underwent EVAR and 51,740 who underwent open repair. In a pooled analysis, patients who underwent EVAR had significantly lower in-hospital mortality than those who underwent open repair (pooled OR=0.56; 95% CI, 0.50 to 0.64; p<0.01). There was a trend toward shorter length of stay in the EVAR group, but the difference was not significant.

In a Cochrane Review published before the results of RCTs were available, Dillon et al concluded that data suggest that endovascular repair is feasible in selected patients with outcomes comparable with best conventional open surgical repair for ruptured AAAs.

Section Summary
For patients with ruptured AAAs to be candidates for endovascular repair, the lesions need to be suitable for the endovascular devices and patients need to be sufficiently stable to undergo CT evaluation.

Two RCTs have published short-term outcomes comparing EVAR with open surgery for patients with ruptured AAA and report that the short-term mortality of EVAR is not significantly different than open surgery. Longer term outcomes of EVAR compared with open surgery for ruptured aneurysms have not been reported.

Numerous nonrandomized studies and systematic reviews have presented comparative data on EVAR versus open surgery for the treatment of ruptured AAAs. Most of these publications report that early mortality is substantially reduced with EVAR compared with open surgery. While some studies use techniques to reduce the possibility of selection bias, the potential for bias in selecting patients for EVAR remains.

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EVAR compared to non-surgical treatment for smaller aneurysms that do not meet current size criteria for surgery or for patients who are ineligible for open surgery

There are a limited number of randomized trials that address patients with aneurysms that cannot be treated by open surgery. This includes patients who have smaller aneurysms that do not meet the size threshold for open surgery, and also patients who cannot undergo open surgery due to prohibitive operative risk.

Caesar Trial

This trial compared the use of EVAR for small AAAs, which did not meet the current thresholds recommended for intervention, with active surveillance. The study enrolled 360 patients, 50-79-years-old, with aneurysms of 4.1-5.4 cm. Patients was randomized to early EVAR treatment or surveillance by ultrasound and/or CT. In the surveillance group, surgery was performed only after the AAA met current recommendations for intervention (≥5.5 cm, growth 1 cm/year, or symptomatic). If repair was indicated, EVAR was performed unless the anatomy of the AAA was unsuitable for EVAR, in which case open repair was performed. Patients were followed for a median of 32.4 months for the primary outcome of all-cause mortality.

The primary outcome occurred at a lower rate than anticipated, thus limiting the power to detect a difference. At final follow-up, there was no significant difference in the main endpoint. Kaplan-Meier estimates of all-cause mortality were 10.1% for the surveillance group compared with 14.5% for the EVAR group (HR: 0.76; 95% CI: 0.30-1.93). Aneurysm-related mortality, aneurysm rupture, and major morbidity rates were also similar between groups. For patients in the surveillance group, the Kaplan-Meier estimate of undergoing aneurysm repair was 59.7% at 36 months and 84.5% at 54 months.

A follow-up publication from the Caesar trial reported on quality-of-life (QOL) outcomes. Patients were assessed with the SF-36 short-form at baseline, 6 months, 12 months, and yearly after that with a mean follow-up of 31.8 months. Following EVAR, QOL scores in the EVAR arm rose while those in the observation arm declined. At 6 months' follow-up, QOL scores in the EVAR group were significantly higher than in the observation group, with significant differences found for overall score (mean difference 5.4, p=0.002), physical domain score (mean difference 3.8, p=0.02), and mental domain score (mean difference 6.0, p=0.001). Over longer periods of time, scores in both the EVAR and observation group declined, and the differences were not significantly different at time periods of one year or longer.

PIVOTAL Trial

The PIVOTAL (Positive Impact of Endovascular Options for Treating Aneurysms Early) trial randomly assigned 728 patients with AAAs of 4-5 cm to early EVAR or ultrasound surveillance. Patients were followed for a mean 20 +/- 12 months for the primary outcomes of aneurysm rupture, aneurysm-related death, and overall mortality. At the final follow-up, overall mortality was the same in both groups at a rate of 4.1%. Aneurysm rupture or aneurysm-related death occurred at a low rate and was also the same between groups at a rate of 0.6%. The HR for the primary outcome measures was 0.99 (95% CI: 0.14-7.06).

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EVAR 2 Trial
The U.K. EVAR Investigators published an RCT of EVAR versus no treatment of AAAs 5.5 cm or larger, but in whom surgery was not an option due to prohibitive surgical risk or patient preference. This trial was the only trial that evaluated patients who were unsuitable for open surgery and compared endovascular repair to no surgical intervention. EVAR 2 randomized 338 patients to either endovascular repair or medical management. Endovascular repair had a considerable 30-day operative mortality and did not improve survival over no intervention. However, the results of this trial are limited, since 20% of patients assigned to medical management underwent elective aneurysm repair in violation of the protocol. In addition, endovascular repair was not performed until a median of 57 days after randomization; during this period, 9 aneurysms ruptured, contributing to the endovascular mortality calculation, biasing results against endovascular repair.

A follow-up publication for this trial reported on longer-term follow-up of 404 patients randomized to EVAR or no treatment. Perioperative mortality in the EVAR group was 7.3%. At the 8-year follow-up point, aneurysm-related mortality was lower in the EVAR group, but overall mortality did not differ (HR: 0.99; 95% CI: 0.78-1.27). There was a high rate of long-term complications in the EVAR group, with 48% of patients having a graft-related complication, and 27% of patients requiring reintervention for complications.

Accompanying editorials provided the following comments.

- While there has been no difference in overall survival in the EVAR 1 trial, only 24% of patients have reached 4-year follow-up, and further study is required. With an enrolment of 1,082 patients, EVAR 1 is powered to show a difference in overall mortality, while the smaller DREAM trial is not.
- Suitability for endovascular repair depends on anatomic factors. In EVAR 1 only 54% of patients were considered suitable candidates, but this ranged from 6% to 100% across the participating institutions, indicating marked variability in the assessment of anatomic suitability.
- Given that the rate of interventions for endovascular repair increases over time, open repair may be recommended for those with longer life expectancies.
- The numbers of elective aneurysm repairs may grow, considering the recent recommendation of the United States Preventive Services Task Force (USPSTF) for screening for AAAs in men who have ever smoked.
- It is estimated that approximately 300,000 aneurysms will be identified in this targeted screening population. Many of these aneurysms will measure less than 5.5 cm in diameter and thus will be managed with periodic imaging surveillance, but patients with larger aneurysms will be faced with choosing between open and endovascular repair. The U.S. AHRQ has commissioned a technology assessment to compare endovascular and open repair in terms of effectiveness, cost, and quality of life.

Systematic Reviews
Based solely on the EVAR 2 trial, the AHRQ report concluded that endovascular repair does not improve survival in patients who are medically unfit for open surgery. As previously discussed, the EVAR 2 trial, and thus the AHRQ assessment, is compromised by the high proportion of patients who crossed over from non-operative to endovascular repair, and by the number of patients who died in the interval between randomization and treatment with EVAR. Professional guidelines based on both randomized and

nonrandomized trials suggest that endovascular repair of infrarenal aortic and/or common iliac aneurysms is reasonable in patients at high risk of complication from open operations.

A Cochrane Review summarized the evidence on interventions for small aneurysms, 4.0-5.5cm in size, either by open surgery or EVAR. There were a total of 4 RCTs identified, including the 2 RCTs on EVAR included in this policy review and an additional 2 RCTs on open surgical repair. Combined analysis of the 2 EVAR trials revealed no difference in mortality at one year (OR: 1.15, 95% CI: 0.59-2.25). There was also no survival benefit for the trials of open surgery, nor was there any benefit apparent when all 4 trials were combined.

A subsequent Cochrane Review (previously outlined) compared EVAR with best medical care for patients with AAA who were considered unfit for open repair. Only the EVAR 2 trial met the authors' inclusion criteria; the authors concluded that "the results of a single trial found no overall short- or long-term benefits of EVAR over no intervention with regard to all-cause mortality."

Section Summary
The evidence does not indicate that EVAR improves outcomes for patients who are not suitable for open surgery, as judged by aneurysm size and or clinical factors that indicate prohibitive risk for open surgery. For small aneurysms, RCT evidence reports that morbidity and mortality outcomes from surveillance are as good as those from early intervention with EVAR. For patients who are at prohibitive operative risk, 1 RCT reports that EVAR is associated with lower aneurysm mortality but no difference in overall mortality, and that there is a high rate of long-term complications and reinterventions with EVAR. This RCT evidence is limited by a high rate of crossovers, primarily from open surgery to EVAR, which may limit the ability to detect a difference between the 2 treatments.

Ongoing Clinical Trials
A search of the ClinicalTrials.gov website on February 24, 2014, using the keywords "abdominal aortic aneurysm" and "endovascular" identified 30 studies, all of which were nonrandomized studies or completed randomized trials. One larger nonrandomized study addressing the efficacy of EVAR in patients with high surgical risk was identified:

- Endovascular Exclusion of Abdominal Aortic Aneurysms in High Risk Patients (NCT00583414). This study will assess the efficacy of endovascular stent-graft implantation in subjects with abdominal aortic or iliac aneurysm with high surgical risk (anticipated mortality >10% with conventional surgery). Enrollment is planned for 400 subjects; the planned study completion date is December 2020.

Summary
Evidence from RCTs comparing EVAR to open repair for elective treatment of aneurysms indicates that neither approach is clearly superior to the other. While EVAR is associated with an early reduction in morbidity and mortality, trials that report outcomes at 5 years or longer show comparable survival for EVAR compared to open repair at these longer time points. Thus, the early advantage of EVAR is balanced out by a higher rate of late complications, leading to comparable long-term outcomes between the two procedures. One trial of patients who were of low-to-moderate surgical risk reported that the early benefit of EVAR was

not evident in this population, raising the question of whether the early benefits of EVAR extend to patients at lower risk for open surgery. Based on these data, EVAR may be considered medically necessary as an alternative to open surgery in patients who are candidates for both procedures.

For patients with ruptured AAAs, evidence from non-randomized, matched comparisons report that EVAR is associated with lower short-term morbidity and mortality. While these studies are prone to selection bias, since the highest risk aneurysms tend to be less suitable for EVAR due to anatomic considerations, RCTs are difficult in this area due to the emergent nature of the condition and logistical considerations. For these reasons, EVAR may be considered medically necessary for ruptured aneurysms.

At least 2 RCTs have evaluated EVAR versus no surgical intervention in patients who were not eligible for open repair, either because of aneurysm size or prohibitive surgical risk. These trials do not report superior outcomes with EVAR and thus do not support use of EVAR in these patients. As a result, EVAR is considered investigational for patients who are not candidates for open surgery due to aneurysm size or prohibitive surgical risk.

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Coding

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Code Type	Code
CPT	34800, 34802, 34803, 34804, 34805, 34806, 34808, 34812, 34813, 34820, 34825, 34826, 34833, 34834, 34841, 34842, 34843, 34844, 34845, 34846, 34847, 34848, 75952, 75953 (codes 0078T, 0079T, 0080T, and 0081T were deleted as of 1/1/2014)
HCPCS	No codes
ICD-9 Diagnosis	441.02, 441.3, 441.4
ICD-9 Procedure	38.44, 39.71

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11/21/2002	Medical Policy Committee review
01/27/2003	Managed Care Advisory Council approval
01/20/2004	Medical Policy Committee review. Format revision. Coverage eligibility unchanged.
01/26/2004	Managed Care Advisory Council approval
01/04/2005	Medical Director review
01/18/2005	Medical Policy Committee review. Format revision. Coverage eligibility unchanged
01/31/2005	Managed Care Advisory Council approval
05/17/2005	Medical Policy Committee review. Format revision. Policy statement changed from endoprostheses (i.e., endovascular grafts) as a treatment of abdominal aortic aneurysms (infrarenal abdominal or aortoiliac aneurysms) to: the use of FDA-approved endoprostheses as a treatment of abdominal aortic aneurysms. Patient selection criteria expanded to include; "The use of FDA-approved endoprostheses as a treatment of abdominal aortic aneurysms may be considered medically necessary as a treatment of abdominal aortic aneurysms in any of the following clinical situations, consistent with the FDA-labeled indications for the AneurRx device." Investigational statement added to address non FDA-Approved devices and situations when patient selection criteria are not met.
05/23/2005	Managed Care Advisory Council approval
07/07/2006	Format revision; including, addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
08/02/2006	Medical Director Review
08/09/2006	Medical Policy Committee approval. Rationale /Source and rationale updated.
06/13/2007	Medical Director review
06/20/2007	Medical Policy Committee approval. Coverage eligibility unchanged. Policy statement added for treatment of ruptured abdominal aortic aneurysm as investigational.
08/06/2009	Medical Policy Committee approval
08/26/2009	Medical Policy Implementation Committee approval. No change to coverage eligibility.
07/01/2010	Medical Policy Committee approval
07/21/2010	Medical Policy Implementation Committee approval. Changed coverage statement from investigational to eligible for coverage with criteria for ruptured abdominal aortic aneurysms.
07/07/2011	Medical Policy Committee review

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07/20/2011	Medical Policy Implementation Committee approval. For clarification, added that the use of endoprostheses approved by the U.S. FDA as a treatment of abdominal aortic aneurysms is considered investigational for certain clinical situations.
06/28/2012	Medical Policy Committee review
07/27/2012	Medical Policy Implementation Committee approval. No change to coverage.
03/04/2013	Coding revised
06/27/2013	Medical Policy Committee review
07/17/2013	Medical Policy Implementation Committee approval. No change to coverage.
07/10/2014	Medical Policy Committee review
07/16/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 07/2015

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

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

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

A. in accordance with nationally accepted standards of medical practice;
B. clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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

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