Name of Policy:  
Periureteral Bulking Agents as a Treatment of Vesicoureteral Reflux  

Policy #: 454       Latest Review Date: January 2014  
Category: Surgery       Policy Grade: A  

Background/Definitions:  
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. 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.
**Description of Procedure or Service:**

Vesicoureteral reflux is the retrograde flow of urine from the bladder upward toward the kidney, and is most commonly seen in children. The primary management strategies have been use of prophylactic antibiotics to reduce urinary tract infections and, for higher grade disease, surgical correction of the underlying reflux. Injection of periureteral bulking agents is proposed as an alternative to surgical intervention.

Treatment of vesicoureteral reflux (VUR) is based on the assumption that VUR predisposes patients to urinary tract infections (UTIs) and renal infection (pyelonephritis) by facilitating the transport of bacteria from the bladder to the upper urinary tract. Pyelonephritis causes renal scarring in as many as 40% of children, and extensive scarring may lead to renal insufficiency and hypertension. The period between first renal scarring from pyelonephritis and the development of hypertension or end-stage renal disease can be 30 to 40 years.

In most cases, VUR is diagnosed during evaluation of UTIs. About one-third of children with UTIs are found to have VUR. The average age for the onset of UTI is two to three years, corresponding to the age when toilet training occurs. There also appears to be a genetic predisposition to VUR, and siblings may also be examined. The gold standard for diagnosis is voiding cystoureography, a procedure that involves catheterization of the bladder. The severity of reflux is described by a grade, typically with the International Reflux Study Group grading system, which grades severity from I (reflux partway up the ureter) to V (massive reflux of urine up the ureter with marked tortuosity and dilation of the ureter and calyces). Determination of VUR grade is not exact, however, due to factors such as bladder pressure, which may vary at the time of measurement. In general, more severe reflux is associated with higher rates of renal injury, and less severe reflux (i.e., Grade I and II) is associated with higher rates of spontaneous resolution and treatment success. Other factors that have been found to be associated with the likelihood of spontaneous resolution of VUR and/or renal injury include age, sex, laterality, presence of renal scars, presence of voiding dysfunction, and history of urinary tract infection.

Treatment strategies for VUR include bladder training, antibiotic prophylaxis, and surgical modification of the ureter to correct the underlying reflux. VUR is likely to resolve spontaneously over a period of 1 to 5 years; lower grades of reflux (i.e., Grades I and II) are associated with a higher probability of spontaneous resolution. The decision to administer prophylactic antibiotic treatment includes the consideration of potential adverse effects of long-term antibiotic treatment, which can include allergic reactions and development of treatment-resistant bacteria resulting in breakthrough UTIs.

Open surgical treatment is typically reserved for patients with high-grade reflux (Grades III and IV) or as salvage therapy for those who are noncompliant with antibiotic therapy or have breakthrough UTIs while receiving prophylactic therapy. Surgical management involves lengthening the intramural ureter by modification of the ureterovesical attachment with reimplantation of the ureter. Success rates for open surgery are reported to be above 95% and nearly 100% for patients with lower grades of reflux. In recent years, there have been advances in surgical technique, including use of a lower abdominal transverse incision that leaves a smaller scar. Combined with a reduction in the use of ureteral stents and prolonged catheterization; the changes have led to shorter hospital stays and reduced surgery-related
morbidity. Moreover, surgeries can now be done on an outpatient basis. Surgery, however, still involves risks associated with anesthesia and potential complications such as ureteral obstruction, infection, and bleeding. Some centers have reported using laparoscopic antireflux surgery, but this is technically difficult and has not become widespread. Robotic-assisted laparoscopic methods are being developed to overcome some of the technical difficulties.

Treatment of VUR remains controversial. There is a lack of good evidence that VUR actually increases the risk of pyelonephritis and renal scarring, and the long period of time before renal scarring, hypertension, and end-stage renal disease makes these serious conditions difficult to study. Moreover, VUR has a relatively high rate of spontaneous resolution, more than 60% over five years, so many children may not benefit from treatment. An important challenge is to identify the subset of children most likely to benefit from VUR treatment. At present, in the absence of definitive answers on the utility of treating VUR or the best treatment option, antibiotic prophylaxis to prevent recurrent UTIs and surgery to treat the underlying reflux remain accepted management strategies.

The use of bulking agents in the treatment of VUR has been reported for over 20 years and has been suggested as an alternative to either antibiotic or surgical therapy. Bulking agents can be injected into tissue around the ureteral orifices to minimize reflux. The STING procedure (sub-ureteral trans-urethral injection) involves the endoscopic injection of a bulking agent into the submucosal bladder wall just below the ureteral opening. In the more recently used modified STING procedure, the needle is placed in the ureteral tunnel and the bulking agent is injected into the submucosal intraureteral space. When successfully injected the compound tracks along the length of the detrusor tunnel and establishes a coapted ureteral tunnel. This endoscopic procedure can be performed in an outpatient setting.

A variety of bulking agents have been tested for biocompatibility and absence of migration. Some of the compounds used in clinical studies are collagen (Contigen, Zyderm, Zyplast), polytetrafluoroethylene paste (Teflon), polydimethylsiloxane (Macroplastique®), calcium hydroxyapatite (Coaptite®), and dextranomer/hyaluronic acid copolymer (Deflux® or Dx/HA).

**Policy:**

**Periureteral bulking agents meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage as a treatment of vesicoureteral reflux Grades II–IV when medical therapy has failed and surgical intervention is otherwise indicated.

The use of **bulking agents as a treatment of vesicoureteral reflux in other clinical situations does not meet** Blue Cross and Blue Shield medical criteria for coverage and is considered **investigational.**

The use of bulking agents is contraindicated in patients with non-functioning kidney(s), hutch diverticuli, duplicated ureter, active voiding dysfunction, and ongoing urinary tract infection.
Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the members' contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

**Key Points:**

Treatment of vesicoureteral reflux (VUR) with periurethral bulking agents is proposed as:

- An alternative to other types of surgery for patients with high-grade VUR (predominantly grades III and IV) who have failed or are noncompliant with prophylactic antibiotics; and
- An alternative to prophylactic antibiotics for patients with lower-grade or high-grade VUR.

Appropriate outcomes for the comparison of bulking agents and other types of surgery are resolution of reflux and reduction in the rate of urinary tract infections (UTIs) and pyelonephritis. Since prophylactic antibiotic use does not treat the underlying reflux, reduction in the rate of UTIs and pyelonephritis are reasonable outcomes for studies comparing antibiotics and bulking agents. Differences in morbidity are also important outcomes for both proposed uses.

An initial literature search was performed in 2005. The policy was updated regularly with a literature review using MEDLINE; most recently, the literature was searched from August 2012 through August 2013. Following is a summary of key literature to date on use of periureteral bulking agents to treat VUR.

**Efficacy of Bulking Agents for VUR**

**Systematic reviews:**

The Cochrane Library conducted a review of randomized controlled trials (RCTs) on treatments for VUR. The Cochrane review addressed a variety of interventions including long-term antibiotic prophylaxis, open surgery, and use of bulking agents and had limited ability to evaluate the efficacy of bulking agents because it combined studies on open surgery and bulking agents in the analysis. The review, however, is useful for examining the assumption that VUR increases the risk of complications. The Cochrane review, last updated in 2011, included 20 trials with a total of 2,324 children. No statistically significant differences were found in the overall risk of UTI or renal parenchymal injury between groups treated with surgery or bulking agents plus antibiotics versus antibiotic prophylaxis alone at any time point between 1 and 24 months. For example, a pooled analysis of data from 5 trials that evaluated repeat positive urine culture by one to two years found a nonsignificant risk ratio (RR) of 0.89 (95% confidence interval [CI]: 0.55-1.44). In addition, a pooled analysis of four trials that evaluated the outcome of new renal parenchymal defects at four to five years after treatment calculated a pooled RR of 1.09 (95% CI: 0.79-1.49). One statistically significant finding was a reduction in febrile UTI by five years with surgery or bulking agent treatment compared to antibiotics alone; in a pooled analysis of two studies (449 children), RR: 0.43; 95% CI: 0.27-
These findings challenge the assumptions underlying the treatment of VUR, since one would expect a reduction in UTI if the hypothesis is correct that VUR is a modifiable risk factor for UTI and renal parenchymal damage.

A systematic review published in 2010 identified randomized trials and observational studies evaluating dextranomer/hyaluronic acid (Dx/HA) treatment for pediatric VUR. A total of 47 studies, mainly retrospective case series, met eligibility criteria. A key inclusion was that studies report the postoperative success rate after a single injection of Dx/HA. Success was defined as resolution of VUR and could also include downgrading to grade 1 VUR. Of 7,303 ureters injected with Dx/HA, 5,633 (77%) were considered treatment successes. There were higher rates of success in children with lower-grade reflux compared to those with high-grade reflux. For example, the 164 children whose preoperative VUR was grade 1 had an 89% success rate compared to a 59% success rate among the 1,109 children with initial grade IV VUR.

**Randomized controlled trials:**

**RCTs comparing periureteral bulking agents to other types of surgery:**

The first RCT comparing periureteral bulking agents to ureteral reimplantation (UR) was published in 2013. Garcia-Aparicio and colleagues in Spain randomized 41 children older than one year of age with VUR grades I-IV to receive endoscopic treatment with Dx/HA (n=22) or UR (n=19). Indications for surgery included recurrent UTIs, persistent VUR after two years of antibiotic prophylaxis, impairment of renal function or another type of impairment due to VUR. A total of 35 refluxing ureters were treated with bulking agents, and 32 refluxing ureters were treated with UR. One year after treatment, 32 of 35 ureters (91.4%) in the Dx/HA group and 32 of 32 ureters (100%) in the surgical reimplantation group were cured; the difference between groups was not statistically significant, \( p=0.23 \). Findings were similar at final follow-up. At five years, 30 of 35 ureters (85.7%) in the Dx/HA group and 100% in the UR group were free of VUR; \( p=0.48 \). One patient in the Dx/HA group and two patients in the UR group experienced complications associated with the treatment. Two patients in the Dx/HA group and none in the UR group experienced fevers posttreatment. Rates of complications and adverse events did not differ significantly between groups. The results of this trial support that there are no large differences between the two treatments, but the study was not powered to detect smaller differences in outcomes and was also likely too small to detect differences in complications and adverse events.

**RCTs comparing periureteral bulking agents to antibiotic prophylaxis:**

Capozza and Caione reported on the results of a study of 61 children with VUR (grades II to IV) who were randomly assigned to receive an endoscopic subureteral implantation (n=40) of Deflux or 12 months of antibiotic prophylaxis (n=21). Entry criteria included grades II to IV reflux present for at least six months. The antibiotic therapy was not specified and presumably was variable. It was not reported whether patients had been receiving antibiotic therapy during the preceding 6 months and experienced breakthrough UTIs, were noncompliant, or showed no evidence of spontaneous resolution of VUR. Therefore it is unknown whether the Deflux treatment was primarily considered an alternative to medical therapy or to surgical therapy. In part, due to the small numbers in the antibiotic control group, the distribution of the different grades of VUR was different in the two groups. Outcomes included improvement in reflux.
grade and measures of renal function; incidence of UTIs was not reported. The only statistically significant outcome reported was the improvement in reflux grade at month 12, with 69% of those in the Deflux group reporting a reflux grade of I or less, compared to only 38% in the antibiotic group. However, these results are not surprising, since antibiotic therapy itself is not intended to improve reflux grade but simply to sterilize the urine while awaiting the spontaneous resolution of VUR. Therefore, the only conclusion is that Deflux results in a higher incidence of VUR resolution compared to spontaneous resolution.

Findings from the Swedish Reflux trial in children were published in 2010. This nonblinded multicenter study included 203 children (128 girls and 75 boys) between the ages of one and two years with grade III to IV reflux. Participants were not required to have failed antibiotic prophylaxis; thus the trial evaluated injection of a bulking agent as an alternative to antibiotic therapy. Most of the participants (194, 96%) were identified after a symptomatic UTI. Recruitment was more difficult than expected, and enrollment was stopped after six years. Participants were randomly assigned to one of three groups: antibiotic prophylaxis (n=69), endoscopic treatment with Deflux (n=66), or surveillance only (n=68).

The study aimed to simulate clinical practice, i.e., prophylactic antibiotics were prescribed without monitoring compliance, rather than ensuring that study participants took a known dose of antibiotics. Primary study outcomes included VUR status, and rates of febrile UTI and kidney damage after two years. Sixty-four of 66 patients randomly assigned to endoscopy received treatment. Fourteen of 19 patients with still dilating VUR after one injection received a second injection; two patients received a third injection. The investigators reported that complications occurred in six of the 64 (9%) individuals who received endoscopic treatment. Overall, 187 participants (92%) completed at least six of the eight follow-up visits; analysis was intention to treat. Two-year cystourethrography was done in 185 of the 203 (91%) patients. Findings from voiding cystourethrography were that VUR had resolved in 9 of 68 (13%) patients in the prophylaxis group, 20 of 52 (38%) in the endoscopy group, and 10 of 65 (15%) in the surveillance group. The proportion of patients in the three groups whose VUR was downgraded to grade I or II was 18 of 68 (26%), 17 of 52 (33%) and 21 of 65 (32%), respectively. There was a significantly greater proportion of patients whose VUR had resolved or had been downgraded in the endoscopy group compared to the prophylaxis (p=0.0002) and surveillance groups (p=0.003), but no statistically significant differences were found between the prophylaxis and surveillance groups. Thirteen patients (20% of the 66 patients randomly assigned to endoscopy) whose VUR had initially resolved or been downgraded experienced recurrences and had stage III or IV VUR at two years.

Febrile UTI rates by treatment group in girls were 8 of 43 (19%), 10 of 43 (23%), and 24 of 42 (57%), respectively, in the prophylaxis, endoscopic, and surveillance groups. Rates were significantly higher in the surveillance group than either the prophylaxis group (p=0.002) or the endoscopic group (p=0.14); rates did not differ significantly in the prophylaxis versus the endoscopic groups. Rates of febrile UTI recurrence during follow-up were dramatically higher in girls (42 of 128, 33%) than boys (7 of 75, 9%). Rates of febrile UTIs in boys were 2 of 26 (8%) in the prophylaxis group, 4 of 23 (17%) in the endoscopic group, and 1 of 26 (4%) in the surveillance group; there were no statistically significant differences between groups. The rate of new renal damage did not differ significantly among groups.
After stratifying findings by gender, the sample sizes in reported analyses were relatively small. There may have been insufficient power to evaluate some of the outcomes of interest, e.g., kidney damage and febrile UTIs. Moreover, findings might not be applicable to children outside of the restricted age range included in the study and to those with lower-grade VUR. Larger studies with a more representative sample of children with VUR are needed to further evaluate the effectiveness of this treatment.

**RCTs comparing different bulking agents:**

Oswald and colleagues randomly assigned 72 children with VUR to receive either Deflux or Macroplastique in addition to antibiotic prophylaxis. Entry criteria included grades II to IV reflux (International Reflux Study Group grading system). Since all patients continued to receive antibiotic therapy, presumably, the bulking procedure was primarily considered an alternative to surgical reimplantation of the ureter. However, the patient selection criteria do not indicate whether patients had failed prior antibiotic therapy or had unresolved VUR. Correction of underlying VUR was similar in the two groups.

Kim and colleagues randomized 85 children aged 2-15 years with VUR (grades II-V) to receive subureteral injections of Macroplastique (n=42) or Deflux (n=43). Eligibility included breakthrough UTI in addition to persistent VUR; most patients had started immediately on antibiotic prophylaxis after diagnosis (exact number not reported). Seventy-three of 85 children (86%) were available for the 3-month follow-up. The cure rate, defined as no evidence of reflux, was 69% in the Macroplastique group and 55% in the Deflux group; the difference between groups was statistically significant, p<0.05. This study did not include a group of patients who received a treatment other than periureteral injection of bulking agents.

**Children With Duplicated Ureters**

No controlled studies have been published that compare bulking agents to other treatments in children with duplicated ureters. However, several case series are available, and these uncontrolled studies suggest reasonable response rates and do not report high complication rates in this population of patients. The largest series to date was published in 2013 by Hunziker and colleagues in Ireland. The study included 123 children with complete duplex systems who were treated with Dx/HA for grade II-V VUR. The mean age of participants was three years (range: 1 month to 12 years). Complete duplicated ureters were unilateral in 100 patients (81%) and bilateral in the remaining 13. A total of 136 refluxing units were treated with endoscopic injections of Dx/HA. Three months after treatment, children were evaluated with voiding cystourethrography and bladder ultrasound. The rate of VUR resolution after one injection was 68.4% (93 of 136 ureters). VUR resolved in an additional 35 ureters (25.7%) after a second injection and in the remaining eight ureters (5.9%) after a third injection. There was only one complication associated with the endoscopic injections, which was a case of frank hematuria. No patients needed ureteral reimplantation, and there was no evidence on ultrasound of delayed vesicoureteral junction obstruction. Five patients (4%) developed febrile UTIs during follow-up.

Other smaller case series have also evaluated bulking agents as a treatment of VUR in patients with duplicated ureters. For example, Molitierno and colleagues included 52 children with
duplex ureters who had VUR grade II-V. (18) Overall, VUR was cured in 44 of 52 patients (85%) after one or two treatments with Dx/HA. Moreover, Lackgren and colleagues evaluated 68 children with duplex ureters and VUR. Forty-three children (63%) had a positive response to treatment, defined as having their reflux resolve to grade 0 or I. There were no complications associated with treatment. Seventeen (25%) children required open surgery.

Adverse Events
According to case series data, injection of periureteral bulking agents is associated with low morbidity rates. Temporary postoperative ureteral obstruction may occur in less than 0.7% of patients following injection of bulking agents; this can be treated with ureteral stenting until the problem resolves. In comparison, an average 2% (range, 0% to 9%) ureteral obstruction and reoperation rate has been reported following ureteral reimplantation. A large series published in 2012 by Puri and colleagues retrospectively reported on 1,551 children injected with Dx/HA for high-grade VUR. The only reported procedure-related complication was hematuria lasting up to 12 hours in three patients. There was no evidence of delayed vesicoureteral junction obstruction. Febrile urinary tract infections occurred in 69 (5%) of patients during follow-up; the median length of follow-up was 5.6 years. Dwyer and colleagues compared the rate of febrile UTIs in 2 cohorts of patients with VUR. (23) The incidence of febrile UTI did not differ significantly in patients who had ureter reimplantation (8%, 16 of 210 cases) and those who had endoscopic injections of Dx/HA (4%, 4 of 106 patients), p=0.24

Summary
Injection of periureteral bulking agents has been proposed as a treatment for vesicoureteral reflux (VUR). Findings of one small RCT published in 2013, as well as other nonrandomized studies, suggest similar rates of reflux resolution compared to ureteral reimplantation surgery. The body of evidence suggests that morbidity rates are similar or lower with bulking agents. Thus, the use of bulking agents to treat VUR as an alternative to other surgical methods is considered medically necessary.

There is insufficient evidence comparing periureteral bulking agents to antibiotic prophylaxis; the single published RCT included a selected population and had a relatively small sample size. Additional, larger studies are needed before conclusions can be drawn about the efficacy of periureteral bulking agents as first-line treatment for patients with VUR.

Technology Assessments, Guidelines and Position Statements
In 2012, The European Association of Urology (EAU) published a guideline on the diagnosis and treatment of VUR in children. The EAU recommends continuous antibiotic prophylaxis as initial treatment for children diagnosed with VUR in the first year of life and for children age one to five years who present with high-grade VUR. For children age one to five with lower grade VUR and no symptoms, surveillance without antibiotic prophylaxis is considered to be a reasonable option. The document states that surgical correction is a treatment option for patients with persistent symptoms and that endoscopic injection of bulking materials can have satisfactory results in children with lower grades of VUR.
In 2010, the American Urological Association (AUA) published an updated guideline on management of primary VUR in children. They recommend that patients older than one year who have a febrile breakthrough UTI while receiving continuous antibiotic prophylaxis be considered for either open surgery or endoscopic injection of bulking agents. Specific bulking agents mentioned were Deflux and Macroplastique. The guideline was based on a review of the evidence, but the authors acknowledged the lack of robust randomized controlled trials.

**Key Words:**
Deflux, Vesicoureteral Reflux, Bulking Agents, VUR

**Approved by Governing Bodies:**
In 2001, Deflux® received premarket application (PMA) approval from the U.S. Food and Drug Administration (FDA) for the “treatment of children with vesicoureteral reflux (VUR) grades II-IV.” Contraindications include patients with nonfunctioning kidney(s), active voiding dysfunction, and ongoing urinary tract infection. Duplicated ureters were initially considered a contraindication to Deflux treatment, but this was changed to a precaution in 2007.

Note: Polytetrafluoroethylene may migrate, causing serious adverse events; this agent is not FDA approved. Coaptite®, Macroplastique®, and Tegress® are categorized by the FDA as “Agent, Bulking, Injectable for Gastro-Urology Use.” Tegress was voluntarily withdrawn from the market by CR Bard as of January 31, 2007.

**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved. Will be reviewed for medical necessity.
Pre-certification requirements: Not applicable

**Current Coding:**

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<th>CPT Code</th>
<th>Description</th>
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<td>52327</td>
<td>Cystourethroscopy (including ureteral catheterization); with subureteric injection of implant material</td>
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<tr>
<th>HCPCS</th>
<th>Description</th>
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<td>L8603</td>
<td>Injectable bulking agent, collagen implant, urinary tract, 2.5 mL syringe, includes shipping and necessary supplies</td>
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L8604  Injectable bulking agent, dextranomer/hyaluronic acid copolymer implant, urinary tract, 1 mL, includes shipping and necessary supplies

L8606  Injectable bulking agents, synthetic implant, urinary tract 1-mL syringe, includes shipping and necessary supplies

References:


Policy History:
Medical Policy Group, October 2010
Medical Policy Administration Committee, November 2010 (2)
Available for comment November 4 through December 20, 2010
Medical Policy Group, September 2012 (2): Update to Key Points and References
Medical Policy Group, October 2013 (2): Removed ICD-9 Diagnosis codes; no change to policy statement.
Medical Policy Panel, October 2013
Medical policy Group, January 2014 (2) No change to policy statements. Literature review through August 2013. Key Points and References updated.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.