

## Corporate Medical Policy

### Beta-Hemolytic Streptococcus Testing AHS – G2159

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#### Description of Procedure or Service

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##### Policy Description

Streptococcus are Gram-positive, catalase-negative bacteria that are further divided into  $\alpha$ -hemolytic, such as *S. pneumoniae* and *S. mutans*;  $\beta$ -hemolytic, such as *S. pyogenes* (Group A), *S. agalactiae* (Group B), and *S. dysgalactiae subsp equisimilis* (Groups C and G); and  $\gamma$ -hemolytic, such as *Enterococcus faecalis* and *E. faecium* (Wessels, 2020a). Streptococcal infections can be manifested in a variety of pathologies, including cutaneous infections, pharyngitis, acute rheumatic fever, pneumonia, postpartum endometritis, and toxic shock syndrome to name a few. Streptococcal infections can be identified using bacterial cultures obtained from blood, saliva, pus, mucosal, and skin samples as well as rapid antigen diagnostic testing (RADT) and nucleic acid-based methodologies (Chow, 2020a; Wessels, 2020a, 2020b).

Note: For prenatal screening of Group B Streptococcus, please review policy Prenatal Screening AHS-G2035.

##### Related Policy

Prenatal Screening AHS – G2035

##### Scientific Background

Bacterial acute pharyngitis is most commonly caused by a Group A Streptococcus (*S. pyogenes* or GAS), accounting for 5-15% of all acute pharyngitis cases in adults. Group C or Group G Streptococcus (*S. dysgalactiae subsp equisimilis* or GCS/GGS) is believed to be a causative agent in 5-10% of the cases of pharyngitis; however, “pharyngitis cause group C or G Streptococcus is clinically indistinguishable from GAS pharyngitis” but is more common in young adults and college students (Chow, 2020a, 2020b). “Diagnosis of infection due to group C streptococci (GCS) and group G streptococci (GGS) depends on identification of the organism in a culture from a clinical specimen. In general, a positive culture from a normally sterile site, such as blood, synovial fluid, or cerebrospinal fluid (CSF), can be considered definitive evidence of infection in the setting of a compatible clinical syndrome. The interpretation of positive cultures for GCS or GGS from the pharynx or from cutaneous sites such as open ulcers or wounds is less straightforward since asymptomatic colonization of the upper airway and skin also occurs (Wessels, 2020a, 2020b).” GAS occurs most frequently in the very young and the elderly; although, GAS infections can occur in any age-group. The rates of severe GAS infections have been increasing in the United States as well as in other developed nations (Schwartz, Facklam, & Breiman, 1990).

The Centor criteria can be used to gauge the likelihood of pharyngitis due to a GAS infection. The four components of the Centor criteria are tonsillar exudates, tender anterior cervical lymphadenopathy, fever, and absence of cough with each criterion being worth one point. Patients who score less than three according to the Centor criteria are unlikely to have pharyngitis due to GAS and do not require strep testing or antibiotics; patients scoring  $\geq 3$  can be tested for GAS pharyngitis (Chow, 2020a, 2020b).

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GAS is associated with bacterial pharyngitis, scarlet fever, acute rheumatic fever, and post-streptococcal glomerulonephritis. Group A strep pharyngitis presents as a sudden-onset of sore throat with odynophagia and fever; it is commonly referred to as “strep throat”. In children, additional symptoms can include abdominal pain, nausea, and vomiting. Viral pharyngitis, which accounts for more than 80% of pharyngitis, typically presents with cough, rhinorrhea, hoarseness, oral ulcers, and conjunctivitis unlike GAS pharyngitis. Rare cases of mucopurulent rhinitis caused by GAS has been reported in children under the age of three (CDC, 2018b). Scarlet fever can accompany strep throat. Besides the typical erythematous rash that typically begins on the trunk before spreading outward, scarlet fever can also present as a flushed face, “and the area around the mouth may appear pale (i.e., circumoral pallor).” “Strawberry tongue” can occur due to “yellowish white coating with red papillae”(CDC, 2018d). Scarlet fever is more easily transmitted than asymptomatic carriers through saliva and nasal secretions. Acute Rheumatic Fever (ARF), besides the characteristic fever, can affect the cardiovascular system (carditis and valvulitis), the musculoskeletal system (arthritis), the integumentary system (subcutaneous nodules and erythema marginatum), and the central nervous system (chorea). “Inadequate or lack of antibiotic treatment of streptococcal pharyngitis increases the risk of someone developing acute rheumatic fever. In approximately one-third of patients, acute rheumatic fever follows subclinical streptococcal infections or infections for which medical attention was not sought (CDC, 2018a).” Post-streptococcal glomerulonephritis (PSGN) presents with edema, hypertension, proteinuria, macroscopic hematuria, lethargy, and, at times, anorexia. “Laboratory examination usually reveals mild normocytic normochromic anemia, slight hypoproteinemia, elevated blood urea nitrogen and creatinine, elevated erythrocyte sedimentation rate, and low total hemolytic complement and C3 complement.” Urine output is usually decreased, and urine examination “often reveals protein (usually <3 grams per day) and hemoglobin with red blood cell casts (CDC, 2018c).”

The virulence factors of GAS include M proteins, a group of more than 80 known proteins that protect the bacteria against phagocytosis; streptolysin O, a thiol-activated cytolysin; hyaluronidase, which hydrolyzes hyaluronic acid within the host tissue; streptokinase, an enzyme that activates plasmin; nicotinamide-adenine dinucleotidase (NADase), a glycohydrolase of uncertain function; and deoxyribonucleases (DNases) A, B, C, and D. Streptolysin O binds to the eukaryotic membrane’s cholesterol to facilitate the characteristic cellular lysis of a GAS infection. Cholesterol and anti-streptolysin O (ASO) antibodies can mitigate streptolysin O damage, and ASO titers often increase following an infection with the peak occurring around four to five weeks post-infection. “Nonsuppurative complications such as rheumatic fever and poststreptococcal glomerulonephritis generally develop during the second or third week of illness... About 80 percent of patients with acute rheumatic fever or poststreptococcal glomerulonephritis demonstrate a rise in ASO titer; however, the degree of ASO titer elevation does not correlate with severity of disease. In patients with suspected rheumatic fever or glomerulonephritis but with an undetectable ASO titer, prompt testing for other antistreptococcal antibodies such as anti-DNase B (detectable for six to nine months following infection), streptokinase, and antihyaluronidase should be performed.” (Stevens & Bryant, 2020a)

Acute rheumatic fever (ARF) can occur two to four weeks following GAS pharyngitis. The five major manifestations of ARF are carditis and valvulitis (up to 70% of patients exhibit this condition with ARF), arthritis (up to 66%), CNS system involvement (10-30%), subcutaneous nodules (0-10%), and erythema marginatum (<6%) (A. Steer & Gibofsky, 2020). A diagnosis of ARF is not predicated by confirmation of a preceding GAS infection; however, it is helpful, especially in diagnosing children and young adults with arthritis and/or carditis. Evidence of GAS should include either a positive throat culture, a positive RADT, or an elevated or rising titer of either ASO or anti-DNase B. These two antibodies are used frequently in clinical practice due to their high sensitivity in diagnosing streptococcal infections (A. Steer & Gibofsky, 2018, 2020; A. C. Steer, Smeesters, & Curtis, 2015). A study by Blyth and Robertson demonstrated that the sensitivity of using only a single antibody in the diagnosis of streptococcus ranged from 70.5-72.7%; however, the combination of ASO and anti-DNase B increased the specificity to 88.6% with a sensitivity of 95.5%. The addition of anti-streptokinase (ASK) did not increase either the sensitivity or specificity of testing (Blyth & Robertson, 2006).

A study in Norway in 2013 shows that necrotizing soft tissue infections can be caused by GAS or GGS/GCS. The mean annual incidence rate is 1.4 per 100,000. During the time period studied (2000-2009),

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61 cases of necrotizing soft tissue infections in Norway were due to GAS while nine cases were due to GCS/GGS. “Our findings indicate a high frequency of streptococcal necrotizing fasciitis in our community. GCS/GGS infections contribute to the disease burden, but differ from GAS cases in frequency and predisposing factors.” They note that “the GCS/GGS patients were older, had comorbidities more often and had anatomically more superficial disease than the GAS patients (Bruun et al., 2013).” A review in 2014 also noted the population most affected by GCS/GGS, but they note that “the case fatality in bacteremia has been reported to be 15-18% (Rantala, 2014).”

Group B Streptococcus (GBS) is frequently found in human gastrointestinal tracts and genitalia and can be spread to the upper respiratory tract of newborns. In neonates, a GBS infection can cause bacteremia, pneumonia, meningitis, and sepsis. GBS can also cause complications in pregnancy, such as urinary tract infections and chorioamnionitis. GBS, in pregnant and postpartum women, is of special concern since it is implicated in up to 31% of cases of bacteremia without a focus, 8% of postpartum endometritis, and 2% of pneumonia; moreover, if left unchecked, GBS can also result in preterm labor and miscarriage. In the adult population at large, GBS infections can be manifest as soft tissue infections, sepsis, and bacteremia (Barshak, 2021; Puopolo, Madoff, & Baker, 2019). “Invasive disease in infants is categorized on the basis of chronologic age at onset. Early- onset disease usually occurs within the first 24 hours of life (range, 0 through 6 days) and is characterized by signs of systemic infection, respiratory distress, apnea, shock, pneumonia, and less often, meningitis (5%–10% of cases). Late-onset disease, which typically occurs at 3 to 4 weeks of age (range, 7 through 89 days), commonly manifests as occult bacteremia or meningitis (approximately 30% of cases); other focal infections, such as osteomyelitis, septic arthritis, necrotizing fasciitis, pneumonia, adenitis, and cellulitis, occur less commonly. Nearly 50% of survivors of early- or late-onset meningitis have long- term neurologic sequelae (encephalomalacia, cortical blindness, cerebral palsy, visual impairment, hearing deficits, or learning disabilities). Late, late-onset disease occurs at 90 days of age and beyond, usually in very preterm infants requiring prolonged hospitalization (Pediatrics, 2018).”

## Type of Testing

Test	Description	Rationale
<b>Culture</b>	Cultures can be taken from a swab of the affected tissue when possible, such as the back of the throat and tonsils (1). The cultures are typically grown on a solid, complex rich medium such as Trypticase Soy Agar (TSA) supplemented with 5% sheep blood so that the zone of b-hemolysis can easily be visualized (2). Culture testing can be supplemented with additional conventional identification tests, such as the Lancefield antigen determination test and the PYR test (3).	The CDC considers the throat culture the ‘gold standard’ (4). This testing method can be time-intensive. “Throat culture also can identify other bacteria that cause pharyngitis less commonly than GAS (eg, group C and group G streptococci, <i>Arcanobacterium haemolyticum</i> ). However, most laboratories do not routinely identify these pathogens in throat cultures unless specifically requested to do so (5).”
<b>Serology</b>	Many possible serological tests can be performed, including a measurement of the antibody titers associated with a streptococcal infection. Virulence factors that can be monitored include hyaluronidase, streptokinase, nicotinamide-adenine dinucleotidase, DNase B, and	Anti-streptococcal antibody titers represent past infections and should not be used to routinely diagnose an acute infection (7).  Antistreptolysin O (ASO) and/or anti-DNase B (ADB) testing can be used to determine prior streptococcal infection associated with disorders such as rheumatic fever and glomerulonephritis.

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	streptolysin O. DNase B and streptolysin O are more frequently used in clinical practice (6).	<p>“An increase in titer from acute to convalescent (at least two weeks apart) is considered the best evidence of antecedent GAS infection. The antibody response of ASO peaks at approximately three to five weeks following GAS pharyngitis, which usually is during the first to third week of ARF, while ADB titers peak at six to eight weeks (8).”</p> <p>Antibody titers are dependent on the age of the patients with children having considerably higher ‘normal’ levels than adults due to frequent exposure to <i>S. pyrogenes</i> (3).</p>
Rapid Antigen Diagnostic Testing (RADT)	RADTs can be performed on a swab at the point of care or can be transported to a lab for testing (9). Numerous RADTs directly detect antigens through an agglutination method or the use of immunoassays, including enzyme-based assays, optical assays, and liposome-based assays that are commercially available (3).	<p>Many RADTs are commercially available but can vary considerably in specificity, sensitivity, and ease of use. “In pediatric patients, if the direct antigen test is negative, and if the direct antigen test is known to have a sensitivity of &lt;80%, a second throat swab should be examined by a more sensitive direct NAAT or by culture as a means of arbitrating possible false-negative direct antigen test results. This secondary testing is not necessarily required in adults. A convenient means of facilitating this 2-step algorithm of testing for <i>Streptococcus pyogenes</i> in pediatric patients is to collect a dual swab initially, recognizing that the second swab will be discarded if the direct antigen test is positive (9).”</p>
Nucleic Acid Amplification Tests (NAATs)	NAATs amplify DNA or RNA to detect the presence of microorganisms. Some are offered as point-of-care (POC) rapid diagnostic tests while others require special laboratory equipment (9). Some NAATs utilize real-time polymerase chain reaction (rt-PCR), such as the Lyra Direct Strep Assay, while others use a helicase-dependent amplification (HDA)-based methodology like the Solana Strep Complete assay. NAATs are often qualitative but specific NAATs can be quantitative. NAATs can vary in their selectivity, sensitivity, and ability to differentiate between strains of streptococci.	<p>More sensitive than antibody-based testing for streptococcus. Direct NAATs usually require the use of enriched broth cultures. “Negative direct NAAT results do not have to be arbitrated by a secondary test (9).”</p>
Matrix-Assisted Laser Desorption	MALDI-TOF mass spectrometry can be used to quickly identify	“For less common organisms, the MALDI- TOF result may not be

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Ionization-Time of Flight (MALDI-TOF)	both gram- negative and gram-positive bacteria once the organism is available in a pure culture on solid medium. The results of the MALDI-TOF test is compared to a known database of spectra of microorganisms for identification (10).	conclusive, and additional bench tests or molecular tests may be required (10).”
<p>(1) Reference: (AACC, 2015)</p> <p>(2) Reference: (Gera &amp; McIver, 2013)</p> <p>(3) Reference: (Spellerberg &amp; Brandt, 2016)</p> <p>(4) Reference: (CDC, 2018b)</p> <p>(5) Reference: (Wald, 2021)</p> <p>(6) Reference: (Stevens &amp; Bryant, 2020a, 2020b)</p> <p>(7) Reference: (Shulman et al., 2012)</p> <p>(8) Reference: (A. Steer &amp; Gibofsky, 2018)</p> <p>(9) Reference: (Miller et al., 2018)</p> <p>(10) Reference: (Freeman &amp; Roberts, 2019)</p>		

## *Clinical Validity and Utility*

Rapid in vitro diagnostic tests (RIDT), such as the Alere I Strep A, have been CLIA-waived by the FDA. These tests provide results more quickly than the traditional “gold standard” bacterial culture testing. A 2018 study comparing rapid antigen GAS testing, the Alere I Strep A test—an RIDT using isothermal nucleic acid amplification, and throat cultures. “The sensitivity and specificity of the molecular test were 98% and 100%, respectively, compared with culture. There was a 9% false-positive rate with the rapid antigen-based testing.... The Alere test is sufficiently sensitive and specific for definitive GAS testing in a pediatric urgent care setting (Weinzierl, Jerris, Gonzalez, Piccini, & Rogers, 2018).” In 2016, Cohen et al extensively reviewed the use of rapid antigen detection tests (RADT) for GAS in children. They reviewed 98 unique studies consisting of a total of 101,121 participants and compared both major types of RADTs—enzyme immunoassays (EIA) and optical immunoassays (OIA). “RADT had a summary sensitivity of 85.6%...There was substantial heterogeneity in sensitivity across studies; specificity was more stable. There was no trade-off between sensitivity and specificity.... The sensitivity of EIA and OIA tests was comparable (summary sensitivity 85.4% versus 86.2%)... Based on these results, we would expect that amongst 100 children with strep throat, 86 would be correctly detected with the rapid test while 14 would be missed and not receive antibiotic treatment (J. F. Cohen, Bertille, Cohen, & Chalumeau, 2016).” Another multicenter study using the Alere I Strep A test on cultures obtained from 481 patients of all ages show that the RIDT had 96.0% sensitivity and 94.6% specificity. The authors conclude that this “could provide a one-step, rapid, point-of-care testing method for GAS pharyngitis and obviate backup testing on negative results (D. M. Cohen et al., 2015).” This study did note that there are newer tests available that have higher sensitivity, but these tests require more time than the Alere I Strep A method.

Due to the time constraints of clinical laboratories and the variability of RADTs, nucleic acid amplification test (NAAT) use has been increasing in clinical settings. The FDA has approved multiple NAATs for the detection of Streptococcus. The Lyra Direct strep assay is an FDA-approved, NAAT that uses real-time PCR to qualitatively detect the presence of GAS and GGS/GCS in throat swab samples. It should be noted, though, that this assay does not distinguish between GGS and GCS. A study by Boyanton et al. evaluated the efficacy of the Lyra Direct method as compared to the traditional, time-consuming culture test for GAS and GGS/GCS. The sample sizes were not large (n = 19 for GAS and n = 5 for GGS/GCS out of a total of 161 samples submitted); however, the Lyra Direct strep assay did correctly detect “all b-hemolytic streptococci...” and “in batch mode, the Lyra assay reduced intra-laboratory turnaround time by 60% (18.1 h versus 45.0 h) but increased hands-on time by 96% (3 min 16 s versus 1 min 40 s per specimen) (Boyanton, Darnell, Prada, Hansz, & Robinson-Dunn, 2016).” The authors note that the RADTs “have largely augmented bacterial culture (the gold standard). However, the performance of commercially available [RADTs] varies greatly depending upon the manufacturer, methodology used (i.e., optical immunoassay, immunochromatographic, or enzyme immunoassay), and the patient population (i.e.,

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pediatric versus adult) being tested. Due to these limitations, nucleic acid amplification tests (NAATs) are being implemented in clinical laboratories (Boyanton et al., 2016).” The Solana method is also an FDA-approved NAAT, but it uses a rapid helicase-dependent amplification (HDA) methodology. Solana is available for either GAS testing or as a panel testing for GAS, GCS, and GGS. A study by Uphoff and colleagues compared the Solana GAS testing to that of conventional culture testing. Their research used 1082 throat swab specimens. The traditional culture tested positive in 20.7% of the samples as compared to 22.6% positive values in the HDA-based methodology. The Solana assay in their results had 98.2% sensitivity and 97.2% specificity. “In 35 min, the HDA method provided rapid, sensitive GAS detection, making culture confirmation unnecessary (Uphoff et al., 2016).” Recently, another study compared an HDA-based method to the Simplex GAS Direct PCR-based method, which is another FDA-approved diagnostic test. The Simplex GAS Direct method does not require initial DNA extraction from the sample, a potential time-saving benefit. The study used 289 throat swabs. The HDA- based method “compared to Simplexa qPCR had sensitivity, specificity, positive predictive value and negative predictive value of 93.1% vs 100%, 100% vs. 100%, 100% vs. 100% and 98.31% vs. 100% respectively... Simplexa qPCR has improved performance and diagnostic efficiency in a high-volume laboratory compared to [HDA- based method] for GAS detection in throat swabs (Church, Lloyd, Larios, & Gregson, 2018).”

The Solana® Strep Complete Assay by Quidel received FDA clearance in 2016. According to Quidel’s FDA application, it is defined as “a rapid in vitro diagnostic test, using isothermal amplification technology (helicase-dependent amplification, HDA) for the qualitative detection and differentiation of *Streptococcus pyogenes* (Group A  $\beta$ -hemolytic *Streptococcus*) and *Streptococcus dysgalactiae* (pyogenic Group C and G  $\beta$ -hemolytic *Streptococcus*) nucleic acids isolated from throat swab specimens obtained from patients with signs and symptoms of pharyngitis, such as sore throat (Lollar, 2016).” This test must be performed using Quidel’s Solana proprietary equipment. According to the 510(k) application, the Solana Strep Complete Assay panel has a clinical sensitivity and specificity for GAS of 98.8% and 98.9%, respectively, as compared to the Lyra Direct Strep Assay’s reported 96.5% sensitivity and 98.0% specificity for GAS. The Lyra Direct Strep Assay is a real-time PCR-based assay that cannot differentiate between the pyogenic strains of streptococci. Concerning the pyrogenic GCS/GGS, the Solana Strep Complete Assay panel has a clinical sensitivity of 100% with a specificity of 99.5% as compared to Lyra Direct Strep Assay’s reported 95.7% sensitivity and 98.3% specificity for GCS/GGS strains. The reported testing time also varies between the two assays with Solana requiring 25 minutes versus 60-70 minutes for the Lyra Direct Strep Assay (Lollar, 2016).

A recent study by Helmig and Gertsen evaluated the accuracy of PCR-based testing for GBS in pregnant women. Their study used rectovaginal swabs from 106 women in gestational weeks 35-37. For each, both a GBC culture and a PCR-based molecular GBS test (Xpert GBS of Cepheid Ltd) were performed. Only one PCR test yielded no result so the invalid PCR-based test rate is <1%. 25/106 of the GBS cultures tested positive as compared to 27/105 of the PCR-based test. The specificity of the PCR-based test was 97.5% with a 100% sensitivity and a 92.6% positive predictive value. The authors conclude that “the PCR test has sufficient accuracy to direct intrapartum antibiotic prophylaxis for GBS transmission during delivery (Helmig & Gertsen, 2017).” A preliminary study in France of 1416 mothers with newborns compared swab cultures and GBS PCR assay for their predictive value of early-onset bacterial sepsis (EOS) in newborns since GBS is the most common cause of EOS. The results show that “the diagnostic values of the two tests highlighted a nonsignificant superiority of intrapartum GBS PCR assay” but that “the negative predictive value was improved with intrapartum PCR assay (negative likelihood ratio [LR]: 0.3 [0.1-0.9] vs. 0.6 [0.4-1.1]).... These results suggest that the intrapartum GBS PCR assay offers a better predictive value of GBS EOS than the usual vaginal culture swab at the 9th month but requires confirmation by large studies (Raignoux et al., 2016).”

Luo et al. “evaluated the overall diagnosis and treatment of acute pharyngitis in the United States, including predictors of test type and antibiotic prescription”. Five categories of tests were identified, which were RADT [rapid antigen detection test], RADT plus culture, other tests, nucleic acid amplification testing (NAAT), and no test. Pharyngitis events from 2011-2015 were examined and a total of 18.8 million pharyngitis events across 11.6 million patients were included. 68.2% of events were found to occur once, with 29.1% requiring further follow-up. 43% of events were diagnosed by RADT and 20% were diagnosed by RADT plus culture. NAAT testing also increased 3.5-fold from 2011-2015 (going from 0.06% to

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0.27%). Antibiotics were used in 49.3% of events as a whole. For RADT plus culture, antibiotics were used 31.2% of the time, for NAAT alone, 34.5%, for RADT alone, 54.2%, for no test, 57.1%. The authors concluded that “Diagnostic testing can help lower the incidence of inappropriate antibiotic use, and inclusion of NAAT in the clinical guidelines for GAS pharyngitis warrants consideration.” (Luo et al., 2019)

Baptista de O Luiz et al. evaluated the “prevalence and persistence of beta-haemolytic streptococci throat carriage and type the bacterial population”. A total of 121 children and 127 young adult volunteers contributed throat swabs (for culture), and these volunteers were screened quarterly for beta-haemolytic bacterial species. Carriage was detected in 34 volunteers (13.7%). Seventeen children were found to carry Group A *Streptococcus*, while seventeen young adults were found to carry four separate subspecies (*Streptococcus dysgalactiae* subsp. *equisimilis* (SDSE), *Streptococcus pyogenes*, *Streptococcus agalactiae* and the *Streptococcus anginosus* group). The authors also identified persistent carriage for as long as 6 months in two children and for as long as 1 year in three young adults. The authors concluded that “prevalence was slightly greater among children, but persistent carriage was greater among young adults, with SDSE being the species most associated with persistence.” (FB, Alves, & Barros, 2019)

Fraser et al. performed a meta-analysis to assess the cost-effectiveness of point-of-care testing for detection of Group A Streptococcus. The authors remarked that this type of testing has seen increased use as an adjunct for managing care, such as for prescribing antibiotics. Thirty-eight studies of clinical effectiveness were included, along with three studies of cost-effectiveness. Twenty-six articles “reported on the test accuracy of point-of-care tests and/or clinical scores with biological culture as a reference standard”. Overall, 21 point-of-care tests were evaluated. The authors identified two populations of interest; “patients with Centor/McIsaac scores of  $\geq 3$  points or FeverPAIN scores of  $\geq 4$  points”. Test sensitivity for these populations ranged from 0.829-0.946 while test specificity ranged from 0.849-0.991. However, the authors did note there was significant heterogeneity and expressed doubts that any single study “accurately captured a test’s true performance”. The authors developed an economic model to explore the cost-effectiveness of this type of testing, and 14 of the 21 tests were included in this model. Per the current National Institute for Health and Care Excellence’s cost-effectiveness thresholds, these tests were not found to be cost-effective. The authors acknowledged significant uncertainties in the estimates, such as penalties for antibiotic over-prescriptions. The authors concluded that “the systematic review and the cost-effectiveness models identified uncertainties around the adoption of point-of-care tests in primary and secondary care settings. Although sensitivity and specificity estimates are promising, we have little information to establish the most accurate point-of-care test.” (Fraser et al., 2020; Kim, Kim, Jang, Nam, & Lim, 2019)

Bilir et al. (2021) studied the cost-effectiveness of point of care nucleic acid amplification tests (NAAT) for streptococcus in the US. Point of care NAAT was compared to rapid antigen detection tests (RADT) and culture. Costs, clinical effects, antibiotic complications, number of patients treated, and antibiotic utilization were studied. Analysis showed that the POC NAAT method would cost \$44 per patient while RADT and culture would cost \$78 per patient. “Compared with RADT + culture, POC NAAT would increase the number of appropriately treated patients and avert unnecessary use of antibiotics.” According to the results, “POC NAAT would be less costly and more effective than RADT + culture; POC NAAT adoption may yield cost savings to US third-party payers. Access to POC NAAT is important to optimize GAS diagnosis and treatment decisions in the United States” (Bilir et al., 2021).

In a metanalysis, Dubois et al. (2021) studied the diagnostic accuracy of rapid antigen detection tests (NADTs) vs rapid nucleic acid tests (RNATs) for diagnosis of group A streptococcal pharyngitis. 38 studies using RNAT were included, with a sensitivity of 97.5% and specificity of 95.1%. RADTs had a sensitivity of 82.3%, but specificity was similar to the sensitivity of RNATs. Overall, RNATs were more sensitive than RADTs. The authors conclude that “the high diagnostic accuracy of RNATs may allow their use as stand-alone tests to diagnose group A streptococcus pharyngitis” (Dubois et al., 2021).

## State and Federal Regulations, as applicable

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The FDA approved the Lyra Direct Strep Assay (k133833) on 04/16/2014 and reclassified it on 07/11/2014. It is a “Real-Time PCR *in vitro* diagnostic test for the qualitative detection and differentiation of Group A  $\beta$ -hemolytic *Streptococcus* (*Streptococcus pyogenes*) and pyogenic Group C and G  $\beta$ -hemolytic *Streptococcus* nucleic acids isolated from throat swab specimens obtained from patients with signs and symptoms of pharyngitis, such as sore throat. The assay does not differentiate between pyogenic Groups C and G  $\beta$ -hemolytic *Streptococcus* (Hojvat, 2014).” The FDA has also approved the Solana Strep Complete Assay by Quidel that is “an *in vitro* diagnostic test for the detection of Group A, C and G beta- hemolytic *Streptococcus* in throat swab specimens from symptomatic patients” on 10/25/2016 (K162274) (FDA, 2016).

On 03/06/2019, the FDA approved GenePOC’s Strep A assay to be performed using GenePOC’s Revogene instrument as a “single-use test for qualitative detection of *Streptococcus pyogenes* (group A *Streptococcus*-GAS) nucleic acids from throat swab specimens obtained from patients with signs and symptoms of pharyngitis (FDA, 2019).”

On November 9, 2020, the FDA approved Mesa Biotech, Inc.’s Accula™ Strep A Test, which is a semi-automated, colorimetric polymerase chain reaction (PCR) nucleic acid amplification test “to qualitatively detect *Streptococcus pyogenes* (Group A  $\beta$ hemolytic *Streptococcus*, Strep A) bacterial nucleic acid from unprocessed throat swabs that have not undergone prior nucleic acid extraction” (FDA, 2020).

A search of “Strep A” on the FDA Medical Devices Database (Devices@FDA) on 07/27/2021 yielded 181 results. A similar search of “Strep B” on 07/27/2021 yielded 21 results (FDA, 2021).

Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA ’88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

**\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

## Policy

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**BCBSNC will provide coverage for  $\beta$  hemolytic streptococcus testing when it is determined the medical criteria or reimbursement guidelines below are met.**

## Benefits Application

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

## When $\beta$ hemolytic streptococcus testing is covered

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Reimbursement is allowed for bacterial culture testing from a throat swab for streptococcal infection for a respiratory illness in the following situations:

1. Patients have a modified Centor criteria score of 3 or greater (See Note 1 below); OR
2. Suspected bacterial pharyngitis in the absence of viral features, including cough, oral ulcers, and rhinorrhea; OR
3. After a negative rapid antigen diagnostic test (RADT) in a symptomatic child or adolescent.

Reimbursement is allowed for blood culture testing for a streptococcal infection in the following situations:

1. In patients who fail to demonstrate clinical improvement and in those who have progressive symptoms or clinical deterioration after initiation of antibiotic therapy; OR

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2. In cases of suspected prosthetic joint infection.

Reimbursement is allowed for bacterial culture testing for a streptococcal infection from a skin swab or pus in cases of skin and/or soft tissue infections.

## **When $\beta$ hemolytic streptococcus testing is not covered**

Reimbursement is not allowed for bacterial culture testing for streptococci from a throat swab in cases of suspected viral pharyngitis.

Reimbursement is not allowed for rapid antigen diagnostic testing (RADT) for a streptococcal infection in the following cases:

1. As a follow-up test to either a positive or negative bacterial culture test for a streptococcal infection; OR
2. As a screening method in an asymptomatic patient (except in cases of children under the age of three years who have a mitigating circumstance, including a symptomatic family member); OR
3. In cases of suspected viral pharyngitis.

Reimbursement is not allowed for serological titer testing, except in cases of suspected acute rheumatic fever or post-streptococcal glomerulonephritis (PSGN).

Reimbursement is not allowed for the simultaneous coding for BOTH amplification and direct probes.

Reimbursement is not allowed for the following tests:

1. Panel tests that screen and identify multiple streptococcal strains (*S. pyogenes* [group A], *S. agalactiae* [group B], *S. dysgalactiae* [groups C/G],  $\alpha$ -hemolytic streptococcus, and/or  $\gamma$ -hemolytic streptococcus), using either immunoassay or nucleic acid-based assays, such as the Solana Strep Complete Assay and the Lyra Direct Strep Assay; OR
2. MALDI-TOF identification of streptococcus; OR
3. Anti-streptolysin O immunoassay (EXCEPT in cases of suspected acute rheumatic fever or post-streptococcal glomerulonephritis (PSGN)); OR
4. The quantification of any strain of streptococcus using nucleic acid amplification, including PCR; OR
5. Hyaluronidase activity or anti-hyaluronidase immunoassay (EXCEPT in cases of suspected acute rheumatic fever or post-streptococcal glomerulonephritis (PSGN)); OR
6. Streptokinase activity or anti-streptokinase immunoassay (EXCEPT in cases of suspected acute rheumatic fever or post-streptococcal glomerulonephritis (PSGN)); OR
7. Nicotinamide-adenine dinucleotidase activity or anti-nicotinamide-adenine immunoassay

## **Policy Guidelines**

**Note 1: Centor criteria includes tonsillar exudates, tender anterior cervical lymphadenopathy, fever, and absence of cough with each criterion being worth one point (Chow, 2020a, 2020b).**

**Note 2: For prenatal screening of Group B Streptococcus, please review policy AHS-G2035.**

## **Guidelines and Recommendations**

**Centers for Disease Control and Prevention (CDC, 2018b, 2018c, 2018e)**

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*Acute Pharyngitis* (CDC, 2018b): Most cases of acute pharyngitis are viral. Only 20-30% of sore throats in children and 5-15% in adults are due to GAS. History and clinical examination can be used to diagnosis viral pharyngitis when clear viral symptoms (e.g., cough, rhinorrhea, hoarseness, oral ulcers, conjunctivitis) are present; these patients do not need testing for group A strep. However, clinical examination cannot be used to differentiate viral and group A strep pharyngitis in the absence of viral symptoms, even for experienced clinicians. The diagnosis of group A strep pharyngitis is confirmed by either a rapid antigen detection test (RADT) or a throat culture. RADTs have high specificity for group A strep but varying sensitivities when compared to throat culture, which is considered the gold standard diagnostic test. Testing for group A strep pharyngitis is not routinely indicated for: children younger than 3 years of age or adults. The CDC also notes that a negative RADT should be followed with a throat culture in children with symptoms of pharyngitis (CDC, 2018b).

The CDC also comments on asymptomatic Group A carriers, stating that these carriers usually do not require treatment. The CDC defines carriers as having “positive throat cultures or are RADT positive, but do not have clinical symptoms or an immunologic response to group A strep antigens on laboratory testing” (CDC, 2018b).

*Scarlet Fever* (CDC, 2018d): Scarlet fever (scarlatina) consists of an erythematous rash caused by GAS and can occur along with acute pharyngitis. “The differential diagnosis of scarlet fever with pharyngitis includes multiple viral pathogens that can cause acute pharyngitis with a viral exanthema. Clinicians need to use either a rapid antigen detection test (RADT) or throat culture to confirm scarlet fever with pharyngitis. RADTs have high specificity for group A strep but varying sensitivities when compared to throat culture. Throat culture is the gold standard diagnostic test. Clinicians should follow up a negative RADT in a child with symptoms of scarlet fever with a throat culture. Clinicians should have a mechanism in place to contact the family and initiate antibiotics if the back-up throat culture is positive” (CDC, 2018d).

*Post-Streptococcal Glomerulonephritis* (PSGN) (CDC, 2018c): PSGN is primarily due to a GAS infection, but rare cases of GCS-induced PSGN have been reported. Clinical features include edema, hypertension, proteinuria, macroscopic hematuria, and lethargy. “The differential diagnosis of PSGN includes other infectious and non-infectious causes of acute glomerulonephritis. Clinical history and findings with evidence of a preceding group A strep infection should inform a PSGN diagnosis. Evidence of preceding group A strep infection can include isolation of group A strep from throat or skin lesions or elevated streptococcal antibodies” (CDC, 2018c).

*Acute Rheumatic Fever* (CDC, 2018a): The CDC notes that no definitive diagnostic test exists for acute rheumatic fever and recommends using the Jones criteria to make a clinical diagnosis.

## **American Association of Pediatrics (AAP), Red Book (Kimberlin DW, 2018)**

The AAP has published the Red Book as guidance for infectious diseases in the pediatric population. Their relevant comments and recommendations include:

- “Children with pharyngitis and obvious viral symptoms (eg, rhinorrhea, cough, hoarseness, oral ulcers) should not be tested or treated for GAS [Group A Streptococcus] infection; testing also generally is not recommended for children younger than 3 years.”
- “Several rapid diagnostic tests for GAS pharyngitis are available...Specificities of these tests generally are high (very few false-positive results), but the reported sensitivities vary considerably (ie, false-negative results occur).”
- “The US Food and Drug Administration (FDA) has cleared a variety of rapid tests for use in home settings. Parents should be informed that home use is discouraged because of the risk of false-positive testing that represents colonization.”
- “Because of the very high specificity of rapid tests, a positive test result does not require throat culture confirmation. Rapid diagnostic tests using techniques such as polymerase chain reaction (PCR), chemiluminescent DNA probes, and isothermal nucleic acid amplification tests have

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been developed...Some studies suggest that these tests may be as sensitive as standard throat cultures on sheep blood agar.”

- “Children with manifestations highly suggestive of viral infection, such as coryza, conjunctivitis, hoarseness, cough, anterior stomatitis, discrete ulcerative oral lesions, or diarrhea, are very unlikely to have true GAS pharyngitis and should not be tested.”
- “Testing children younger than 3 years generally is not indicated. Although small outbreaks of GAS pharyngitis have been reported in young children in child care settings, the risk of ARF is so remote in young children in industrialized countries that diagnostic studies for GAS pharyngitis generally are not indicated for children younger than 3 years.”
- “In contrast, children with acute onset of sore throat and clinical signs and symptoms such as pharyngeal exudate, pain on swallowing, fever, and enlarged tender anterior cervical lymph nodes, without concurrent viral symptoms and/or exposure to a person with GAS pharyngitis, are more likely to have GAS infection and should have a rapid antigen test and a throat culture if the rapid test result is negative, with treatment initiated if a test result is positive.”
- “Testing asymptomatic household contacts for GAS infection is not recommended except when the contacts are at increased risk of developing sequelae of GAS infection, such as ARF or acute glomerulonephritis; if test results are positive, such contacts should be treated.”
- “Testing asymptomatic household contacts usually is not helpful. However, if multiple household members have pharyngitis or other GAS infections, simultaneous cultures of all household members and treatment of all with positive cultures or rapid antigen test results may be of value.”
- “In suspected invasive GAS infections, cultures of blood and of focal sites of possible infection are indicated.”
- “Laboratory evidence of antecedent GAS infection should be confirmed in all cases of suspected ARF [acute rheumatic fever], and evidence includes an increased or rising ASO or anti-DNAase B titer, or a positive rapid antigen or streptococcal throat culture. Because of the long latency between GAS infection and presentation with chorea, such laboratory evidence may be lacking in cases where chorea is the major criteria.”
- “Post-treatment throat swab cultures are indicated only for patients who are at particularly high risk of ARF [acute rheumatic fever] (eg, those living in an area with endemic infection).”

## **American Heart Association (AHA) (Gewitz Michael et al., 2015; Puopolo, Lynfield, & Cummings, 2019)**

The AHA published a revision to the Jones criteria for diagnosis of acute rheumatic fever in 2015. In it, they note the importance of identifying laboratory evidence of a Group A Streptococcal infection. The AHA lists three clinical features that can serve as evidence for a preceding Group A Streptococcus infection, which are as follows:

- “Increased or rising anti-streptolysin O titer or other streptococcal antibodies (anti-DNASE B). A rise in titer is better evidence than a single titer result.”
- “A positive throat culture for group A  $\beta$ -hemolytic streptococci.”
- “A positive rapid group A streptococcal carbohydrate antigen test in a child whose clinical presentation suggests a high pretest probability of streptococcal pharyngitis.” (Gewitz Michael et al., 2015)

## **2017 Institute for Clinical Systems Improvement (ICSI) (Short et al., 2017)**

In 2017, the ICSI updated their guidelines titled *Diagnosis and treatment of respiratory illness in children and adults*. They give the following consensus recommendation: “It is the consensus of the ICSI work group to NOT test for Group A Streptococcal (GAS) pharyngitis in patients with modified Centor criteria scores less than three or when viral features like rhinorrhea, cough, oral ulcers and/or hoarseness are present. Testing should generally be reserved for patients when there is a high suspicion for GAS and for whom there is intention to treat with antibiotics (Short et al., 2017).” The Centor

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criteria include age of patient, physical state of the tonsils and lymph nodes, temperature, and presence or absence of cough (Walker & Habboushe, 2018).

## **American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) (Metlay et al., 2019)**

The ATS and IDSA published a joint guideline on the diagnosis and treatment of community-acquired pneumonia in adults. The guideline notes that group A *Streptococcus* may be associated with influenza pneumonia. Their relevant recommendations are listed below:

- “We recommend not obtaining sputum Gram stain and culture routinely in adults with CAP managed in the outpatient setting (strong recommendation, very low quality of evidence).”
- “We recommend not obtaining blood cultures in adults with CAP managed in the outpatient setting (strong recommendation, very low quality of evidence).” (Metlay et al., 2019)

## **Infectious Diseases Society of America (IDSA)( Miller et al., 2018; Stevens et al., 2014)**

The 2014 update of the IDSA’s guidelines concerning skin and soft tissue infections included a recommendation (strong; moderate-quality evidence) of “Gram stain and culture of the pus or exudates from skin lesions of impetigo and ecthyma are recommended to help identify whether *Staphylococcus aureus* and/or  $\beta$ -hemolytic *Streptococcus* is the cause, but treatment without these studies is reasonable in typical cases.” They make a similar recommendation in the cases of pus from carbuncles and abscesses as well as pyomyositis; however, they do not recommend (strong, moderate) a “Gram stain and culture of pus from inflamed epidermoid cysts”. As for erysipelas and cellulitis, “cultures of blood or cutaneous aspirates, biopsies, or swabs are not routinely recommended (strong, moderate) ...cultures of blood are recommended (strong, moderate), and cultures and microscopic examination of cutaneous aspirates, biopsies, or swabs should be considered in patients with malignancy on chemotherapy, neutropenia, severe cell-mediated immunodeficiency, immersion injuries, and animal bites (weak, moderate).” (Stevens et al., 2014)

IDSA and the American Society for Microbiology (ASM) published a guideline in 2018 titled “A Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases”. This guideline includes items on the laboratory diagnosis of pharyngitis, which are as follows:

- For *Streptococcus pyogenes*, direct NAAT, nucleic acid probe tests, or a rapid direct antigen test (followed by a culture or NAAT test if negative) may all be performed.
- For Groups C and G  $\beta$ -hemolytic streptococci, a NAAT may be performed, or a combination of throat culture and antigen tests on isolates for groups C and G streptococci may be performed.

Other relevant comments include:

- “A rapid antigen test for *Streptococcus pyogenes* may be performed at the point of care by healthcare personnel or transported to the laboratory for performance of the test...in pediatric patients, if the direct antigen test is negative, and if the direct antigen test is known to have a sensitivity of <80%, a second throat swab should be examined by a more sensitive direct NAAT or by culture as a means of arbitrating possible false-negative direct antigen test results...this secondary testing is not necessarily required in adults”
- “Direct and amplified NAATs for *Streptococcus pyogenes* are more sensitive than direct antigen tests and, as a result, negative direct NAAT results do not have to be arbitrated by a secondary test.”

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“Detection of group C and G  $\beta$ -hemolytic streptococci is accomplished by throat culture in those patients in whom there exists a concern for an etiologic role for these organisms. Only large colony types are identified, as tiny colonies demonstrating groups C and G antigens are in the *Streptococcus anginosus* (*S. milleri*) group.” (Miller et al., 2018)

## **American Academy of Otolaryngology-Head and Neck Surgery Foundation (Mitchell et al., 2019)**

Although the main focus of this guideline is the tonsillectomy procedure in children, there are some relevant comments. The Academy notes that “In practice, streptococcal carriage is strongly suggested by positive strep cultures or other strep tests when the child lacks signs or symptoms of acute pharyngitis.” (Mitchell et al., 2019) IDSA endorsed this guideline in February 2019 (IDSA, 2019a).

## **American Academy of Orthopaedic Surgeons (AAOS, 2019)**

Although this guideline focuses on management of periprosthetic joint infections, there is a relevant recommendation, which states that “synovial fluid aerobic and anaerobic bacterial cultures” have moderate evidence to support their use to “aid in the diagnosis of prosthetic joint infection (PJI)” (AAOS, 2019). IDSA endorsed this guideline in March 2019 (IDSA, 2019b).

## **2011 Pediatric Infectious Diseases Society (PIDS) and Infectious Diseases Society of America (IDSA)(Bradley et al., 2011)**

The 2011 joint PIDS-IDSA guidelines concerning pediatric community-acquired pneumonia (CAP) recommended (strong recommendation; moderate-quality evidence) that “blood cultures should not be routinely performed in nontoxic, fully immunized children with CAP managed in the outpatient setting” and that “blood cultures should be obtained in children who fail to demonstrate clinical improvement and in those who have progressive symptoms or clinical deterioration after initiation of antibiotic therapy”. Concerning inpatient services, they recommend (strong recommendation; low-quality evidence) that “blood cultures should be obtained in children requiring hospitalization for presumed bacterial CAP that is moderate to severe, particularly those with complicated pneumonia”; however, “in improving patients who otherwise meet criteria for discharge, a positive blood culture with identification or susceptibility results pending should not be routinely preclude discharge of that patient with appropriate oral or intravenous antimicrobial therapy. The patient can be discharged if close follow-up is assured (weak recommendation; low-quality evidence)”. For pneumococcal bacteremia, they do not recommend repeated blood cultures to document resolution (weak recommendation; low-quality evidence), but they do recommend “repeated blood cultures to document resolution of bacteremia...caused by *S. aureus*, regardless of clinical status (strong recommendation; low-quality evidence)”. With respect to sputum gram stain and culture, “sputum samples for culture and Gram stain should be obtained in hospitalized children who can produce sputum” (weak recommendation; low-quality evidence). They do not recommend using urinary antigen detection testing “for the diagnosis of pneumococcal pneumonia in children; false-positive tests are common (strong recommendation; high-quality evidence) (Bradley et al., 2011).”

## **American College of Obstetricians and Gynecologists (ACOG, 2020)**

The ACOG issued Committee Opinion #797 in 2020. ACOG recommends that “Regardless of planned mode of birth, all pregnant women should undergo antepartum screening for GBS at 36 0/7–37 6/7 weeks of gestation, unless intrapartum antibiotic prophylaxis for GBS is indicated because of GBS bacteriuria during the pregnancy or because of a history of a previous GBS-infected newborn” (ACOG, 2020).

## **American Society for Microbiology (ASM, 2020)**

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The ASM endorsed the above ACOG recommendation, stating that “The recommended screening interval has changed from 35-37 weeks (per CDC 2010 guidelines) to 36 0/7 to 37 6/7 weeks (ACOG 2019 recommendations)”. The guideline also recommends performing “antimicrobial susceptibility testing on all GBS [Group B Streptococcus] isolates from pregnant women with penicillin allergy” (ASM, 2020).

## National Institute for Health and Care Excellence (NICE, 2019)

NICE published an update on “rapid tests for group A streptococcal infections in people with a sore throat”. They stated that “rapid tests for strep A infections are not recommended for routine adoption for people with a sore throat. This is because their effect on improving antimicrobial prescribing and stewardship, and on patient outcomes, as compared with clinical scoring tools alone, is likely to be limited.” (NICE, 2019)

## Billing/Coding/Physician Documentation Information

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: 83789, 86060, 86063, 86215, 86317, 86318, 87040, 87070, 87071, 87077, 87081, 87430, 87650, 87651, 87652, 87797, 87798, 87799, 87880*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

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## Policy Implementation/Update Information

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# Beta-Hemolytic Streptococcus Testing AHS – G2159

- 1/1/19 New policy developed. BCBSNC will provide coverage for  $\beta$  hemolytic streptococcus testing when it is determined to be medically necessary because the medical criteria and guidelines are met. BCBSNC does not provide coverage for investigational services. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (sk)
- 10/1/19 Policy statement revised to read: BCBSNC will provide coverage for  $\beta$  hemolytic streptococcus testing when it is determined the medical criteria or reimbursement guidelines below are met. Wording revised in the Covered Section: “Medically necessary” changed to “reimbursement is allowed.” Wording revised in the Not Covered section. “Not Medically Necessary” and “Investigational” changed to read “Reimbursement is not allowed...” Deleted coding grid. Notification given 10/1/2019 for effective date of 12/2/2019. (an)
- 12/10/19 Reviewed by Avalon 3rd Quarter CAB. Codes 87797 and 87798 added to Billing/Coding section. (sk)
- 3/10/20 Specialty Matched Consultant Advisory Panel review 2/19/2020. (sk)
- 11/10/20 Reviewed by Avalon 3rd Quarter 2020 CAB. Description section updated. Related policy added. Regulatory section updated. Billing/Coding section updated with deletion of the following codes: 87045, 87147, 87653, and 87802. Code 87799 added to Billing/Coding section. Policy Guidelines updated. References updated. (sk)
- 3/09/21 Specialty Matched Consultant Advisory Panel review 2/17/2021. (sk)
- 11/16/21 Reviewed by Avalon 3rd Quarter 2021 CAB. Description section updated. Regulatory section updated. Policy Guidelines updated. References updated. (sk)

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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.