β-Hemolytic Streptococcus Testing

Policy Number: AHS – G2159 – β - Hemolytic Streptococcus Testing	Prior Policy Name and Number, as applicable:
Original Effective Date: 05/15/2022 Current Effective Date: 03/01/2024	

I. Policy Description

Streptococcus are Gram-positive, catalase-negative bacteria that are further divided into α-hemolytic, such as *S. pneumoniae* and *S. mutans*; β-hemolytic, such as *S. pyogenes* (Group A), *S. agalactiae* (Group B), and *S. dysgalactiae subsp equisimilis* (Groups C and G); and γ-hemolytic, such as *Enterococcus faecalis* and *E. faecium* (Wessels, 2022). 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, 2023; Wessels, 2022).

For prenatal screening of Group B Streptococcus, please review policy AHS-G2035.

II. Related Policies

Policy Number	Policy Title
AHS-G2035	Prenatal Screening (Nongenetic)

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

1) For the detection of a streptococcal infection causing respiratory illness, bacterial culture testing from a throat swab **MEETS COVERAGE CRITERIA** when **one** of the following conditions is met:
   a) When the individual has a modified Centor criteria score of 3 or greater (see Note 1 below).
   b) When the individual is suspected of having bacterial pharyngitis in the absence of viral features, (e.g., cough, oral ulcers, rhinorrhea).

c) Following a negative rapid antigen diagnostic test (RADT) in a symptomatic child or adolescent.

2) Blood culture testing for a streptococcal infection **MEETS COVERAGE CRITERIA** when **one** of the following conditions is met:
   a) For individuals who fail to demonstrate clinical improvement.
   b) For individuals who have progressive symptoms or clinical deterioration after the initiation of antibiotic therapy.
   c) In cases of suspected prosthetic joint infection.

3) In cases of skin and/or soft tissue infections, bacterial culture testing for a streptococcal infection from a skin swab or from pus **MEETS COVERAGE CRITERIA**.

4) For individuals with suspected acute rheumatic fever (ARF) or post-streptococcal glomerulonephritis (PSGN), the following testing **MEETS COVERAGE CRITERIA:**
   a) Serological titer testing.
   b) Anti-streptolysin O immunoassay.
   c) Hyaluronidase activity or anti-hyaluronidase immunoassay.
   d) Streptokinase activity or anti-streptokinase immunoassay.

5) In cases of suspected viral pharyngitis, bacterial culture testing for streptococci from a throat swab **DOES NOT MEET COVERAGE CRITERIA**.

6) Except in cases of asymptomatic children under the age of three years who have a mitigating circumstance (including a symptomatic family member), RADT for a streptococcal infection **DOES NOT MEET COVERAGE CRITERIA** in **any** of the following situations:
   a) As a follow-up test for individuals who have had a bacterial culture test for a streptococcal infection.
   b) As a screening method in an asymptomatic patient.
   c) For individuals with suspected viral pharyngitis.

7) For all situations not described above, serological titer testing **DOES NOT MEET COVERAGE CRITERIA**.

8) Simultaneous ordering of **both** direct probe and amplification probe for the same organism in a single encounter **DOES NOT MEET COVERAGE CRITERIA.**

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

9) For all situations not described above, testing with an anti-streptolysin O immunoassay, a hyaluronidase activity or anti-hyaluronidase immunoassay, **or** a streptokinase activity or anti-streptokinase immunoassay **DOES NOT MEET COVERAGE CRITERIA.**

10) For all situations, the following tests **DO NOT MEET COVERAGE CRITERIA**:

a) Panel tests that screen and identify multiple streptococcal strains (*S. pyogenes* [group A], *S. agalactiae* [group B], *S. dysgalactiae* [groups C/G], □-hemolytic streptococcus, and/or □-hemolytic streptococcus), using either immunoassay or nucleic acid-based assays (e.g., Solana Strep Complete Assay, Lyra Direct Strep Assay).

b) MALDI-TOF identification of streptococcus.

c) The quantification of any strain of streptococcus using nucleic acid amplification, including PCR.

d) Nicotinamide-adenine dinucleotidase activity or anti-nicotinamide-adenine immunoassay.

NOTES:

Note 1: Centor criteria includes tonsillar exudates, tender anterior cervical lymphadenopathy, fever, and absence of cough with each criterion being worth one point (Chow, 2023).

IV. Table of Terminology

Term	Definition
AAOS	American Academy of Orthopaedic Surgeons
AAP	American Association of Pediatrics
ACOG	American College of Obstetricians and Gynecologists
ADB	Anti-DNase B
AHA	American Heart Association
ARF	Acute rheumatic fever
ASK	Anti-streptokinase
ASM	American Society for Microbiology
ASO	Anti-streptolysin O
ATS	American Thoracic Society
C3	Complement component 3
CAP	Community-acquired pneumonia
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare and Medicaid Services
CNS	Central nervous system
CSF	Cerebrospinal fluid
DNA	Deoxyribose nucleic acid
DNases	Deoxyribonucleases
EIA	Enzyme immunoassays
EOS	Early-onset bacterial sepsis
FDA	Food and Drug Administration
GAS	Group A *Streptococcus*
GBS	Group B *Streptococcus*

GCS	Group C *Streptococcus*
GGS	Group G *Streptococcus*
HDA	Helicase-dependent amplification
ICSI	Institute for Clinical Systems Improvement
IDSA	Infectious Diseases Society of America
LDTs	Laboratory developed Tests
LR	Likelihood ratio
MALDI-TOF	Matrix-assisted laser desorption/ionization-Time of flight
NAAT	Nucleic acid amplification test
NADase	Nicotinamide adenine dinucleotidase
NADTs	Rapid antigen detection tests
NICE	National Institute for Health and Care Excellence
OIA	Optical immunoassays
PCR	Polymerase chain reaction
PIDS	Pediatric Infectious Diseases Society
PJI	Prosthetic joint infection
POC	Point of care
PSGN	Post-streptococcal glomerulonephritis
PYR	Pyrrolidonyl aminopeptidase
qPCR	Quantitative PCR
RADT	Rapid antigen diagnostic testing
RIDT	Rapid in vitro diagnostic tests
RNA	Ribonucleic acid
RNATs	Rapid nucleic acid tests
rt-PCR	Real-time polymerase chain reaction
SDSE	*Streptococcus dysgalactiae* subspecies e*quisimilis*
TSA	Trypticase soy agar

V. Scientific Background

Bacterial acute pharyngitis is caused most often 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, 2023). "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, 2022). 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 et al., 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 ≥3 can be tested for GAS pharyngitis (Chow, 2023)

Group A *Streptococcus* 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, 2022b). 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, 2022d). Scarlet fever is more easily transmitted than asymptomatic carriers through saliva and nasal secretions. Acute Rheumatic Fever (AFR), 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, 2022a). 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, 2022c).

The virulence factors of GAS include M proteins, a group of more than 80 known proteins that protein 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 bind to the eukaryotic membrane's cholesterol to facilitate the characteristic cellular lysis of a GAS infection. Cholesterol and anti-streptolysis 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, 2022).

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%) (Steer & Gibofsky, 2022). 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 (Steer & Gibofsky, 2022; Steer et al., 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 show 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), 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 infections 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, 2022; Puopolo et al., 2022). "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
Culture	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, *Arcanobacterium haemolyticum*). However, most laboratories do not routinely identify these pathogens in throat cultures unless specifically requested to do so" (5).
Serology	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 streptolysin O. DNase B and streptolysin O are more frequently used in clinical practice (6).	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. "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). Antibody titers are dependent on the age of the patients with children having considerably higher 'normal' levels than

		adults due to frequent exposure to *S. pyrogenes* (3).
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).	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 <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 Streptococcus pyogenes 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).
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.	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).
Matrix-Assisted Laser Desorption Ionization-Time	MALDI-TOF mass spectrometry can be used to quickly identify both gram-negative and gram-positive bacteria	"For less common organisms, the MALDI-TOF result may not be

of Flight (MALDI-TOF)	once the organism is available in a pure culture on solid medium. The results of the MALDI-TOF test are compared to a known database of spectra of microorganisms for identification (10).	conclusive, and additional bench tests or molecular tests may be required" (10).
(1) (AACC, 2021);(2) (Gera & McIver, 2013); (3) (Spellerberg & Brandt, 2016); (4) (CDC, 2022b); (5) (Wald, 2022); (6) (Stevens & Bryant, 2022); (7) (Shulman et al., 2012); (8) (Steer & Gibofsky, 2022); (9) (Miller et al., 2018); (10) (Freeman & Roberts, 2023)		

Clinical Utility and Validity

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 et al., 2018). In Cohen et al. (2016)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" (Cohen et al., 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" (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. (2016) 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 et al., 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., 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 et al. (2016) 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 et al., 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 β-hemolytic Streptococcus) and Streptococcus dysgalactiae (pyogenic Group C and G β-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 (2017)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 that the usual vaginal culture swab at the 9th month but requires confirmation by large studies" (Raignoux et al., 2016).

Luo et al. (2019) "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. Overall, 68.2% of events were found to occur once, with 29.1% requiring further follow-up. Furthermore, 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 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).

O. Luiz et al. (2019) 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 six months in two children and for as long as one 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" (O. Luiz et al., 2019).

Fraser et al. (2020) 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 ≥ 3 points or FeverPAIN scores of ≥ 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 et al., 2019)

Bilir et al. (2021) studied the cost-effectiveness of point of care (POC) 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. A total of 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).

McCarty et al. (2022) studied the clinical utility on the GenMark Dx ePlex® blood culture identification gram-positive panel. The panel results were evaluated and compared to MALDI-TOF mass spectrometry and traditional antimicrobial susceptibility testing. One hundred Gram-Positive bacteria were represented. "The positive percent agreement (PPA) was 97/97 with 2 false positives." The study included chart reviews of 80 patients. The average time for organism identification was 24.4 hours faster, and the average time for optimization was 29.2 hours faster for the eight patients identified with organisms such as streptococci. The authors "confirm high sensitivity and specificity of the FDA-cleared GenMark Dx ePlex BCID-GP Panel compared to MALDI-TOF MS on bacterial isolates and identify opportunities for earlier optimization of antimicrobial therapy that may also be accompanied by potential cost savings (McCarty et al., 2022).

VI. Guidelines and Recommendations

Centers for Disease Control and Prevention

Acute Pharyngitis (CDC, 2022b): Most cases of acute pharyngitis are viral. Only 20-30% of sore throats in children and 5-15% in adults are due to group A *Streptococcus* (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 three years of age or for adults. Clinicians can use a positive RADT as confirmation of group A strep pharyngitis in children, though it also notes that a negative RADT should be followed with a throat culture in children with symptoms of pharyngitis (CDC, 2022b).

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, 2022b).

Scarlet Fever (CDC, 2022d): 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, 2022d).

Post-Streptococcal Glomerulonephritis (PSGN) (CDC, 2022c): 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. As such, "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
- Skin lesions
- Elevated streptococcal antibodies" (CDC, 2022c).

Acute Rheumatic Fever (CDC, 2022a): "The differential diagnosis of acute rheumatic fever is broad due to the various symptoms of the disease. The differential diagnosis may include but is not limited to: rheumatoid arthritis, juvenile idiopathic arthritis, septic arthritis, systemic lupus erythematosus, serum sickness, Lyme disease, infective endocarditis, viral myocarditis, Henoch-Schonlein purpura, gout, sarcoidosis, leukemia, and Hodgkin's disease." The CDC notes that no definitive diagnostic test exists for acute rheumatic fever and recommends using the Jones criteria (endorsed by the American Heart Association) to make a clinical diagnosis, which "n ow includes the addition of subclinical carditis as a major criteria and stratification of the major and minor

criteria based upon epidemiologic risk (e.g., low, moderate, or high risk populations)" (CDC, 2022a).

American Association of Pediatrics (AAP)

The AAP has published the Red Book (Kimberlin et al., 2021) 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 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)."

Regarding the management of infants at risk of group B streptococcal disease, a list of recommendations was provided. The relevant points are included below:

- "Early-onset GBS infection is diagnosed by blood or CSF culture. Common laboratory tests such as the complete blood cell count and C-reactive protein do not perform well in predicting early-onset infection, particularly among well-appearing infants at lowest baseline risk of infection."
- "Evaluation for late-onset GBS disease should be based on clinical signs of illness in the infant. Diagnosis is based on the isolation of group B streptococci from blood, CSF, or other normally sterile sites. Late-onset GBS disease occurs among infants born to mothers who had positive GBS screen results as well as those who had negative screen results during pregnancy. Adequate IAP does not protect infants from late-onset GBS disease" (Puopolo et al., 2019).

American Heart Association (AHA)

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 β-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 et al., 2015).

Institute for Clinical Systems Improvement (ICSI)

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 criteria include age of patient, physical state of the tonsils and lymph nodes, temperature, and presence or absence of cough (Centor & McIsaac, 2022).

American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA)

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)

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 □-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 cutaneious aspirates, biopsies, or swabs are not routinely recommended (strong, moderate) …cultures of blood are recommended (strong, moderate), and cultures and microscopic examination of cutaneious 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).

The 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 β-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."
- "Detection of group C and G β-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

Although the 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

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)

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)

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). This committee opinion was reaffirmed in 2022.

American Society for Microbiology

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)." Concerning identification of group B *streptococcus*, the ASM propounds the following:

"Recommendation: Acceptable phenotypic and proteomic methods of identification of candidate isolates include CAMP test, latex agglutination, and mass spectrometry."

"Recommendation: Nucleic acid amplification-based identification of GBS from enrichment broth is acceptable, but not sufficient for all patients."

"Recommendation: Latex agglutination directly from enrichment broth and direct-from-specimen immunoassays are unacceptable methods for GBS detection."

The guideline also recommends performing "antimicrobial susceptibility testing on all GBS [Group B Streptococcus] isolates from pregnant women with penicillin allergy", and most recently the ASM included options for vancomycin reporting (Filkins et al., 2021).

National Institute for Health and Care Excellence

The 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).

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: https://www.cms.gov/medicare-coverage-database/search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

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 β -hemolytic *Streptococcus* (*Streptococcus pyogenes*) and pyogenic Group C and G β -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 β-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 βhemolytic Streptococcus, Strep A) bacterial nucleic acid from unprocessed throat swabs that have not undergone prior nucleic acid extraction" (FDA, 2020).

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). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VIII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
86060	Antistreptolysin 0; titer
86063	Antistreptolysin 0; screen
86215	Deoxyribonuclease, antibody
86317	Immunoassay for infectious agent antibody, quantitative, not otherwise specified
86318	Immunoassay for infectious agent antibody(ies), qualitative or semiquantitative, single step-method (eg, reagent strip);
87040	Culture, bacterial; blood, aerobic, with isolation and presumptive identification of isolates (includes anaerobic culture, if appropriate)
87070	Culture, bacterial; any other source except urine, blood or stool, aerobic, with isolation and presumptive identification of isolates
87071	Culture, bacterial; quantitative, aerobic with isolation and presumptive identification of isolates, any source except urine, blood or stool
87077	Culture, bacterial; aerobic isolate, additional methods required for definitive identification, each isolate
87081	Culture, presumptive, pathogenic organisms, screening only;

87430	Infectious agent antigen detection by immunoassay technique, (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], fluorescence immunoassay [FIA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative; Streptococcus, group A
87650	Infectious agent detection by nucleic acid (DNA or RNA); Streptococcus, group A, direct probe technique
87651	Infectious agent detection by nucleic acid (DNA or RNA); Streptococcus, group A, amplified probe technique
87652	Infectious agent detection by nucleic acid (DNA or RNA); Streptococcus, group A, quantification
87797	Infectious agent detection by nucleic acid (DNA or RNA), not otherwise specified; direct probe technique, each organism
87798	Infectious agent detection by nucleic acid (DNA or RNA), not otherwise specified; amplified probe technique, each organism
87799	Infectious agent detection by nucleic acid (DNA or RNA), not otherwise specified; quantification, each organism
87880	Infectious agent antigen detection by immunoassay with direct optical (ie, visual) observation; Streptococcus, group A

Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

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X. Review/Revision History

Effective Date	Summary
03/01/2024	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. The following edits were made for clarity:

	All CC edited for clarity and consistency Language that notes "except in these cases" does not match with general formatting of our policies. The "Except in cases of suspected acute rheumatic fever (ARF) or post-streptococcal glomerulonephritis (PSGN)," language that was seen in former CC6 and CC8.c., 8.e., and 8.f. was moved into a new CC that addresses tests allowed for ARF and PSGN and a new CC that notes that these tests aren't allowed in other situations. New CC4: "4) For individuals with suspected acute rheumatic fever (ARF) or post-streptococcal glomerulonephritis (PSGN), the following testing MEETS COVERAGE CRITERIA: a) Serological titer testing. b) Anti-streptolysin O immunoassay. c) Hyaluronidase activity or anti-hyaluronidase immunoassay. d) Streptokinase activity or anti-streptokinase immunoassay." And new CC9: "9) For all situations not described above, testing with an anti-streptolysin O immunoassay, a hyaluronidase activity or anti-hyaluronidase immunoassay, or a streptokinase activity or anti-streptokinase immunoassay DOES NOT MEET COVERAGE CRITERIA." Former CC6, now CC7, now reads: "7) For all situations not described above, serological titer testing DOES NOT MEET COVERAGE CRITERIA."
03/10/2023	Updated the background, guidelines and recommendations, and evidence based scientific references. Literature review did not necessitate any modifications to coverage criteria. All CC edited for clarity and consistency. Removed Note 2, as it is not mentioned in CC and the reference to AHSG2035 is already made in the "Policy Description" Coding Enhancement: Removed CPT code 83789, updated code description for 87880
05/15/2022	Initial Policy Implementation