Clinical Policy Title: Molecular tests for group A streptococcus

Clinical Policy Number: 18.01.04

Effective Date: July 1, 2016
Initial Review Date: February 17, 2016
Most Recent Review Date: March 6, 2018
Next Review Date: March 2019

Policy contains:
- Group A streptococcus.
- Pharyngitis.
- Rapid antigen detection test.

Related policies:

CP# 07.01.09 Strep tests

ABOUT THIS POLICY: Select Health of South Carolina has developed clinical policies to assist with making coverage determinations. Select Health of South Carolina’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Select Health of South Carolina when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Select Health of South Carolina’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Select Health of South Carolina’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Select Health of South Carolina will update its clinical policies as necessary. Select Health of South Carolina’s clinical policies are not guarantees of payment.

Coverage policy

Select Health of South Carolina considers the use of molecular testing for group A streptococcus (group A strep) clinically proven, and therefore medically necessary for suspected cases of the condition (Shulman, 2012; Snellman, 2013; Short, 2017).

Limitations:

None.

Alternative covered services:

Rapid strep and throat culture.

Background
Group A strep bacteria are spread through contact with droplets from an infected person's cough or sneeze, and live in a person's nose and throat. In developed countries, 15 percent of school-age children and 4--10 percent of adults will have a group A strep episode of pharyngitis every year (Shulman, 2012).

Most group A strep infections cause relatively mild (noninvasive) illnesses such as strep throat, scarlet fever, and impetigo (a skin infection). More than 10 million noninvasive group A strep infections (primarily throat and superficial skin infections) occur annually in the United States. Occasionally, these bacteria can cause severe and even life-threatening (invasive) diseases. Cases of invasive group A strep infections, such as necrotizing fasciitis and streptococcal toxic shock syndrome, occur less frequently but are associated with higher rates of death.

Acute group A strep pharyngitis has certain characteristic epidemiological and clinical features. The disorder is primarily a disease of children 5-15 years of age, and, in temperate climates, it usually occurs in the winter and early spring. Patients with group A strep pharyngitis commonly present with sore throat (generally of sudden onset), pain on swallowing, and fever. Headache, nausea, vomiting, and abdominal pain may also be present, especially in children. On examination, patients have tonsillopharyngeal erythema, with or without exudates, often with tender, enlarged anterior cervical lymph nodes (lymphadenitis). Other findings may include a beefy, red, swollen uvula; petechiae on the palate; excoriated nares (especially in infants); and a scarlatiniform rash. However, none of these findings are specific for group A strep pharyngitis. Conversely, the absence of fever or the presence of clinical features such as conjunctivitis, cough, hoarseness, coryza, anterior stomatitis, discrete intra-oral ulcerative lesions, viral exanthema, and diarrhea strongly suggests a viral rather than a streptococcal etiology.

The traditional throat culture test to diagnose group A strep typically takes 2-3 days for results to be returned from labs. The rapid strep test, in which the throat and tonsils are swabbed to collect bacteria, can produce results in 10-15 minutes, improving the chances for effectiveness to rapidly commence.

Diagnosis of group A strep pharyngitis has traditionally been made by swabbing the throat and testing for GAS pharyngitis by rapid antigen detection test and/or culture.

- Routine use of back-up throat cultures for those with a negative rapid antigen detection test is not necessary for adults in usual circumstances, because of the low incidence of group A strep pharyngitis in adults and because the risk of subsequent acute rheumatic fever is generally low in adults with acute pharyngitis.
- Anti-streptococcal antibody titers are not recommended in the routine diagnosis of acute pharyngitis as they reflect past but not current events (Shulman, 2012).

The clinical significance of the number of group A strep colonies on the throat culture plate is problematic. Although patients with true acute group A strep pharyngitis are likely to have more strongly positive cultures than patients who are streptococcal carriers (i.e., individuals with chronic group A strep colonization of the pharynx), there is too much overlap in this regard to permit accurate differentiation on this basis alone using rapid antigen detection tests. A major disadvantage of throat
cultures is the delay (overnight or longer) in obtaining results. Rapid antigen detection tests have been developed for the identification of group A strep pharyngitis directly from throat swabs, with shorter turnaround time. In November 2014, Roche Diagnostics received approval from the U.S. Food and Drug Administration (FDA) for the cobas® Liat® system, a molecular test and the first to provide a result in 15 minutes. In April 2015, Alere received similar approval for its Alere™ i Strep A Rapid Molecular Test, which is designed to detect group A strep bacteria in throat swab specimens in under eight minutes (Brooks, 2015). Other similar products have since been introduced into practice.

A 2012 practice guideline from the Infectious Disease Society of America included recommendations for rapid diagnosis of group A strep pharyngitis, but made no mention of use of polymerase chain reaction molecular testing. The guideline also recommended confirming negative results in children, most often with a culture (Shulman, 2012). The European Society for Clinical Microbiology and Infectious Diseases 2012 guideline on acute sore throat noted the Centor clinical scoring system or rapid antigen test can be helpful in targeting antibiotic use. Patients who are most likely to have group A strep have 3-4 Centor criteria. The Society advised physicians to use the rapid antigen test, but if the test is negative, throat culture is not needed (ESCMID, 2012).

An Institute for Clinical Systems Improvement guideline cited a 2003 study (Uhl, 2003) of polymerase chain reaction testing that renders a culture not necessary, although the testing requires 30 - 60 minutes to perform, and longer for lab results to be obtained. The 2013 guideline concludes the test can replace rapid antigen testing and cultures for group A strep (Snellman, 2013).

A 2017 updated guideline from the Institute upheld earlier recommendations. Its authors recommended not testing for group A strep in patients with modified Centor criteria scores <3 or when viral features like rhinorrhea, cough, oral ulcers, and/or hoarseness are present. Instead, testing should be done on patients for which there is a high suspicion for group A strep, and for whom antibiotic treatment is intended (Short, 2017).

Searches

Select Health of South Carolina searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on February 2, 2018. Search terms were: “Alere i Strep A Rapid Molecular Test,” “cobas Liat,” and “group A streptococcus.”

We included:
• **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.

• **Guidelines based on systematic reviews.**

• **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

A 2014 meta-analysis of 48 studies compared sensitivity and specificity of diagnosing group A strep pharyngitis using either optical immunoassay (19 studies) or molecular (six studies) techniques. Molecular techniques were found to be superior to optical immunoassay in sensitivity (0.92 versus 0.86) and specificity (0.99 versus 0.94). In addition, findings from studies of the molecular technique varied less than did findings from the optical immunoassay studies (Lean, 2014). Of the six studies of molecular techniques, one of the more recent was a 2011 trial of 306 patients that used group A strep polymerase chain reaction assay including DNA, with a sensitivity of 96.0 percent, and a specificity of 98.6 percent (Slinger, 2011).

A recent trial found that 25.7 percent of 101 children with sore throat tested positive for group A strep using the Alere i strep A test, compared to just 0.7 percent of those without sore throat, leading to the conclusion that clinician judgment and Centor score without such an adjunctive test were not sufficiently accurate for prescribing antibiotics (Orda, 2016a). An accompanying article by the same team of Australian researchers calculated positive and negative etiological predictive values of 88 - 100 percent and 97 - 99 percent for swab samples from children with and without sore throat, using Alere TestPack +Plus Strep A. The team stated the traditional culture for streptococcus was “impracticable” because of the lengthy time awaiting a result (Orda, 2016b).

The Alere i strep A test was compared to a bacterial culture in 481 children and adults. The Alere test had a 96.0 and 94.6 percent sensitivity and specificity compared to bacterial culture, which rose to 98.7 and 98.5 percent when adjudicated by polymerase chain reaction. The 13 subjects with no group A strep growth nevertheless had positive results from the Alere i strep A test using polymerase chain reaction (Cohen, 2015).

The cobas Liat (molecular) strep A assay was used to detect strep A bacteria in 427 patients (over 95 percent of whom were age 21 and younger), as was the rapid antigen detection test. Sensitivity and specificity results were partially equivalent, i.e., 97.7 and 93.3 percent for cobas Liat and 97.7 and 84.5 percent for rapid antigen detection test (Wang, 2017).
A Mayo Clinic study of 198 specimens tested for *Streptococcus pyogenes* (a type of group A bacteria) compared the cobas Liat group A strep test to the (traditional) LightCycler polymerase chain reaction assay; both found 84 samples were positive and 114 were negative (Uhl, 2016). Two staff members of the Mayo Clinic, where nucleic acid amplification tests for *Streptococcus pyogenes* (flesh-eating bacteria within group A) have been used for over a decade, contend that these tests should replace the traditional antigen detection and culture for detecting bacterial pharyngitis, based on existing evidence (Pritt, 2016).

Relative efficacy of cobas Liat and Alere i strep A tests have yet to be assessed. However, these were compared for detection of influenza A and B viruses. The sensitivities to the A and B viruses for Alere were 71.3 and 93.3 percent, and 100 percent for both using the cobas Liat test. Specificities were 100 percent for both viruses for both tests. The lower sensitivity numbers for Alere for detecting influenza A virus were due to low-positive samples below the test’s detection limit (Nolte, 2016).

Results for some other molecular-based methods of testing for group A strep, not yet approved by the FDA, have been reported. In one case, the Simplexa™ group A strep direct assay had sensitivity and specificity of 97.4 and 95.2 percent in 1,352 samples tested for group A strep pharyngitis (Tabb, 2015). A study of 796 swabs using illumigene group A streptococcus DNA amplification assay documented the detection of group A strep in all 74 direct culture-positive specimens and 100 of 102 extracted culture-positive specimens (Anderson, 2013).

A comparison of two molecular tests for group A strep included the Alere™ i Strep A test and the BD Veritor™ System for 216 (mostly pediatric) samples. Alere i and BD Veritor had a sensitivity/specificity of 100/91.3 percent and 76.2/93.6 percent, respectively, when compared to group A strep culture. The BD Veritor missed 13 confirmed positive cases, all detected by the Alere i. The Alere i showed superior performance over the BD Veritor in detecting of group A strep pharyngitis and could potentially assist in reducing over- and under-utilization of antibiotics (Berry, 2018).

A comparison of the Hologic® group A strep direct assay with the SimplexaTM group A direct assay was made for 289 throat swabs. Results were very similar; 60 samples were positive for strep, 54 by both methods, four by Simplexa alone, and two by Holigic alone. Because Simplexa results are returned the same day, compared to 48 – 72 hours for culture, the new test would improve efficiency and treatment while maintaining efficacy (Church, 2018).

A systematic review of 14 studies compared sensitivity and specificity data for detecting influenza A and B using various tests, some of which were molecular tests Sofia FIA, BD Veritor and Alere i. Each test consistently provided sensitivities and specificities >70 percent, suggesting that effective results might occur when used for group A strep diagnosis (Koski, 2017).

**Policy updates:**
A total of three guidelines/other and three peer-reviewed references have been added to, and one guideline/other and seven peer-reviewed references removed from, this policy in February 2018.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Church (2018)</td>
<td>Key points:</td>
</tr>
<tr>
<td>Comparing molecular strep A test with traditional test</td>
<td>• Comparison of the traditional Hologic® group A strep direct assay with the SimplexaTM group A direct assay for 289 throat swabs</td>
</tr>
<tr>
<td></td>
<td>• Simplexa results returned the same day, Holigic takes 48-72 hours</td>
</tr>
<tr>
<td></td>
<td>• 60 samples were positive for strep, 54 by both methods, four by Simplexa alone, and two for Hologic alone</td>
</tr>
<tr>
<td></td>
<td>• Hologic would improve efficiency and treatment while maintaining efficacy.</td>
</tr>
<tr>
<td>Wang, 2016</td>
<td>Key points:</td>
</tr>
<tr>
<td>Efficacy of cobas Liat Strep A assay vs. rapid antigen detection test (RADT)</td>
<td>• Throat specimens from 427 patients tested with cobas Liat Strep A assay and RADT.</td>
</tr>
<tr>
<td></td>
<td>• Sensitivity and specificity of cobas Liat test were 97.7% and 93.3% to reference culture.</td>
</tr>
<tr>
<td></td>
<td>• Sensitivity and specificity of cobas Liat test were 97.7% and 84.5% vs. RADT.</td>
</tr>
<tr>
<td></td>
<td>• Sensitivity and specificity equal, cobas Liat had 15-minute turnaround time.</td>
</tr>
<tr>
<td>Uhl, 2016</td>
<td>Key points:</td>
</tr>
<tr>
<td>Efficacy of Light Cycler PCR assay vs. Liat strep A assay for S. Pyogenes throat swab</td>
<td>• LightCycler PCR assay and Liat strep A assay used for 198 specimens.</td>
</tr>
<tr>
<td></td>
<td>• Each method produced 84 positive results and 114 negative results.</td>
</tr>
<tr>
<td></td>
<td>• Sensitivity and specificity of Liat strep A assay were 100.0% and 98.3%.</td>
</tr>
<tr>
<td>Orda, 2016b</td>
<td>Key points:</td>
</tr>
<tr>
<td>Etiological predictive value for Alere TestPack +Plus Strep A</td>
<td>• Test of 101 children ages 3–15 with and without sore throat for Strep A.</td>
</tr>
<tr>
<td></td>
<td>• Positive and negative etiological predictive values were 88%–100% and 97%– 99%.</td>
</tr>
<tr>
<td></td>
<td>• Traditional cultures are “impracticable” because of 1–2 day wait for results.</td>
</tr>
<tr>
<td>Cohen, 2015</td>
<td>Key points:</td>
</tr>
<tr>
<td>Alere i strep test compared to bacterial culture</td>
<td>• Multicenter prospective trial of 481 children and adults to detect GAS.</td>
</tr>
<tr>
<td></td>
<td>• Sensitivity/specificity of Alere i are 96.0% and 94.6% compared to bacterial culture.</td>
</tr>
<tr>
<td></td>
<td>• Rates increased to 98.7% and 98.5% when adjudicated by PCR.</td>
</tr>
<tr>
<td></td>
<td>• Thirteen subjects with no GAS growth had positive results from Alere i test.</td>
</tr>
</tbody>
</table>

References

Professional society guidelines/other:


**Peer-reviewed references:**


**CMS National Coverage Determinations (NCDs):**

No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**

No LCDs identified as of the writing of this policy.
Commonly submitted codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>87651</td>
<td>Illumigene for Group A Streptococcus</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICD-10 Code</th>
<th>Description</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>J02.0</td>
<td>Streptococcal pharyngitis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HCPCS Level II Code</th>
<th>Description</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>