Corporate Medical Policy

ANA/ENA Testing AHS – G2022

File Name: ana_ena_testing
Origination: 01/01/2019
Last CAP Review: 02/2020
Next CAP Review: 02/2021
Last Review: 04/2020

Description of Procedure or Service

Definition
The antinuclear antibody (ANA) assay is used to detect autoantibodies (AAB) against intracellular antigens, originally known as antinuclear antibodies (Tan, 1989). The name antinuclear for the ANA test, maintained for historical and laboratory coding purposes, does not convey that autoantibodies to cell compartments other than the nucleus are also detected (Chan et al., 2015). Commonly used as part of the initial diagnostic workup to screen for evidence of systemic autoimmunity (Satoh et al., 2007), detection and identification of AABs are important in the diagnosis of systemic autoimmune rheumatic diseases (SARDs) such as systemic lupus erythematosus (SLE), Sjogren’s syndrome (SjS), mixed connective tissue disease (MCTD), systemic sclerosis (SSc), and idiopathic inflammatory myopathies (IIMs) (Tebo, 2017)

Related Policies
Immune Cell Function Assay
Vectra DA Blood Test for Rheumatoid Arthritis
General Inflammation Testing

***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

BCBSNC will provide coverage for ANA/ENA Testing when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

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 ANA/ENA Testing is covered

Reimbursement for testing for antinuclear antibodies (ANA) is allowed for individuals in whom the clinical suspicion of autoimmune diseases is high based on signs, symptoms and other factors.

Reimbursement for ENA panel testing of specific autoantibodies such as nRNP, SS-A, SS-B, Sm, RNP, Sc170, or Jo1 is allowed in patients with abnormal, raised antibody titer or abnormal immunological findings in serum and clinical correlation with the appropriate autoimmune disorder.
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Reimbursement for testing of dsDNA is allowed up to four (4) times per year after an initial positive ANA test, and clinical correlation.

Reimbursement for testing of specific antibodies when ANA test is negative or low positive is allowed only in the following situations:

- Testing for Anti-Jo-1 in unique clinical subset of myositis
- Testing for Anti-SSA in the setting of lupus or Sjogren’s syndrome

When ANA/ENA Testing is not covered

Reimbursement is not allowed for monitoring of disease with ANA testing or ANA titers is considered not medically necessary.

Reimbursement is not allowed for ANA and/or ENA testing of individuals with nonspecific symptoms including, but not limited to, fatigue and musculoskeletal pain if not present with other symptoms suggestive of SLE.

Reimbursement is not allowed for testing of ANA and/or ENA in individuals during wellness visits or general encounters without abnormal findings.

Reimbursement is not allowed for testing of specific antibodies in the absence of a positive ANA test in all other situations.

Serum biomarker panel testing with proprietary algorithms and/or index scores for the diagnosis of systemic lupus erythematosus is considered investigational for all applications.

Policy Guidelines

Background

Autoimmune diseases are estimated to affect 5% of the US population (Sirotti et al., 2017), are associated with increased morbidity and mortality, and are among the leading causes of death (under 65 years) and disability for women in the US (Simon et al., 2017).

The systems by which the immune system maintains tolerance to an individual's own antigens can be overcome by release of intracellular antigens following excessive cell death, ineffective clearance of apoptotic debris, inflammation induced modification of self-antigens, or molecular mimicry, leading to the production of antibodies against self-antigens or autoantibodies (AAB) (Suurmond & Diamond, 2015). Autoantibodies mediate both systemic inflammation and tissue injury and may play a role in the pathogenesis of many autoimmune diseases (Suurmond & Diamond, 2015). Generally, AAB development precedes the clinical onset of autoimmune disease (Damoiseaux, Andrade, Fritzler, & Shoenfeld, 2015) and has predictive value (Satoh et al., 2007) thus AABs serve as good serological markers to screen for evidence of autoimmunity (Aggarwal, 2014). Autoantibodies can target a variety of molecules (including nucleic acids, lipids, and proteins) from many cellular localizations (nucleus, cytoplasm, cell surface, extracellular) (Suurmond & Diamond, 2015), and different specific AABs are associated with particular diagnoses, symptoms, unique syndromes, subsets of disease, and clinical activity (Satoh et al., 2007). See Table 1 from Suurmond and Diamond (2015), below:
However, serum AAB are present in 18.1% of the general population, and titers are higher in female and increase with age (Selmi et al., 2016). Additionally, only in a few cases does the antibody titer correlates with the severity of clinical manifestations or the response to treatment (Damoiseaux et al., 2015). The use of ANA detection as a diagnostic test originated with the observation of the LE cell (Hargraves, Richmond, & Morton, 1948). Since then, several tests have been developed to detect these antibodies.

The indirect immunofluorescence (IIF) test is the most widely used assay for the detection of AAB and remains the reference method of choice (ACR, 2015). Detection of ANAs by the IIF technique demonstrates binding to specific intracellular structures within the cells, resulting in staining patterns reported using the consensus nomenclature and representative patterns defined by The International Consensus on ANA staining Patterns (ICAP) initiative (Chan et al., 2016) and the degree of binding reflected by the fluorescence intensity or titer (Tebo, 2017). The test takes advantage of a HEp-2 cell line, which have large, easy to visualize, nuclei and contain nearly all of the clinically important autoantigens, making these cells ideal for the detection of the corresponding AABs (Bloch, 2018). The ANA IIF assay using HEp-2 slide has a high sensitivity for screening of SARDs and efforts to harmonize the nomenclatures for testing and reporting (Chan et al., 2015) have made this a powerful screening tool (Tebo, 2017). The test takes advantage of a HEp-2 cell line, which have large, easy to visualize, nuclei and contain nearly all of the clinically important autoantigens, making these cells ideal for the detection of the corresponding AABs (Bloch, 2018). The ANA IIF assay using HEp-2 slide has a high sensitivity for screening of SARDs and efforts to harmonize the nomenclatures for testing and reporting (Chan et al., 2015) have made this a powerful screening tool (Tebo, 2017). The frequency of ANA in SLE and SSc is 95–100%, 50–70% in SJS and 30–50% in rheumatoid arthritis (RA) (Satoh et al., 2007), however their isolated finding in an otherwise healthy individual has a low positive predictive value which needs to be integrated with other laboratory parameters and patient risk factors (Selmi et al., 2016).

Disadvantages of the indirect immunofluorescence test include its labor-intensiveness, significant training requirements for competence, subjectivity in titer and pattern recognition, and because the staining pattern usually does not identify the responsible autoantibody, additional testing may be required (Bloch, 2018; Tebo, 2017). Automated image analysis provides a viable option for distinguishing between positive and negative results, although the ability to assign specific patterns is insufficient to replace manual microscopic interpretation (Yoo, Oh, Cha, Koh, & Kang, 2017).

If SLE is suspected based on the clinical picture following a positive ANA screen, the sera should be tested for antibodies to double-stranded DNA (dsDNA). Anti-dsDNA antibodies are present in two-thirds of patients with SLE, and they have a good association with disease activity and lupus nephritis. Serial monitoring of anti-dsDNA antibodies has modest correlation with disease activity (Aggarwal, 2014).

A positive ANA screen should also be followed by identification of sub-specificities by screening for antibodies to extractable nuclear antigens (ENAs). ENAs were identified by using saline extract

### Table 1. Autoantibody recognition in systemic autoimmune disease

<table>
<thead>
<tr>
<th>Location</th>
<th>Antibody</th>
<th>Antigen</th>
<th>Disease</th>
<th>PRR recognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear</td>
<td>Anti-Ro (SS-a)</td>
<td>Ro-RNP complex</td>
<td>SLE, Sjögren’s syndrome</td>
<td>TLR7</td>
</tr>
<tr>
<td></td>
<td>Anti-La (SS-b)</td>
<td>La antigen</td>
<td>SLE, Sjögren’s syndrome</td>
<td>TLR7</td>
</tr>
<tr>
<td></td>
<td>Anti-Sm</td>
<td>Small nuclear RNP</td>
<td>SLE</td>
<td>TLR7</td>
</tr>
<tr>
<td></td>
<td>Anti-dsDNA</td>
<td>dsDNA</td>
<td>SLE</td>
<td>TLR9</td>
</tr>
<tr>
<td></td>
<td>Anti-histone</td>
<td>Histones</td>
<td>SLE (drug-induced)</td>
<td>TLR2 and TLR4</td>
</tr>
<tr>
<td></td>
<td>Anti-S-70</td>
<td>Topoisomerase I</td>
<td>Systemic sclerosis/CREST syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anti-centromere</td>
<td>Centromere</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytoplasmic/ mitochondrial</td>
<td>ANCA</td>
<td>Myeloperoxidase (p-ANCA) and proteinase 3 (c-ANCA)</td>
<td>Vasculitis, Wegener’s granulomatosis</td>
<td>TLR4</td>
</tr>
<tr>
<td></td>
<td>ACA</td>
<td>Cardiolipin</td>
<td>Antiphospholipid syndrome, SLE</td>
<td>NLPPR</td>
</tr>
<tr>
<td>Modified proteins</td>
<td>AEPA</td>
<td>Citrullinated proteins</td>
<td>RA</td>
<td>TLR4</td>
</tr>
<tr>
<td></td>
<td>Anti-Carp</td>
<td>Carbamylated proteins</td>
<td>RA</td>
<td></td>
</tr>
<tr>
<td>Extracellular</td>
<td>RF</td>
<td>RF (IgG)</td>
<td>Antiphospholipid syndrome</td>
<td>TLR47</td>
</tr>
<tr>
<td></td>
<td>Lupus anticoagulant</td>
<td>α3 Chain of basement membrane collagen (type IV collagen)</td>
<td>Goodpasture’s syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RF</td>
<td>RF (IgG)</td>
<td>RA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phospholipids</td>
<td>α3 Chain of basement membrane collagen (type IV collagen)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACA, anti-cardiolipin antibody.
of nuclei as the antigen. Antibodies to ENA can be determined using double immunodiffusion, immunoblotting, ELISA or bead-based assay using recombinant or affinity-purified antigens. Different ENAs have an association with different connective tissue diseases (Aggarwal, 2014). See Table 1 above (Suurmond & Diamond, 2015).

Reflex tests for positive ANA screens have been proposed to improve appropriateness in diagnosis of SARDs and avoid unnecessary second level testing. For specific autoantibodies responsible for certain fluorescent ANA patterns, such as homogeneous, speckled, fine grainy (Scl70-like), nucleolar, centromeric or speckled cytoplasmic, the identification of precise autoantibody markers is considered essential while for others it is not deemed to be necessary (Tonutti et al., 2016). See Table 1 from Tonutti et al, 2016, below.

| Table 1 |
| ANA-reflex test procedure with titres ≥1:160 and typical patterns |
| **ANA-IIF pattern on HEP-2 cells** | **Reflex test(s)** |
| Nuclear homogeneous (≥1:160) | Antibodies to intracellular specific antigens (ENA) and to dsDNA/nucleosomes |
| Nuclear speckled (≥1:160) | Anti-dsDNA and antibodies to intracellular specific antigens (ENA), possibly including anti-RNA polymerase III |
| Nuclear Scl70-like (≥1:160) | Antibodies to intracellular specific antigens (ENA), possibly including anti-PM/Scl |
| Cytoplasmic speckled (≥1:160) | Antibodies to intracellular specific antigens (ENA), including anti-RNA synthetases and anti-P ribosomal |
| Pleomorphic PCNA-like (any titre) | Anti-PCNA |
| Centromere | No confirmation necessary if high titre. Execute specific test for anti-CENP B only in dubious cases (low titre or centromeric pattern not clearly seen) |

Proprietary tests exist for the assessment of SLE. For example, the “SLE-key” by ImmunArray is a molecular diagnostic test that is intended to help rule out an SLE diagnosis. This test determines the pattern of circulating antibodies and compares it to the proprietary pattern of antigens, “iCHIP”. The pattern is compared to both SLE-affected and healthy control patterns, and an algorithm is used to assess the patient’s likelihood of being affected with SLE. iCHIP was developed based on 250 affected and 250 healthy patients, and out of a 163 patient sample, the key was validated to “rule out” SLE at 94% sensitivity, 75% specificity, and 93% negative predictive value (ImmunArray, 2016, 2017). Another set of proprietary tests offered are from Exagen, under the “AVISE” line. Their line of tests includes tests for prognosis (10 biomarkers including various autoantibodies such as anti-C1q and antiribosomal P), diagnosis (10 biomarkers, includes ENA panel), and monitoring (6 biomarkers, includes anti-dsDNA and anti-C1q). AVISE CTD (standing for connective tissue disease) is intended to assist with the differential diagnosis of several autoimmune diseases and includes several ANA biomarkers, as well as an ENA panel. Other tests offered, such as AVISE Anti-CarP (evaluates autoantibodies to carbamylated proteins for rheumatoid patients) still include ANA components (AVISE, 2020).

**Clinical Utility and Validity**

A variety of manual or automated single or multiplex immunoassays have been introduced to make the process of detecting autoantibodies more efficient, including enzyme-linked immunoabsorbant assays (ELISA), fluorescent microsphere assays, and chemiluminescence immunoassays—each with different performance characteristics (Tebo, 2017). In these assays, a panel of purified native or recombinant autoantigens is prepared, and each antigen is immobilized on a solid surface (microtiter plate, fluorescent microsphere, or membrane) and incubated with diluted human serum (Bloch, 2019). The advantages of these alternative approaches to ANA IIF testing include their suitability for high-throughput testing, semi-quantification of test results, the lack of subjectivity, and the consolidation of ANA-related tests in a single platform as a positive test also provides identification of the responsible autoantibody (Bloch, 2019; Tebo, 2017). It has been estimated that solid phase assays may decrease the labor cost of ANA testing by as much as 95 percent (Bloch, 2019).
recent study which evaluated the performance of an automated chemiluminescence immunoassay (CIA) and fluorescence enzyme immunoassay (FEIA) and compared their performance to that of IIFA, both FEIA and CIA screen significantly outperformed IIF, with a higher specificity for FEIA and higher sensitivity for CIA (van der Pol, Bakker-Jonges, Kuijpers, & Schreurs, 2018). The use of solid phase assays as the initial test for the detection of ANA is concerning because the number of autoantigens that are included in solid phase assays is limited compared with the number that are present in the HEp-2 cell substrate, thus limiting sensitivity (Bloch, 2019). Consequently, IIF remains the gold standard, and in cases of strong clinical suspicion of SARD and a negative screen from a solid phase assay, IIF should be performed (van der Pol et al., 2018).

Tipu et al investigated the specificity and pattern for ANA in systemic rheumatic disease patients. 4347 samples were sent, and 397 were positive for ANA. Of these 397, 96 were positive on the anti-ENA screen and tested for anti-ENA reactivity. Anti-SSA antibodies were found in 59 of these samples. The most common ANA patterns were “coarse” and “fine-speckled” (43 and 22 of 81 respectively). However, no specific ANA pattern was associated with anti-ENA reactivity (Tipu & Bashir, 2018).

Kim et al performed a meta-analysis comparing ANA measurement by automated indirect immunofluorescence (AIIF) and manual indirect immunofluorescence (MIIF). 22 studies including 6913 positive and 1818 negative samples of manual indirect immunofluorescence (MIIF) were included. Among this cohort, 524 samples with combined systemic rheumatic diseases (SRDs), 132 systemic lupus erythematosus (SLE) samples, and 104 systemic sclerosis (SSc) samples, and 520 controls were available. Positive concordance (PC) between AIIF and MIIF was 93.7%, although PC of total pattern and titer were lower. Clinical sensitivities of AIIF vs MIIF were 84.7% vs 78.2% for combined SRDs, 95.5% vs 93.9% for SLE, and 86.5% vs 83.7% for SSc. Clinical specificities of AIIF vs MIIF were 75.6% vs 79.6% for combined SRDs, 74.2% vs 83.3% for SLE, and 74.2% vs 83.3% for SSc. The authors concluded that the sensitivities did not differ between methods, but the specificities of SLE and SSc were statistically significant changes (Kim et al., 2019).

Applicable Federal Regulations
A search for “antinuclear” on the FDA website on January 16, 2020 yielded 26 results. 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.

Guidelines and Recommendations
American College of Rheumatology (ACR, 2015; Rouster-Stevens et al., 2014; Yazdany et al., 2013)
The American College of Rheumatology published a statement on the Methodology of Testing for Antinuclear Antibodies (ACR, 2015) which states:

1. The ACR supports the immunofluorescence antinuclear antibody (ANA) test using Human Epithelial type 2 (HEp-2) substrate, as the gold standard for ANA testing.
2. Hospital and commercial laboratories using alternative bead-based multiplex platforms or other solid phase assays for detecting ANAs must provide data to ordering healthcare providers on request that the alternative assay has the same or improved sensitivity compared to IF ANA.
3. In-house assays for detecting ANA as well as anti-DNA, anti-Sm, anti-RNP, anti-Ro/SS-A, anti-La/SS-B, etc., should be standardized according to national (e.g., CDC) and/or international (e.g., WHO, IUIS) standards.
4. Laboratories should specify the methods utilized for detecting ANAs when reporting their results.
The ACR also have developed a list of 5 tests, treatments or services that are commonly used in rheumatology practice, but their value should be questioned. The ANA testing was the first on the final top 5 items list with level of evidence Grade 1C. In their review, the Task Force considered recommendations currently published by CAP, ACR, ISLM. They have issued the following recommendation: “Do not test antinuclear antibody (ANA) subserologies without a positive ANA and clinical suspicion of immune-mediated disease (Yazdany et al., 2013).” For their list of 5 tests for pediatric rheumatology, two pertain to ANA testing (Rouster-Stevens et al., 2014). “Do not order autoantibody panels unless positive ANAs and evidence of rheumatic disease. There is no evidence that autoantibody testing (including ANA and autoantibody panels) enhances the diagnosis of children with musculoskeletal pain in the absence of evidence of rheumatic disease as determined by a careful history and physical examination.” They also state, “Do not repeat a confirmed positive ANA in patients with established JIA or SLE (Rouster-Stevens et al., 2014).”

**Canadian Rheumatology Association (CRA)**

In the 2018 CRA guidelines and recommendations for assessing and monitoring SLE, they state, “Best clinical practice includes a complete history and physical examination at baseline, with laboratory monitoring possibly including but not limited to complete blood count (CBC), liver enzymes, creatine kinase, creatinine and estimated glomerular filtration rate (eGFR), urine routine/microscopic (urinalysis), urine protein-creatinine ratio, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), complements (C3, C4), anti-dsDNA, antinuclear antibodies, antibodies to extractable nuclear antigens, antiphospholipid antibodies (aPL), lupus anticoagulant (LAC), anticardiolipin (aCL), anti-β2-glycoprotein I (anti-β2-GP1), and lipid profile. Follow-up (sic) laboratory monitoring will depend on the patient’s clinical status and may include CBC, eGFR, urinalysis, urine protein-creatinine ratio, CRP, and/or ESR, C3, C4, and anti-dsDNA antibodies (Keeling et al., 2018).”

**ChoosingWisely Canada**

The CRA also made a recommendation regarding ANA through ChoosingWisely Canada. In it, they note “Don’t order ANA as a screening test in patients without specific signs or symptoms of systemic lupus erythematosus (SLE) or another connective tissue disease (CTD)” (CRA, 2019).

**British Society for Rheumatology (BSR) (Gordon et al., 2018)**

In 2018, the BSR released their guidelines concerning the management of SLE in adults. With a Grade B recommendation, they state that the diagnosis of SLE requires at least one immunological abnormality alongside clinical features of the disease. “If there is a clinical suspicion of lupus, blood tests (including serological marker tests) should be checked.” Also, with a Grade B recommendation they state that a positive ANA test in the absence of clinical features of an autoimmune rheumatic disease is of poor value since approximately 5% of all adults will test positive; moreover, a negative ANA test result indicates low probability of SLE since 95% of SLE patients will test positive. “The presence of anti-dsDNA antibodies [Grade B], low complement levels [Grade C] or anti-Smith (Sm) antibodies [Grade C] are highly predictive of a diagnosis of SLE in patients with relevant clinical features. Anti-Ro/La and anti-RNP antibodies are less-specific markers of SLE [Grade C] as they are found in other autoimmune rheumatic disorders as well as SLE [Grade C].” They do state the following: “All lupus patients should be tested for aPLs because their presence indicates a group at increased risk of arterial/venous thrombotic events and adverse pregnancy outcomes.” Regarding the use of antibodies in monitoring the disease, they state, “Serial anti-dsDNA antibodies and C3 and C4 levels are useful because rising, high anti-dsDNA antibodies and falling, low complement levels are associated with flare, particularly in patients with LN. In general, concomitantly rising anti-dsDNA titres and decreasing C3 and/or C4 levels are more important predictors of current or impending flares than the absolute levels, and levels of anti-dsDNA antibodies may actually fall at the time of flare (Gordon et al., 2018).” They specifically state that ANA, anti-Sm, and anti-RNP antibodies do not require repeat testing.
The BSR also makes the following recommendation through ChoosingWisely UK: “Testing ANA and ENAs should be reserved for patients suspected to have a diagnosis of a connective tissue disease, e.g. lupus. Testing ANA and ENAs should be avoided in the investigation of widespread pain or fatigue alone. Repeat testing is not normally indicated unless the clinical picture changes significantly” (BSR, 2018).

**European League Against Rheumatism/American College of Rheumatology (EULAR/ACR, 2019)**

The EULAR/ACR published a joint guideline to develop new classification criteria for systemic lupus erythematosus (SLE). In it, they stated that antinuclear antibodies (ANA) “at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test” was to be an “entry criterion”: if absent, the condition is not SLE; if present, apply additive criteria such as leukopenia or oral ulcers. Antiphospholipid antibodies, complement proteins, and SLE-specific antibodies (anti-dsDNA antibodies, Anti-Smith antibodies) are all included as additive criteria for SLE diagnosis (Aringer et al., 2019).

**American Academy of Pediatrics (AAP, 2019)**

The AAP released guidelines through ChoosingWisely. In it, they state “Do not order antinuclear antibody (ANA) and other autoantibody testing on a child unless there is strong suspicion or specific signs of autoimmune disease” (AAP, 2019).

**European Dermatology Forum S1 (2017)**

This guideline addresses sclerosing diseases of the skin, such as localized scleroderma, systemic sclerosis and overlap syndromes.

The guideline recommends against routine screening for antinuclear antibodies. Screening for extractable nuclear antigens is also only recommended to “confirm or exclude” systemic sclerosis. The Forum also mentions that both rheumatoid factor and anti-cyclic citrullinated peptide antibodies may be detected in systemic sclerosis, but are associated with arthritis (Knobler et al., 2017).

**European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN, 2018)**

The ESPGHAN notes that positivity for circulating autoantibodies is “key” for diagnosis of autoimmune hepatitis (AIH). They also state that identifying certain autoantibodies may differentiate between the two types of AIH (“ANA and SMA characterize AIH-1; anti-LKM1 and anti-LC-1 define AIH-2”) (Mieli-Vergani et al., 2018).

**Billing/Coding/Physician Documentation Information**

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. They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: 86038, 86039, 86225, 86235, 0039U, 0062U*

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.
Scientific Background and Reference Sources


ANA/ENA Testing AHS – G2022


Policy Implementation/Update Information

1/1/19 New policy developed. BCBSNC will provide coverage for ANA/ENA Testing when it is determined to be medically necessary because the medical criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (an)

5/14/19 Reviewed by Avalon 1st Quarter 2019 CAB. In the “When Covered” section, 2nd statement revised to read: ENA panel testing of specific autoantibodies such as nRNP, SS-A, SS-B, Sm, RNP, Sc170, or Jo1 considered medically necessary in patients with abnormal, raised antibody titer or abnormal immunological findings in serum and clinical correlation with the appropriate autoimmune disorder. The following statement was added: Testing of specific antibodies when ANA test is negative or low positive is considered medically necessary only in the following situations: Testing for Anti-Jo-a in unique clinical subset of myositis or Testing for Anti-SS-A in the setting of lupus or Sjorgren’s syndrome. Added codes 81599, 0039U, 0062U to the Billing/Coding section. Medical Director review 4/2019. (an)

10/29/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (gm)

03/10/20 Specialty Matched Consultant Advisory Panel review 2/19/2020. No change to policy statement. (eel)

5/12/20 Reviewed by Avalon 1st Quarter 2020 CAB. Medical Director review 4/2020. Description, Policy Guidelines, and References updated. When not covered section clarified with “Reimbursement is not allowed for testing of ANA and/or ENA in individuals during wellness visits or general encounters without abnormal findings.” (eel)
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.