The identification and diagnosis of autoimmune disorders can present nurse practitioners (NPs) with unique challenges. Nearly 100 autoimmune disorders have been identified, and women are disproportionately affected. In the initial stages of these diseases, symptoms can be vague, such as fatigue, arthralgia, weight loss, and unexplained fever, complicating the approach to evaluation. It is important for the NP to recognize possible symptoms and early presentation of autoimmune disorders so that appropriate testing and referrals to specialists can be initiated for prompt diagnosis.

Selecting the initial laboratory tests that are sensitive and specific to each disease and correctly interpreting the results is essential. A “shotgun” approach to diagnostic testing should be avoided to reduce unnecessary costs and delays in diagnosis. The NP providing primary care for patients with autoimmune disorders also has an important role in improving outcomes by coordinating care among specialists, providing patient counseling, monitoring for any complications, and addressing reproductive health. This article presents three of the most...
Box 1. Initial diagnostic tests if suspicion for rheumatoid arthritis

- Rheumatoid factor
- Anti-citrullinated peptide antibodies
- Erythrocyte sedimentation rate
- C-reactive protein
- Complete blood count
- Comprehensive metabolic panel
- Plain radiographs of hands and feet

common autoimmune disorders, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and Sjögren syndrome (SS), along with current recommendations for the NP on initial testing, referrals, and primary care considerations.

When a patient presents with complaints of constitutional symptoms such as fatigue and generalized pain, or concerns with joint pain, skin rashes, or even recurrent miscarriage, the NP may suspect an autoimmune disorder and recommend further testing. Choosing the appropriate tests will help to prevent misdiagnosis and unnecessary costs for the patient and can help to expedite specialty consultations.2 The antinuclear antibody (ANA) titer is commonly ordered as an initial test when evaluating for possible autoimmune or rheumatologic conditions. The NP will want to consider a few caveats when ordering and interpreting an ANA titer, which is a highly sensitive but not specific test. For example, most patients with SLE will have a positive ANA. However, other rheumatologic and nonspecific autoimmune disorders such as SS, Hashimoto’s thyroiditis, and even type 1 diabetes mellitus can cause the ANA titer to be positive.2 Once a patient has a positive ANA titer, it is rarely useful to repeat the test. ANA levels can fluctuate and are not an indication of disease activity.2 Repeating a negative ANA has been proven to have little clinical value and results in high costs.3 Furthermore, the American College of Rheumatology (ACR) recommends against ordering additional autoantibody panels unless the ANA titer is positive.4 Rheumatoid factor (RF) titers are commonly ordered when evaluating for rheumatologic conditions. The higher the titer, the more likely a patient will have poor outcomes related to erosive joint disease and systemic manifestations. However, a positive RF is not exclusive to RA. Patients with SLE, SS, and other connective tissue disorders may have a positive RF as well.2 The ACR provides clinical practice guidelines, including recommendations for autoimmune testing based on current evidence and cost-effectiveness on their website. NPs can also find information on reproductive health concerns on this site: rheumatology.org.4

Rheumatoid arthritis

Rheumatoid arthritis is a chronic systemic autoimmune disease that primarily affects the synovial joints. The disease is more common in women than men, and symptoms typically present in middle age. The exact cause of RA is unknown, but genetic susceptibility has been documented. Other risk factors for development of RA include smoking, obesity, and periodontal disease.5

Patients commonly present with symmetric and polyarticular joint pain and swelling, initially in the metacarpophalangeal and proximal interphalangeal joints of the hands, as well as in the wrists, thumbs, and toes. Arthritis in the larger joints of shoulders, elbows, knees, and ankles indicates more severe or advanced disease. Other vague symptoms patients with RA may report include achiness or stiffness, which is worst in the morning, carpal tunnel-type symptoms, weight loss, fatigue, or depression.5

The NP seeing a patient with symptoms of RA should promptly initiate testing, as early diagnosis leads to improved outcomes. The appropriate antibody screening includes RF and anti-citrullinated peptide antibodies (ACPA). However, a negative RF does not entirely rule out RA.6 ACPA have high specificity to RA and can be useful in diagnosis and prognosis. These antibodies can be detected many years before RF is detected or before onset of RA symptoms. The presence of ACPA is also associated with more progressive and destructive RA disease (Box 1).5,7,8

The NP also should consider including a biomarker test for systemic inflammation, either an erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).5,8 Screening for infection, anemias, and other chronic disease with a complete blood count (CBC) and complete metabolic panel (CMP) can be useful.5 Finally, plain radiographs of the hands and feet should be performed to assess for joint swelling or erosion, although changes may not be evident in early RA.5,8

Patients with seropositivity or clinical presentation of RA should immediately be referred to a rheumatology specialist for further evaluation and management. Early treatment of RA leads to improved long-term outcomes. Patients with RA require a multidisciplinary approach to care and often benefit from physical and occupational therapy to improve chronic pain, strength, and daily functioning. The NP providing primary care for the patient with RA should consider possible interactions with or contraindications to the rheumatologic medications and consult with the specialist as needed. Mon-
Systemic lupus erythematosus

Systemic lupus erythematosus is another chronic autoimmune disease that can manifest in numerous ways, making diagnosis difficult. Patients typically have patterns of relapsing and remitting symptoms that can range from mild to life-threatening. SLE is no longer considered to be a “rare” disease and has a higher incidence in women and Black and Hispanic people, most commonly during child-bearing ages. Both hereditary and environmental factors are believed to play a role in its development.

Typically, patients initially present with constitutional complaints such as unexplained fever, fatigue, or weight loss. Other common presenting symptoms include joint pain, unexplained rashes and hair loss, Raynaud phenomenon, and concomitant miscarriages. SLE can also affect the urinary, cardiovascular, respiratory, immune, and nervous systems. The NP should consider screening for SLE in any patient who presents with unexplained symptoms that involve two or more systems.

The NP should begin the diagnostic workup for suspected SLE with an ANA test. The majority of patients with SLE have a positive ANA. Complement C3 and C4 levels are useful in assessing for SLE, as decreases in these proteins reflect active immune disease. The NP can consider ordering an ESR or CRP to assess for systemic inflammation indicating disease severity. The CMP and CBC are useful in assessing for hematologic issues or organ system involvement. A urinalysis should be ordered to assess for proteinuria, which can indicate manifestations of lupus nephritis. If the initial ANA is positive, antibody tests such as anti-double-stranded DNA, anti-Smith, anti-RNP, antiphotolipin, and antiphospholipid antibodies (aPL) may subsequently be ordered by the NP. The patient, however, should be referred to a rheumatology specialist for further evaluation. These additional antibody tests are not recommended as part of the initial screening for SLE. If the ANA is negative but the NP still suspects SLE based on the patient’s presentation, a rheumatology referral is warranted (Box 2).

In addition to prompt recognition of SLE symptoms, testing, and referral for diagnosis, the NP has an important role in the primary care of patients with SLE. The NP can educate these patients on the importance of monitoring comorbidities such as renal and cardiovascular disease and provide coordination between other specialists, such as dermatology or nephrology. Patients should be educated on recognizing the signs of flare ups and how these can be managed. The NP can facilitate efforts on tobacco cessation, weight control, and physical activity, which will help to address chronic pain and comorbidities related to SLE. Patients should be educated on the importance of annual eye exams and avoiding sun exposure. Individuals with SLE may be at increased risk for cervical neoplasia and should be regularly screened for cervical cancer. Age-appropriate immunizations should be recommended, including vaccines for human papillomavirus, pneumococcus, influenza, and herpes zoster.

These individuals also are at a 2.53-fold increased risk for osteoporosis, especially if glucocorticoids (GC) have been part of their treatment regimen, and they should be advised on ways to maintain optimal bone health. When assessing these patients, the NP should consider that none of the existing fracture risk assessment tools has been validated for use in patients with SLE. Patients with SLE should begin bone density screening at menopause or possibly even sooner depending on additional risk factors such as prior GC use, renal disease, and vitamin D deficiency.

Women with SLE that is stable or with low disease activity can safely use most forms of contraception.

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<th>Box 2. Initial laboratory testing if suspicion for systemic lupus erythematosus</th>
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Autoimmune disorders such as RA, SLE, and SS can be difficult to recognize and diagnose in women, especially in their early stages. Symptoms can be vague and overlap with numerous other conditions.

The CDC US Medical Eligibility Criteria for Contraceptive Use has categorized all combination hormonal contraceptives, all progestin-only contraceptives, and hormonal IUDs as category 2 for use by women with SLE who are aPL negative. Category 2 indicates a condition for which the advantages of using the method generally outweigh the theoretical or proven risks.¹⁷ The CDC advises that women with positive aPL status should avoid the use of any of the hormonal contraceptive methods due to increased thrombosis risk.¹⁷ Unless they have severe thrombocytopenia, they can use the nonhormonal IUD.¹⁷

The ACR published contraceptive guidelines in 2020 that provide some differing recommendations. The ACR recommends against the use of the transdermal estrogen-progestin patch because greater estrogen exposure can increase the risk for SLE flare or thrombosis.⁹ The ACR also recommends that women with moderate or severe disease activity, including lupus nephritis, should utilize progestin-only or IUD forms of contraception.⁹ Hormone replacement therapy for menopausal symptoms is also contraindicated in women with a positive aPL.⁹

Women with SLE considering pregnancy should consult with their rheumatology specialist to discuss any additional antibody testing that may be needed, as well as possible medication changes necessary prior to conception. Women with a positive aPL are at increased risk for thrombosis and pregnancy loss and should consult with maternal-fetal medicine specialists.⁹

**Sjögren syndrome**

Along with RA and SLE, SS is a relatively common chronic, systemic autoimmune disease. Sjögren syndrome typically manifests in middle-aged women and involves lymphocytic infiltration and inflammation of the exocrine glands.¹⁸ The pathogenesis of SS is believed to be an interaction between genetic factors and environmental and viral triggers.¹⁹

Patients with SS typically present with sicca symptoms including dryness of the eyes, oral cavity, larynx, pharynx and vagina. They may report general symptoms such as fatigue, arthralgia or myalgia, depression, and anxiety.²⁰ On exam, the NP may note swollen or tender parotid glands and multiple dental caries.²¹ Patients may also experience numerous systemic manifestations such as peripheral neuropathy, xerosis, and pulmonary or renal disease.²₀,²¹ Finally, individuals with SS are at increased risk for the development of lymphoma compared to the general population.¹⁸

Diagnosing SS can be challenging even for specialists. Multiple classification criteria have been created over the past couple of decades by panels of experts in the United States and internationally. These criteria each considered different laboratory and physical findings as a means of diagnosis. In 2016, the ACR and the European League Against Rheumatism published a consensus classification criteria for diagnosis of SS.²² Diagnosis and management is primarily addressed by rheumatology specialists in collaboration with specialists in ophthalmology and dental or oral medicine. Patients suspected of having SS undergo salivary gland biopsies, saliva testing, and ophthalmologic testing of tear production and the conjunctiva.²²

If the NP suspects a patient may have SS, autoimmune laboratory testing can be ordered, which would include the ANA, RF, and additionally anti-SSA/Ro antibodies. Due to low specificity, however, these tests carry less weight in determining diagnosis. Regardless of the results of the laboratory testing, if an NP suspects a patient may have SS based on presentation, the patient should be referred for specialty evaluation and testing.¹⁹,²²

The NP in primary care can be instrumental in recognizing symptoms of SS, monitoring for complications, and coordinating the multidisciplinary team involved in the care of these patients. The NP should educate patients with SS on the importance of avoiding alcohol and smoking, practicing excellent oral hygiene, and utilizing products such as artificial tears, saliva substitute, and chewing gum to ease their sicca symptoms.²³ The NP should also stress the importance of regular examinations to monitor for lymphoma.¹⁸ Patients with SS can safely use all forms of contraception and menopausal hormone replacement therapy.⁹ Patients also should be
counseled that some of the immunomodulatory treatments used in SS are contraindicated with pregnancy and breastfeeding.20

Conclusion
Autoimmune disorders such as RA, SLE, and SS can be difficult to recognize and diagnose in women, especially in their early stages. Symptoms can be vague and overlap with numerous other conditions. Understanding which diagnostic tests to order as well as their sensitivity and specificity can aid in prompt diagnosis and appropriate specialty referrals. In addition to initial testing and referrals, the NP providing primary care can be instrumental in coordinating multidisciplinary care and educating these patients on health promotion and monitoring for disease complications. Early recognition, diagnosis, and effective management are essential for improved outcomes in patients with autoimmune disorders.

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