A SUPPLEMENT TO

Rheumatology News

This supplement is supported by Exagen Diagnostics, Inc.

DIAGNOSING CTD IN CLINICAL PRACTICE

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Introduction

More than 11 million individuals in the United States suffer from autoimmune connective tissue disease (CTD).[1] One of the primary challenges facing the physicians who manage this population is the accurate determination of the specific disease(s) when overlapping symptoms are highly prevalent. Accurate diagnosis is critical for patient management, especially early in the disease course, to enable the appropriate course of treatment. The problem with differential diagnosis lies in the unspecified symptoms that often occur with CTD. Rheumatoid Arthritis (RA), Sjögren's Syndrome, Systemic Lupus Erythematosus (SLE), antiphospholipid syndrome (APS), systemic sclerosis, and polymyositis/dermatomyositis (PM/DM), to name a few, all present with a similar spectrum of symptoms, including fatigue, fever, muscle and joint pain, among others. Judgment based on symptoms alone can result in misdiagnosis and, in turn, improper treatment.[2] At the same time, prompt diagnosis is crucial because treatment early in the disease course can prevent irreversible joint and organ damage, thereby improving patient and economic outcomes.[1,3] Clinicians must look beyond symptomology for assistance in formulating a precise diagnosis. This is where classification criteria and serologic testing can be useful in a patient's clinical work-up.

The American College of Rheumatology (ACR) classification criteria for rheumatic diseases were initially developed as a categorization tool for clinical studies. The ACR criteria have since extended into the clinical setting for diagnostic purposes, in spite of the fact that they were never intended as such. As documented in the literature, using the ACR criteria as a diagnostic tool can lead to delayed or misdiagnosis of CTD.[2,4,5] Likewise, the Systemic Lupus International Collaborating Clinics (SLICC) guidelines are not always reliable diagnostic criteria in clinical practice.[6]

Another valuable tool clinicians use to help with the diagnosis of CTD is serologic testing. The traditional model of cascading serologic testing is a challenge for the patient as it can be stressful, burdensome, costly, and often results in a significant delay of diagnosis. CTD diagnostic testing usually begins with an anti-nuclear antibody (ANA), but while ANA testing is highly sensitive it can result in many false positives due to its low specificity. ANA alone also does not provide enough information to serologically identify most disease states. Due to this limitation, physicians usually run

additional serologies depending on the patient's symptoms and their clinical suspicion.

The high prevalence of overlapping symptoms often causes challenges because with a cascading testing model clinicians are running serologic tests for a single disease model when they potentially need to be looking for multiple diseases. Common overlap scenarios occur between RA, SLE, Sjögren's Syndrome, Mixed CTD (MCTD) and fibromyalgia, as well as with the population of undiagnosed, symptomatic patients that are present in every practice. Symptoms such as fatigue, arthralgias, and myalgias are also present across the spectrum of CTD. Therefore, a large and growing number of physicians find it useful to validate their suspicions by simultaneously ordering multiple categories of serologic testing such as the various extractable nuclear antigen antibodies (ENA) tests, RA markers, APS testing, and autoimmune thyroid assays, amongst others. Additionally, quality and standardization of testing plays a critical role so a physician can be confident in the accuracy of results as well as the precision of the lab and testing platforms.

Avise CTD is a validated 22-marker diagnostic tool that helps clinicians accurately differentiate overlapping symptoms in order to support a confident diagnosis (**Figure 1**). Avise CTD includes ENA markers to help distinguish CTD, an RA panel to help rule-in or rule-out Rheumatoid Arthritis, an APS panel to help with risk for thrombosis and cardiovascular events, and a thyroid panel to help rule-in or rule-out Graves' disease and Hashimoto's disease. Additionally, Avise CTD incorporates biologically-relevant CB-CAPs (Cell-Bound Complement Activation Products) technology to deliver a test with 80% sensitivity and 86% specificity for SLE—a performance that cannot be found with any other CTD diagnostic panel.[7] This convenient comprehensive panel provides physicians with the information needed to help accurately rule-in and rule-out disease.

Developed to support physicians early in a patient's clinical work-up, Avise CTD can be useful in a myriad of clinical scenarios such as with new patients/PCP referrals; for undifferentiated patients where potential overlap exists; and with previously diagnosed patients whose symptoms are not under control. This scientifically proven diagnostic may help avoid delays in needed therapy and also prevent the administration of inappropriate treatments and any potential adverse effects from those medications. As a result, earlier and more accurate diagnosis with the addition of Avise CTD to the clinical workup can benefit both patient and provider by ascertaining diagnosis sooner and alleviating patient anxiety.

The following pages highlight case studies from respected Rheumatologists across the nation to help illustrate the value and utility of the Avise CTD in clinical practice.

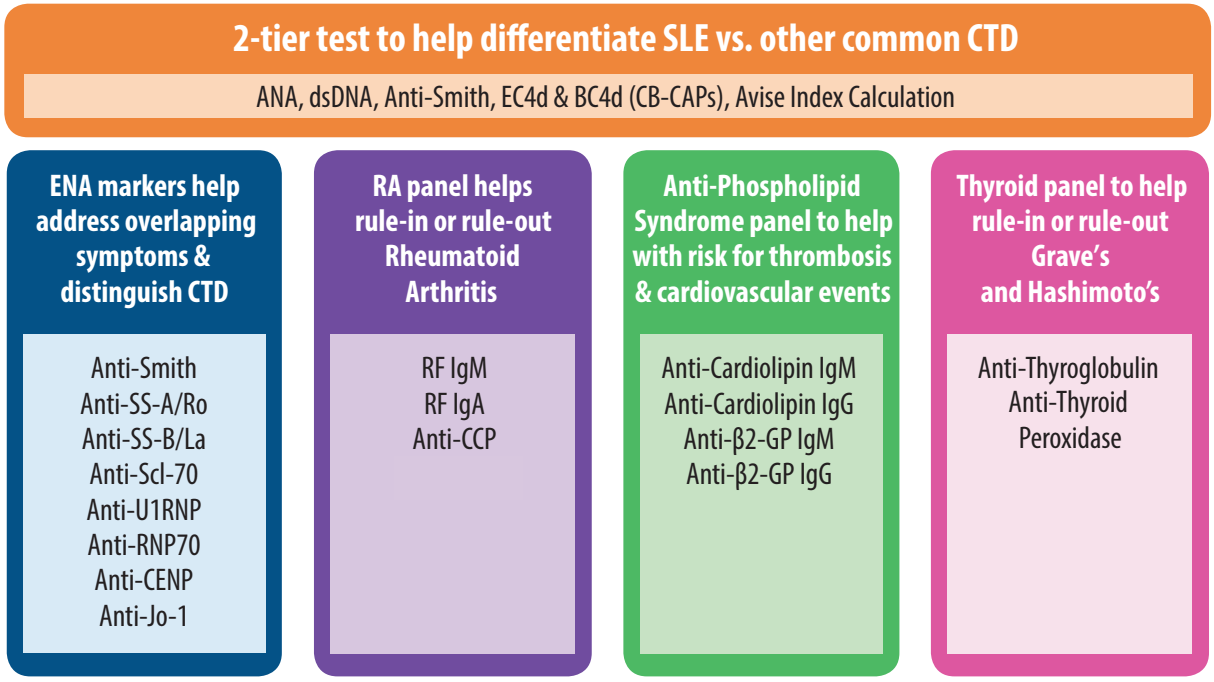

FIGURE 1. Avise CTD Offers a Comprehensive Panel to Help With the Differential Diagnosis of Autoimmune CTD

Case 1

John Goldman, MD, MACR, FACP, CCD | Chief of Rheumatology, Emory St. Joseph's Hospital, Atlanta, GA

A 39-year-old Caucasian female patient first saw Dr. Goldman in November 2013 with the chief complaint of Rheumatoid Arthritis and multiple painful nodules. Based on chart notes, the patient began noticing symptoms including joint pain, stiffness, deformities, muscle weakness, and finger color change in cold weather in the summer of 2004. She has a history of positive ANA, Rheumatoid Factor (RF), cyclic citrullinated peptide (CCP), and Raynaud's in her teens and was diagnosed with undifferentiated CTD. Her family history consists of hypertension, high cholesterol, arthritis, cancer, and osteoporosis. The patient had been on a variety of medications, including methotrexate, sulfasalazine, leflunomide (Arava), infliximab (Remicade), certolizumab (Cimzia), and hydroxychloroquine (Plaquenil). She did not respond to sulfasalazine, leflunomide, and infliximab and was intolerant to some of the disease-modifying antirheumatic drugs (DMARDs). Dr. Goldman put the patient on tocilizumab (Actemra) SQ, but not all symptoms were resolved.

Over the course of 8 months and 2 follow-up visits, the patient remained symptomatic with complaints of swollen hands, ankles, and other joints; problems with thinking; and increasing nodule pain. As a result, Dr. Goldman ordered Avise CTD and Avise SLE Prognostic to confirm that the patient truly had overlap disease, identify the diseases involved, and determine if there could be a risk for organ involvement.

The Avise CTD results showed positive markers of ANA by ELISA and IIF with a speckled pattern, anti-U1RNP, anti-RNP70, RF IgM, anti-CCP, anti-mutated citrullinated vimentin (MCV), and anti-thyroid peroxidase. The Avise SLE Prognostic markers were negative and the Cell-Bound Complement Activation Product markers—EC4D and BC4D—while negative were borderline, which could indicate developing SLE.

Positive Markers	Results	Reference Range
ANA by IIF	1:640 (Speckled)	Negative (<1:80); Positive (≥1:80)
ANA by ELISA	107 Units	<20 (Negative); 20-59 (Positive); ≥60 (Strong Positive)
Anti-U1RNP	108 U/mL	<5 (Negative); 5-10 (Equivocal); >10 (Positive)
Anti-RNP70	102 U/mL	<7 (Negative); 7-10 (Equivocal); >10 (Positive)
Rheumatoid Factor IgM	91 U/mL	<3.5 (Negative); 3.5-5 (Equivocal); >5 (Positive)
Anti-CCP	170 U/mL	<7 (Negative); 7-10 (Equivocal); >10 (Positive)
Anti-MCV	138 U/mL	<20 (Negative); ≥20-70 (Positive); >70 (Strong Positive)
Anti-Thyroid Peroxidase	535 IU/mL	<60 (Negative); 60-100 (Equivocal); >100 (Positive)

The Avise results, along with the clinical assessment, provided Dr. Goldman with the information necessary to make a confident diagnosis of MCTD consisting of Rheumatoid Arthritis, potential SLE/Lupus, and Hashimoto's Thyroiditis. He was also able to rule-out internal organ involvement. Her disease activity measures remained high: Rapid 3 = 9.3, DAS28CRP = 4.19, DAS28ESR = 5.35, CDAI = 39, and SDAI = 39.45. Her VECTRA DA was high at 51. Based on this information, Dr. Goldman made adjustments to her medications: prednisone 1 mg QD, folic acid 1 mg QD, methotrexate 20 mg QW, probiotic QD, daily vitamin QD, and Actemra SQ 162 mg/0.9 ml Q2W, and requested a follow up in 3 months to evaluate her status.

Did You Know?

In a recent study, elevated CB-CAPs (Cell-Bound Complement Activation Products), EC4d & BC4d, were proven to deliver a **22% higher sensitivity than reduced C3/C4**. Among SLE patients with low disease activity (SELENA-SLEDAI subscore=0), CB-CAPs were 26% more sensitive than C3/C4.

Additionally, when the Avise algorithm is added, the sensitivity for CB-CAPs continues to increase up to 41% in patients with less active disease.[8]

Case 2

Soha Dolatabadi, MD | Private Practice, Los Angeles, CA

A 62 year-old African American female was referred to Dr. Dolatabadi by her PCP with the chief complaint of leg pain and history of chronic obstructive pulmonary disease (COPD), peripheral vascular disease, transient ischemic attack (TIAs), hypertension and hypothyroidism. The patient was diagnosed with SLE 25 years ago by a Rheumatologist based on her clinical presentation of arthritis and headaches, along with previous unspecified serology.

During the initial assessment, the patient admitted to having mouth sores, hair loss, pain and swelling of the joints, as well as insomnia, Raynaud's, intermittent rash and shortness of breath. Through her clinical examination, Dr. Dolatabadi discovered diminished breath sound at the base of both lungs, decreased range of motion in the right shoulder and swelling in the metacarpophalangeal joints (MCPs). The patient also had significant tenderness all over her body, including the classic tender points indicating potential fibromyalgia.

Based on the patient's history and initial clinical assessment, Dr. Dolatabadi had multiple suspicions she wanted to confirm through serology, including SLE, MCTD or SLE/RA overlap, along with probable anti-phospholipid syndrome. Dr. Dolatabadi was also confident that this patient has fibromyalgia syndrome. As a result, Dr. Dolatabadi ordered Avise CTD and Avise SLE Prognostic in anticipation of receiving valuable information to rule-in or rule-out possible SLE, RA, other CTDs and/or cardiovascular involvement.

The Avise CTD and Avise SLE Prognostic test results came back positive for ANA by ELISA and IIF with a homogeneous pattern, EC4d and BC4d, Rheumatoid Factor IgM, anti-Cardiolipin IgM, anti-ß2-Glycoprotein IgM and anti-PS/PT IgM - all other markers were negative.

The Avise results, along with the clinical assessment, provided Dr. Dolatabadi with information needed to rule-in SLE and rule-out MCTD. With this diagnosis, Dr. Dolatabadi optimized the patient's hydroxychloroquine to 400mg po daily and kept her on 17.5mg of methotrexate weekly along with acetylsalicylic acid (ASA) 81mg po daily and clopidogrel (Plavix) to control SLE and fibromyalgia overlap. She plans to monitor the patient's levels of hydroxychloroquine and methotrexate in 3 months using Avise HCQ and Avise MTX to determine if the exposure to these drugs is fully optimized, as well as retest for confirmation of APS.

Positive Markers	Results	Reference Range
ANA by IIF	1:320 (Homogeneous)	Negative (<1:80); Positive (≥1:80)
ANA by ELISA	109 Units	<20 (Negative) 20-59 (Positive) ≥60 (Strong Positive)
EC4d	17 Net MFI	≤12 (Negative); >12-75 (Positive); >75 (Strong Positive)
BC4d	137 Net MFI	≤48 (Negative); >48-200 (Positive); >200 (Strong Positive)
Rheumatoid Factor IgM	6.7 U/mL	<3.5 (Negative); 3.5-5 (Equivocal); >5 (Positive)
Anti-Cardiolipin IgM	95 CU	≤20 (Negative); >20 (Positive)
Anti-ß2-Glycoprotein IgM	124 CU	≤20 (Negative); >20 (Positive)
Anti-PS/PT IgM	42 U/mL	≤30 (Negative); >30 (Positive)

Ruling-Out Primary Fibromyalgia

Fibromyalgia is a common non-autoimmune disorder that is difficult to diagnose because its symptoms often mimic those of CTD. A misdiagnosis can lead to inappropriate or delayed treatment and unnecessarily expose the patient to the hazards of powerful drugs. Therefore, it is important that comprehensive CTD tests are considered to help with the differential diagnosis and to rule-out fibromyalgia by exclusion.[11,12]

Case 3

James Mossell, DO | Tift Regional Medical Center, Tifton, GA

A 53-year-old African American female patient was referred to Dr. Mossell in 2014 by her primary care physician (PCP) with complaints of polyarthralgias, reoccurring rash on chest and arms, fatigue, and dry eyes and mouth—all of which could be suggestive of SLE/Lupus or other CTD. Because the symptoms and examination did not clearly indicate a specific disease, Dr. Mossell ordered Avise CTD to help distinguish the overlapping symptoms. The test report came back with a positive ANA (nucleolar IIF pattern) and elevated anti-MCV.

Positive Markers	Results	Reference Range
ANA by IIF	1:320 (Nucleolar)	Negative (<1:80); Positive (≥1:80)
ANA by ELISA	29 Units	<20 (Negative); 20-59 (Positive); ≥60 (Strong Positive)
Anti-MCV	37 U/mL	<20 (Negative); ≥20-70 (Positive); >70 (Strong Positive)

Based on these results and the clinical assessment, Dr. Mossell was able to rule-in Rheumatoid Arthritis with possible overlap with SLE/Lupus. Treating for RA due to joint inflammation and positive anti-MCV, Dr. Mossell initially put the patient on methotrexate; however, she was intolerant, so he prescribed prednisone, leflunomide (Arava), and hydroxychloroquine (Plaquenil). At that time, the patient decided to get a second opinion at Emory University in Atlanta, GA and was told it was unlikely she had RA, but they could not arrive at a specific diagnosis.

Three months later, the patient came back to Dr. Mossell. She developed numerous subcutaneous nodules that were biopsied and appeared consistent with panniculitis; there was no evidence of cancer or infection. Because of these symptoms and failure to respond to treatment, Dr. Mossell repeated the Avise CTD to see if any new serologic data presented. The results were very similar with the previous Avise CTD, showing positive ANA (nucleolar IIF pattern) and elevated anti-MCV.

Still suspecting developing disease and potential RA/Lupus overlap, Dr. Mossell repeated the Avise CTD three months later at the patient's next visit. These results again indicated a positive ANA (nucleolar IIF pattern). However, the anti-MCV was negative, the Cell-Bound Complement Activation Products markers—EC4d and BC4d—were positive and the Avise Index was also positive at 0.6. This was consistent with Dr. Mossell's suspicion and what he saw clinically: her disease seemed to have evolved from suspected RA to SLE/Lupus. The patient is continuing leflunomide, hydroxychloroquine, and prednisone, but still has nodules, so Dr. Mossell plans to put her on rituximab (Rituxan) or belimumab (Benlysta). He will also run the Avise HCQ monitoring test in 6 months to make sure HCQ exposure is optimized and the patient is compliant.

Positive Markers	Results	Reference Range
ANA by IIF	1:80 (Nucleolar)	Negative (<1:80); Positive (≥1:80)
EC4d	53 Net MFI	≤12 (Negative); >12-75 (Positive); >75 (Strong Positive)
BC4d	100 Net MFI	≤48 (Negative); >48-200 (Positive); >200 (Strong Positive)

Case 4

Patricia Hopkins, MD | Private Practice, Quincy, MA

A 61-year-old Caucasian female patient presented to Dr. Hopkins for her initial visit with a Rheumatologist citing osteoporosis symptoms. The patient has a history of illnesses dating back to her early 20s including thyroid disease, osteoporosis, Hodgkin's lymphoma, and episcleritis. She had multiple surgeries, including shoulder replacement and hysterectomy, and claimed to always be sick. Upon examination, Dr. Hopkins learned the patient was experiencing dry eyes and mouth and was using various eye drops that provided no relief. These symptoms, as well as noted autoimmune events, led Dr. Hopkins to believe that this patient had Sjögren's Syndrome.

To confirm suspicion, Dr. Hopkins ordered the Avise CTD diagnostic and Avise SLE Prognostic so she could obtain a full serologic panel of ENA, RA, APS, and autoimmune thyroid auto-antibodies in a single test to help determine disease state and assess risk for organ involvement. In the meantime, Dr. Hopkins prescribed cevimeline (Evoxac) for the ocular dryness and requested that the patient come back in 1 month for a follow-up to review her Avise CTD test results.

The Avise CTD and Avise SLE Prognostic test results indicated a speckled ANA IIF pattern, elevated BC4d, RF IgM, anti-Cardiolipin IgM & IgA, anti-b2-Glycoprotein 1 IgM & IgA, and anti-Phosphatidylserine/Prothrombin (PS/PT) IgM. As suspected, the patient's ANA IIF pattern was indicative of Sjögren's, the elevated BC4d introduced potential overlap, but most importantly, Avise SLE Prognostic uncovered the patient's potential risk for thrombosis and cardiovascular events due to the positive APS markers. With these results and clinical presentation, Dr. Hopkins is treating the patient for overlap disease represented by Sjögren's Syndrome. She placed the patient on hydroxychloroquine (Plaquenil) in addition to her current dose of cevimeline and will monitor for any signs of heart involvement at her next follow-up appointment in 2 months.

Positive Markers	Results	Reference Range
ANA by IIF	1:320 (Speckled)	Negative (<1:80); Positive (≥1:80)
BC4d	70 Net MFI	≤48 (Negative); >48-200 (Positive); >200 (Strong Positive)
Rheumatoid Factor IgM	5.5 U/mL	<3.5 (Negative); 3.5-5 (Equivocal); >5 (Positive)
Anti-Cardiolipin IgM	>774.0 CU	≤20 (Negative); >20 (Positive)
Anti-Cardiolipin IgA	44 CU	≤20 (Negative); >20 (Positive)
Anti-β2-Glycoprotein IgM	112 CU	≤20 (Negative); >20 (Positive)
Anti-β2-Glycoprotein IgA	40 CU	≤20 (Negative); >20 (Positive)
Anti-PS/PT IgM	141 U/mL	≤30 (Negative); >30 (Positive)

Avise Prognostic testing offers help in determining risk for thrombosis, cardiovascular events, Lupus Nephritis, or Neuropsychiatric SLE. Get risk assessment testing for organ involvement at the same time you run the Avise CTD[13-15]:

Risk of Thrombosis & Cardiovascular Events
- Anti-Phosphatidylserine/Prothrombin (PS/PT) IgM & IgG
- Anti-Cardiolipin IgM, IgG, & IgA
- Anti-β2-Glycoprotein IgM, IgG, & IgA

Risk for Lupus Nephritis
- Anti-C1q

Risk for Neuropsychiatric Lupus
- Anti-Ribosomal P

Case 5

Nimesh Dayal, MD | Arthritis Center of Orlando, Ocoee, FL

A 51-year-old Caucasian female patient was referred to Dr. Dayal by her PCP with a positive ANA and a 7-year history of left parotid gland swelling and hypothyroidism. The swelling was initially thought to be caused by an infection, so the patient was treated by her PCP with antibiotics that provided quick symptom relief. She was also prescribed levothyroxine for her hypothyroidism. Sometime after, the patient had a recurrence of the left parotid gland swelling. An MRI revealed numerous cystic changes throughout both glands. The PCP ran additional laboratory tests, including ANA, and referred the patient to a Rheumatologist for further evaluation.

Upon examination, Dr. Dayal learned the patient was experiencing dry eyes and dry mouth and that the levothyroxine appeared to be working because no thyroid disease symptoms presented. In view of this and patient history, Dr. Dayal was suspicious for primary Sjögren's Syndrome and Hashimoto's disease. To confirm his suspicions, and rule-out potential overlap, Dr. Dayal ordered Avise CTD and Avise SLE Prognostic.

The Avise CTD results came back with positive ANA (speckled IIF pattern), anti-SS-A/Ro, anti-SS-B/La, RF IgM & IgG, anti-thyroglobulin, and anti-thyroid peroxidase. In addition, all Avise SLE Prognostic markers were negative.

Positive Markers	Results	Reference Range
ANA by IIF	1:640 (Speckled)	Negative (<1:80); Positive (≥1:80)
ANA by ELISA	155 Units	<20 (Negative); 20-59 (Positive); ≥60 (Strong Positive)
Anti-SS-A/Ro	>240 U/mL	<7 (Negative); 7-10 (Equivocal); >10 (Positive)
Anti-SS-B/La	>320 U/mL	<7 (Negative); 7-10 (Equivocal); >10 (Positive)
Rheumatoid Factor IgM	17 U/mL	<3.5 (Negative); 3.5-5 (Equivocal); >5 (Positive)
Rheumatoid Factor IgA	146 U/mL	<14 (Negative); 14-20 (Equivocal); >20 (Positive)
Anti-Thyroglobulin	3376 IU/mL	<280 (Negative); 280-344 (Equivocal); >344 (Positive)
Anti-Thyroid Peroxidase	906 IU/mL	<60 (Negative); 60-100 (Equivocal); >100 (Positive)

These results, along with the clinical evaluation, helped Dr. Dayal form a diagnosis of primary Sjögren's Syndrome and Hashimoto's disease as well as rule-out any potential risk of organ involvement. He prescribed hydroxychloroquine (Plaquenil) in addition to keeping the patient's current dose of levothyroxine and has seen improvement of symptoms since her last follow-up visit.

Why Test for Autoimmune Thyroid?

It is well known that patients with CTD have a higher incidence of autoimmune thyroid disease. Symptoms of these diseases strongly mimic one another and studies have shown that overlap of autoimmune thyroid often exists with[16,17]:

- RA
- Sjögren's Syndrome
- Scleroderma
- SLE/Lupus

When developing Avise CTD, anti-thyroglobulin and anti-thyroid peroxidase were added, at our physicians' request, to make the Avise diagnostic more comprehensive and to increase utility in clinical practice.

A supplement to

Rheumatology News

Diagnosing CTD in Clinical Practice is a supplement to *Rheumatology News*.

Editorial assistance was provided to the authors by *Rheumatology News* and Exagen Diagnostics, Inc.

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