Myositis

Laboratory Support for Classification and Diagnosis

CLINICAL BACKGROUND

Myositis is a general inflammation of the muscles caused by muscle injury, cancer, drugs, infection, genetic defects, or autoimmune disease. The most severe forms of myositis are autoimmune diseases called the idiopathic inflammatory myopathies (IIMs), which include polymyositis, dermatomyositis, inclusion body myositis (IBM), and necrotizing myopathy (NM). Because these are systemic diseases, affected individuals may exhibit extramuscular symptoms such as skin rashes, lung disease, joint pain, arthritis, Raynaud phenomenon, and "mechanic's hands."[1]

Idiopathic inflammatory myopathies are relatively rare causes of myositis, with a prevalence of fewer than 33 cases per 100,000 individuals in the United States.[2] Polymyositis is the predominant type of IIM in adults. In children, juvenile dermatomyositis (JDM) is the predominant type of IIM. Polymyositis and dermatomyositis are more often observed in women, whereas IBM is more often diagnosed in middle-aged men. NM is mostly associated with use of statin drugs, but is also observed in "statin-naïve patients" (although some of these patients may have been exposed to natural statins in foods).[3-5]

Polymyositis and dermatomyositis commonly overlap with other autoimmune connective tissue diseases, such as systemic lupus erythematosus (SLE), Sjögren syndrome, systemic sclerosis, and rheumatoid arthritis.[6] Although generally thought to be less severe in these overlap syndromes, myositis symptoms may be similar in intensity, or worse, than those of primary myositis.[7]

The differential diagnosis of IIMs and overlap myositis begins with the exclusion of muscular dystrophy and myopathies of known cause (eg, infectious, metabolic, drug-induced, or neurologic). Diagnosis is aided by imaging, electromyography, biopsy, testing levels of muscle enzymes in serum, and the detection of myositis-specific and myositis-associated antibodies. In addition, the detection of certain antibodies may have prognostic value. This Clinical Focus provides information on the available laboratory tests and their use. This information is provided for informational purposes only and is not intended as medical advice. A physician's test selection and interpretation, diagnosis, and patient management decisions should be based on his/her education, clinical expertise, and assessment of the patient.

Owing to overlapping features and phenotypes associated with a given antibody, test results should be interpreted carefully in light of clinical and other laboratory data.

INDIVIDUALS SUITABLE FOR TESTING

- Individuals with symptoms of IIM (eg, unexplained muscle weakness, rash, evidence of systemic disease)

TEST AVAILABILITY

Quest Diagnostics offers tests and panels that may be useful for classifying or diagnosing myositis **(Table 1)**.

TEST SELECTION AND INTERPRETATION

Idiopathic Inflammatory Myopathies

The EULAR/ACR classification criteria for the idiopathic inflammatory myopathies (IIMs) include biopsy (if available), clinical, and laboratory evaluation **(Table 2)**.[8] The criteria have been incorporated into a web-based calculator (http://www.imm.ki.se/biostatistics/calculators/iim/) that estimates the probability that a patient has IIM and what type.

On initial evaluation, about 80% to 90% of myositis patients have elevated creatine kinase (CK) associated with muscle damage.[9] Using elevated CK to diagnose IIMs has limitations, however. CK levels may be only slightly elevated, or normal, due to lack of muscle mass or the presence of circulating CK inhibitors or CK antibodies.[10] Normal CK levels may also be observed in patients with IBM, as well as those with juvenile or amyopathic dermatomyositis (see below). Another limitation is that CK and other muscle enzymes are not specific markers of polymyositis/dermatomyositis. Serum elevations may be due to other types of muscle disease (muscular dystrophies, rhabdomyolysis), hypothyroidism, cardiac, or liver disease. Consequently, tests employing antibody markers, rather than muscle enzymes, are used to specifically diagnose and classify IIMs.

The classical myositis-specific antibodies include Jo-1, EJ, OJ, PL-7, and PL-12 synthetase antibodies, as well as Mi-2 and SRP antibodies. Of these, only Jo-1 antibody is currently included in the EULAR/ACR criteria.[7] Others are anticipated to be included in future updates.[8] Together, these antibodies are found in about 50% of patients with polymyositis/dermatomyositis and are often mutually exclusive **(Figures 1 and 2)**.[1]

Table 1. Laboratory Tests for Classification and Diagnosis of Myositis

Test Code	CPT Code(s)[a]	Test Name	Clinical Use
823	84460	Alanine Aminotransferase (ALT)	Diagnose PM/DM
227	82085	Aldolase	Diagnose PM/DM
TBD		Anti-HMGCR	Diagnose statin-induced myopathy
TBD		Anti-interstitial Lung Disease Panel	Diagnose interstitial lung disease
TBD		Anti-sIBM	Diagnose sporadic inclusion body myositis
38075[b]	84182 (x4), 86235	Antisynthetase Antibody Panel 1 Includes Jo-1, EJ, OJ, PL-7, and PL-12 antibodies.	Diagnose antisynthetase syndrome in a symptomatic patient
822	84450	Aspartate Aminotransferase (AST)	Diagnose PM/DM
374	82550	Creatine Kinase (CK), Total	Diagnose PM/DM
5810(X)	86235	Jo-1 Antibody	Diagnose PM/DM
593	83615	Lactate Dehydrogenase (LD)	Diagnose PM/DM
90995[c]	83516 (x5), 86235 (x2)	Myositis AssessR™ Includes EJ (test code 90998), OJ (test code 90999), PL-7 (test code 90996), PL-12 (test code 90997), Mi-2 (test code 17172), Ku (test code 18855), and SRP (test code 16318) antibodies.	Diagnose PM/DM
10185(X)[c]	86235 (x3), 83516 (x5)	Myositis AssessR™ plus Jo-1 Antibodies Includes Myositis AssessR™ (test code 90995) and Jo-1 (test code 5810[X]) antibodies	Diagnose PM/DM (Jo-1 provides a more definitive diagnosis)
94777[b]	84182 (x6), 86235 (x5)	Myositis Specific 11 Antibodies Panel Includes Jo-1, EJ, OJ, PL-7, PL-12, SRP, Mi-2α, Mi-2β, MDA-5, NXP-2, and TIF1-γ antibodies.	Diagnose PM/DM (Jo-1 provides a more definitive diagnosis) Diagnose NM Diagnose cancer-associated DM Diagnose juvenile DM Diagnose amyopathic DM
94646	86235	Anti-PM/Scl-100 Antibody, EIA	Diagnose overlap of PM/DM with systemic sclerosis
18855	83516	Ku Autoantibodies	Diagnose overlap of PM with SLE or systemic sclerosis
38568	86235	Sjögren's Antibody (SS-A)	Diagnose overlap of PM/DM with Sjögren syndrome, SLE, or systemic sclerosis
38567	86235	Sm/RNP Antibody	Diagnose overlap of PM with SLE or systemic sclerosis

DM, dermatomyositis; PM, polymyositis; NM, necrotizing myopathy; SLE, systemic lupus erythematosus; TBD, to be determined, available in 2019.

[a] The CPT codes provided are based on AMA guidelines and are for informational purposes only. CPT coding is the sole responsibility of the billing party. Please direct any questions regarding coding to the payer being billed.

[b] This test was developed and its analytical performance characteristics have been determined by Quest Diagnostics. It has not been cleared or approved by the U.S. Food and Drug Administration. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.

[c] Panel components may be ordered separately.

Table 2. IIM Diagnostic Criteria[8]

If no other cause is present, sum of points is ≥5.5 (≥6.7 with biopsy), and age of onset is

- ≥18 years, then classify patient as having
  - DM if rash[a] is present with muscle weakness[b]
  - PM (or NM) if rash[a] is absent with muscle weakness[b]
  - IBM if rash[a] is absent with muscle weakness[b], as well as clinical[c] or biopsy[d] features
  - ADM if rash[a] is present without muscle weakness[b]
- <18 years, then classify patient as having
  - JDM if rash[a] is present with muscle weakness[b]
  - Juvenile IIM (not JDM) if rash[a] is absent with muscle weakness[b]

Criteria	Points without biopsy	Points with biopsy
Biopsy		
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibers		1.7
Perimysial or perivascular infiltration or both of mononuclear cells		1.2
Perifascicular atrophy		1.9
Rimmed vacuoles		3.1
Clinical		
Age of onset of first symptom assumed to be related to the disease		
≥18 years and <40 years	1.3	1.5
≥40 years	2.1	2.2
Objective symmetric weakness, usually progressive, of the		
proximal upper extremities	0.7	0.7
proximal lower extremities	0.8	0.5
Neck flexors are relatively weaker than neck extensors	1.9	1.6
Proximal muscles are relatively weaker than distal muscles in the legs	0.9	1.2
Heliotrope rash	3.1	3.2
Göttron papules	2.1	2.7
Göttron sign	3.3	3.7
Dysphagia or oesophageal dysmotility	0.7	0.6
Laboratory		
Jo-1 (anti-histidyl-tRNA synthetase) autoantibody present	3.9	3.8
Elevated serum levels of creatine kinase (CK)[e] or lactate dehydrogenase (LD)[e] or aspartate aminotransferase (ASAT/AST/SGOT)[e] or alanine aminotransferase (ALAT/ALT/SGPT)[e]	1.3	1.4

ADM, amyopathic DM; dermatomyositis, DM; IBM, inclusion body myositis; IIM, idiopathic inflammatory myopathy; JDM, juvenile DM; PM, polymyositis; NM, necrotizing myositis.

[a] Heliotrope rash, Göttron sign, or Göttron papules.

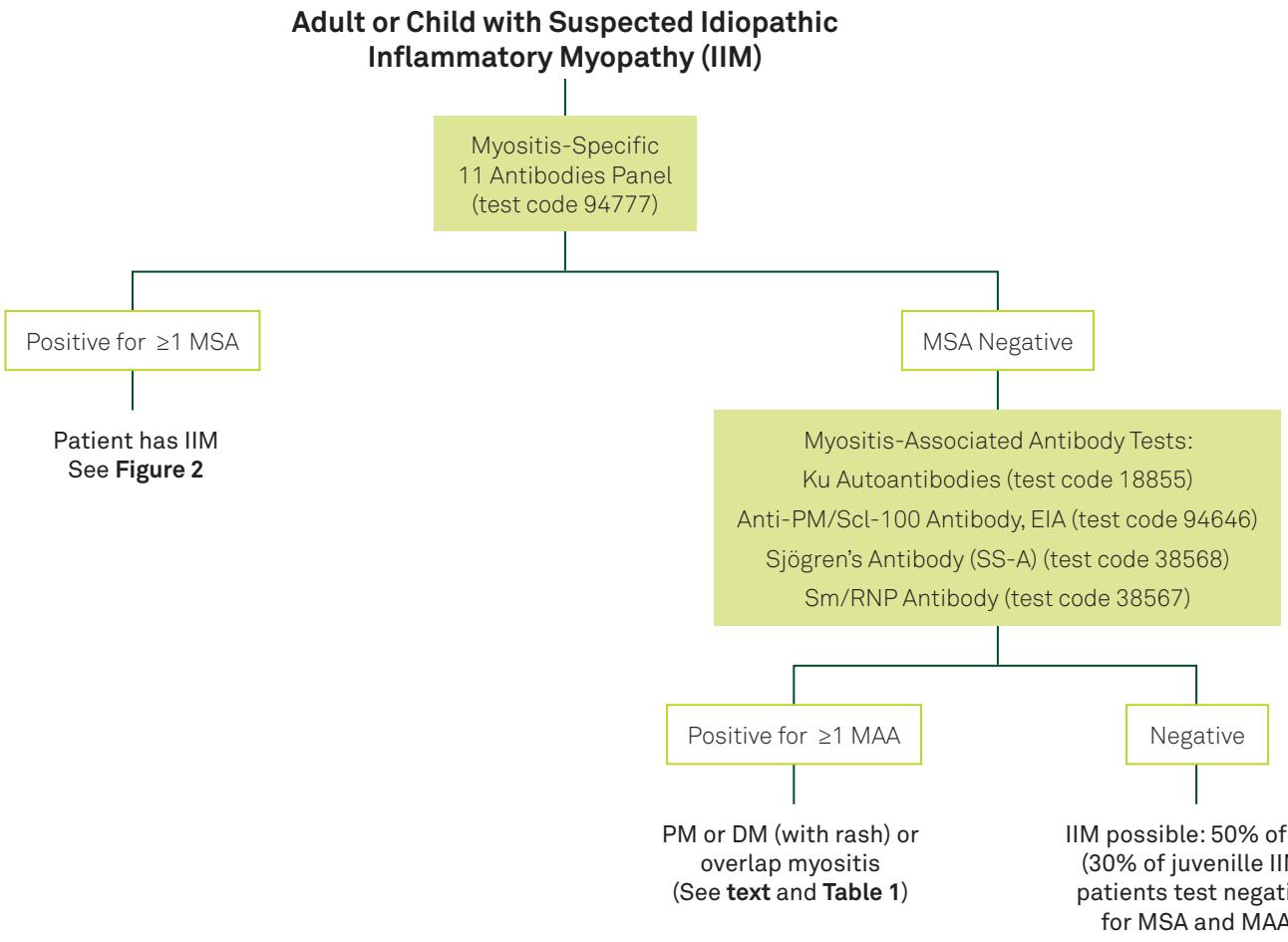
[b] Objective symmetric weakness, usually progressive of the upper or lower extremities; neck flexors weaker than extensors; or proximal leg muscles weaker than distal.

[c] Finger flexor weakness that does not improve in response to treatment.

[d] Rimmed vacuoles present.

[e] Serum levels above the upper limit of normal.

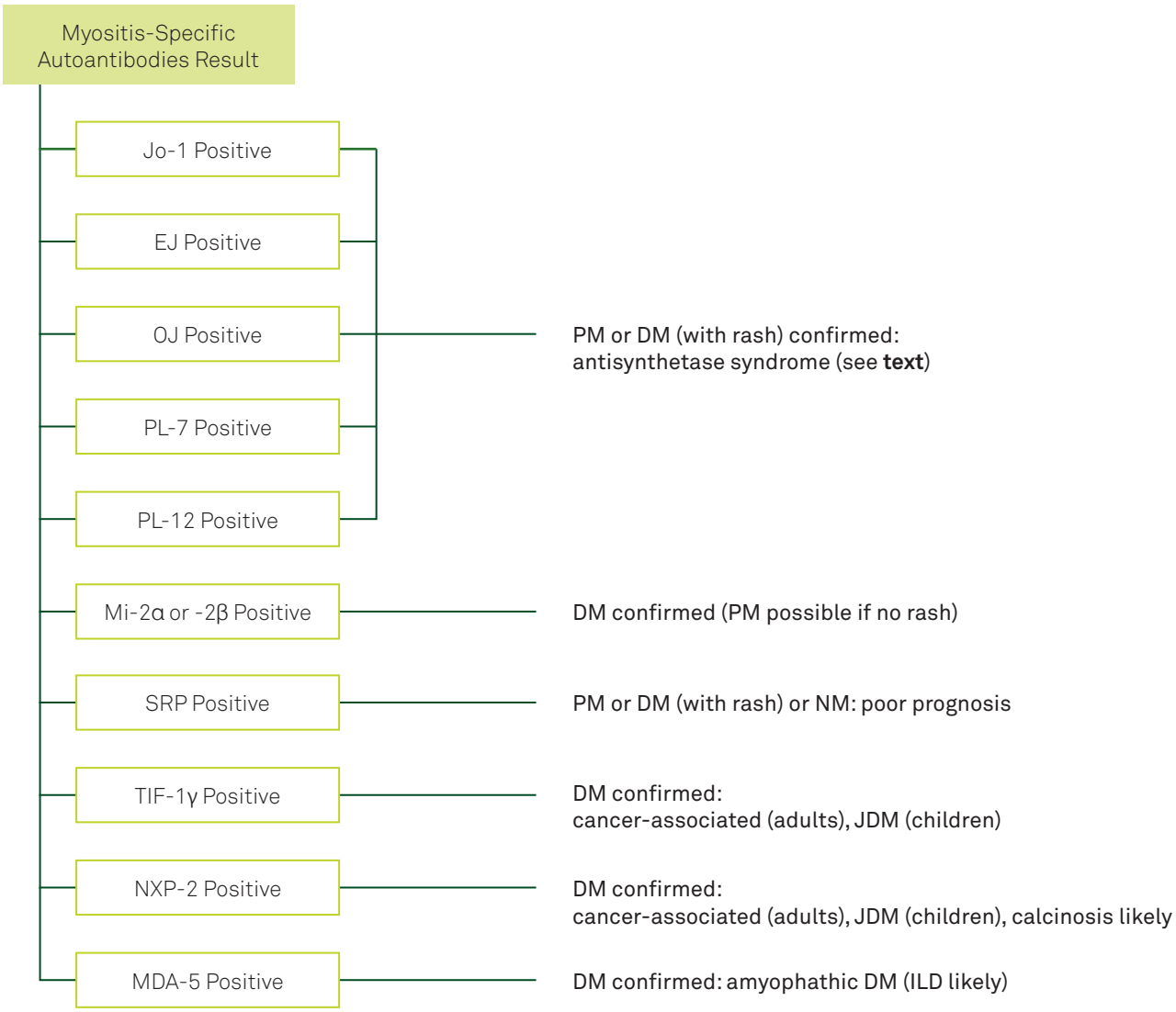
Figure 1. Idiopathic Inflammatory Myopathy: Selecting the Appropriate Laboratory Tests



DM, dermatomyositis; IBM, inclusion body myositis; IIM, idiopathic inflammatory myopathy; MAA, myositis-associated antibody; MSA, myositis-specific antibody; NM, necrotizing myopathy; PM, polymyositis.

This algorithm is intended as a guide for using Quest Diagnostics laboratory tests to diagnose IIM. It is based on references **1, 3, 4,** and **11-23**. The algorithm is provided for informational purposes only and is not intended as medical advice. A physician's test selection and interpretation, diagnosis, and patient management decisions should be based on his/her education, clinical expertise, and assessment of the patient.

Figure 2. Interpretation of Myositis- Specific Antibodies Panel (Test Code 94777) and Antisynthetase Panel 1 (Test Code 38075)



DM, dermatomyositis; IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; JDM, juvenile DM; NM, necrotizing myopathy; PM, polymyositis.

Positivity for 1 or more myositis-specific antibodies confirms a diagnosis of IIM. This algorithm is intended as a guide for using Quest Diagnostics laboratory tests to diagnose IIM. It is based on references **1, 3, 4,** and **12-22**. The algorithm is provided for informational purposes only and is not intended as medical advice. A physician's test selection and interpretation, diagnosis, and patient management decisions should be based on his/her education, clinical expertise, and assessment of the patient.

Jo-1 antibody is observed in 21% of patients with polymyositis and in 11% of those with dermatomyositis.[1] It is 100% specific for polymyositis/dermatomyositis.[12,13] Thus, Jo-1 positivity is a major contributor to a definitive IIM diagnosis.[8] The remaining classical myositis-specific antibodies occur less frequently than Jo-1[1] but are also highly specific (97% to 100%) for polymyositis/dermatomyositis.[12,15,16] Accordingly, a positive test result for any of the classical myositis-specific antibodies is highly suggestive of polymyositis or dermatomyositis (with rash, **Table 2**). A negative test result does not rule out either polymyositis or dermatomyositis, however, as classical myositis-specific antibodies are not detected in 50% of patients with these IIMs.

The type of myositis-specific antibody detected correlates with clinical phenotype, disease severity, and treatment response:

- Mi-2 antibodies are associated with dermatomyositis rash with few other extramuscular signs.[1] Detection of Mi-2 antibodies suggests that the patient may respond well to standard immunosuppressive therapy.[24]
- Although SRP antibody is associated with few extramuscular signs,[1] it is associated with severe disease onset and a poor response to standard immunosuppressive therapy.[15,20,24] In addition, SRP antibodies are also highly associated with NM.[3] Detection of an SRP antibody thus suggests a need for more aggressive treatment.[15,20,24]
- Synthetase antibodies are associated with antisynthetase syndrome in IIM patients for whom arthralgia and interstitial lung disease are the most prevalent extramuscular symptoms.[1] Patients with antisynthetase syndrome typically have a moderate response to standard immunosuppressive therapy.[24] Depending on the type of synthetase antibody, symptoms vary. A meta-analysis of 3,487 patients (27 studies) indicated that[1]:
  - Jo-1 antibody is associated with a significantly higher risk of myositis, arthralgia, and mechanic's hand compared with non-Jo-1 antibodies.
  - Non-Jo-1 antibodies are associated with a significantly higher risk of fever and interstitial lung disease compared with Jo-1 antibody.
  - The risk of Raynaud phenomenon does not differ significantly between patients with Jo-1 antibodies and those with non-Jo-1 antibodies.

Myositis-associated antibodies (Ku, PM/Scl , Sjögren's antibody [SS-A], and Smith [Sm]/U1-RNP antibody) are less specific for polymyositis and dermatomyositis and are found in 1% to 13% of these patients.[1] Ku and SS-A are found in 9% to 14% of IBM patients, who otherwise have low, or undetectable, myositis-specific or associated antibodies (≤3% of patients).[1] Thus, a positive test result for a myositis-associated antibody in a symptomatic patient suggests the presence of either polymyositis, dermatomyositis (with rash), or IBM; overlap myositis is also a possibility (discussed below).

Cancer- and Juvenile-associated Dermatomyositis

Additional myositis-specific antibodies include TIF1-γ (p155) and NXP-2 (p140) antibodies, which are prevalent in adults with cancer-associated dermatomyositis and children with juvenile dermatomyositis.

In adults with dermatomyositis, TIF1-γ antibody has a sensitivity of 78% and a specificity of 89% for cancer.[17] NXP-2 is detected in 31% of adults with cancer-associated adult dermatomyositis and, when combined with TIF1-γ measurement, improves the sensitivity for detecting cancer.[18] Positive test results for either TIF1-γ or NXP-2 antibodies identify cancer in 83% of adults with dermatomyositis and are thus highly suggestive of malignancy.[18]

TIF1-γ can be detected in 35% of children with juvenile dermatomyositis, making it the most prevalent myositis-specific antibody among this group.[19] NXP-2 is also prevalent, detected in 22% of these patients.[19] Classical myositis-specific antibodies are generally far less prevalent in children, so including both TIF1-γ and NXP-2 in the panel improves sensitivity for juvenile dermatomyositis over the classical myositis-specific antibodies alone.[19]

Unlike in adults, TIF1-γ antibody is not associated with cancer in children.[20] However, the presence of NXP-2 is highly associated with disease severity and calcinosis, which affects nearly one-third of patients with juvenile dermatomyositis and is a major cause of morbidity in this group.[20]

Amyopathic Dermatomyositis

MDA-5 antibody, another myositis-specific antibody, is prevalent in patients with clinically amyopathic dermatomyositis. These patients have rashes in the absence of clinical myositis. The unique cutaneous phenotype includes cutaneous and oral ulcerations, painful palmar papules, alopecia, and panniculitis.[25] The presence of MDA-5 antibody

is associated with a high likelihood of interstitial lung disease. Dermatomyositis patients with interstitial lung disease typically have a poorer prognosis because of rapid disease progression. A positive result for the MDA-5 antibody suggests that the patient is more than 18 times as likely to have interstitial lung disease as those who test negative.[21] Early detection of interstitial lung disease by identifying the MDA-5 antibody may improve prognosis by prompting intensive immunosuppressive therapy early in the disease.[22]

Overlap Myositis

Myositis-associated autoantibodies are most often detected in patients with overlap myositis syndromes. Ku, PM/Scl, Sm/RNP, and SS-A antibodies are found in 13% to 32% of these patients.[1] A positive result for the PM/Scl antibody suggests overlap of polymyositis (or dermatomyositis with rash) with systemic sclerosis. Ku or Sm/RNP antibodies suggest overlap with SLE or systemic sclerosis. The presence of Sjögren's antibody suggests overlap with SLE, Sjögren syndrome, or systemic sclerosis **(Table 1)**.[23]

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