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Interpretation Guide

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AVISE Interpretation Guide

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SLE Associated Markers

Marker (method)	AVISE CTD	AVISE Lupus	SLE Monitor	SLE Prognostic	AVISE APS	AVISE Vasculitis	Associated Disease	Sensitivity	Description
EC4d (FC)	●	●	●				Systemic Lupus Erythematosus (SLE)	46% [1]	Cell-bound complement activation products (CB-CAPs) EC4d & BC4d are measures of classical complement activation. CB-CAPs are primarily associated with SLE and 66% of patients have EC4d and/or BC4d elevated.[1] EC4d significantly correlates with fluctuations in SLE disease activity.[2]
BC4d (FC)	●	●					SLE	53% [1]	
TC4d (FC)	●						SLE	58% [3]	CB-CAP TC4d is a measure of classical complement activation. TC4d is positive in 58% of SLE patients and is also present in roughly 25% of SLE patients who test negative for EC4d and BC4d.
TIgG (FC)	●						SLE	31% [3]	TIgG and TIgM autoantibody formation against T Cell antigens is common in SLE. 40% of SLE patients will test positive for one or both T Cell autoantibodies.
TIgM (FC)	●						SLE	30% [3]	
C3 (IT)			●				SLE	33% [1]	C3/C4 proteins are integral components of the complement system. Low C3/C4 levels are associated with SLE and 44% of patients have one or both proteins abnormally low.
C4 (IT)			●				SLE	32% [1]	
Anti-C1q IgG (ELISA)			●	●			Lupus Nephritis/ SLE Disease Activity	58% [4]	Antibodies against the complement protein C1q are found in 58% of SLE patients with active lupus nephritis. Anti-C1q levels are associated with renal activity.[2] However, low positive levels of anti-C1q have also been found in up to 8% of patients with other diseases, such as infection, and normal healthy individuals.
Anti-dsDNA IgG (ELISA and IFA)	●	●					SLE	33% [1]	Anti-dsDNA positivity provides a high positive predictive value due to the high specificity for SLE. In the AVISE Lupus algorithm, patients are first screened using an anti-dsDNA ELISA assay. Those who test positive are then confirmed with the *Crithidia luciliae* IFA assay, a more specific method for detecting clinically significant anti-dsDNA in SLE. Approximately 50% of anti-dsDNA ELISA results are confirmed with *Crithidia luciliae*.
Anti-dsDNA (CIA)			●				SLE Disease Activity	46% [5, 6]	The Chemiluminescent Immunoassay (CIA) method measures quantitative levels of anti-dsDNA, which significantly correlate with SLE disease activity. Due to its expanded dynamic range, CIA can detect very low levels of anti-dsDNA antibodies and correlates closely with the Farr assay.
Anti-Nuclear Antibodies IgG (ANA) (ELISA and IFA)	●	●					Autoimmune Diseases	89% in SLE [1]	A positive ANA test suggests the presence of autoantibodies, which may indicate an autoimmune disorder like SLE. However, it is not specific to one autoimmune disease and can also be positive in healthy individuals. Further testing is typically required to confirm a diagnosis and determine the specific condition.
Anti-Ribosomal P IgG (ELFA)				●			Neuropsychiatric Lupus	9% [7]	Antibodies against Ribosomal P are highly specific for SLE and can be present in anti-dsDNA or anti-Smith negative patients. Anti-Ribosomal P antibodies have been shown to associate with neuropsychiatric SLE manifestations.
Anti-Smith IgG * (ELFA)	●	●					SLE	14% [1]	Anti-Smith is highly specific for SLE, but has comparatively low sensitivity for the disease.

ENA Markers

Marker (method)	Associated Disease	Sensitivity	Description
Anti-CENP IgG (ELFA)	CREST Syndrome	20-60% [8]	Antibodies to CENP protein-B are found in 20-60% of patients with CREST syndrome, a limited form of scleroderma.
Anti-Jo-1 IgG (ELFA)	Polymyositis/ Dermatomyositis (PM/ DM)	20-30% [9]	Antibodies against Jo-1 are highly specific for DM/PM and are present in 25% of DM/PM patients. DM/PM patients who are positive for anti-Jo-1 may have interstitial pneumonitis and tend to have a severe form of the disease with a tendency to relapse.
Anti-RNP70 IgG (ELFA)	Mixed Connective Tissue Disease (MCTD)	90% [10]	RNP70 antibodies specifically target the 70 kDa protein of the U1-snRNP complex and are present in 90% of MCTD patients. Unlike anti-U1RNP, anti-RNP70 is more specific for MCTD and occurs in only 12% of SLE patients.
Anti-Scl-70 IgG (ELFA)	Scleroderma	28-70% [11]	Antibodies to Scl-70 are present in up to 70% of scleroderma patients. Anti-Scl70 is highly specific for diffuse cutaneous scleroderma and associates with interstitial lung disease (ILD).
Anti-SSA/Ro52 IgG (ELFA)	Myositis, SLE, Sjögren's Disease & Scleroderma	20-70% [12]	Ro52 antibodies are found in multiple autoimmune conditions. Anti-Ro52 has been shown to associate with ILD in patients with Sjögren's disease or scleroderma.
Anti-SSA/Ro60 IgG (ELFA)	SLE, Sjögren's Disease, Myositis & Scleroderma	20-65% [12]	Ro60 antibodies are found in multiple autoimmune conditions. Anti-Ro60 is commonly found in both SLE and Sjögren's disease.
Anti-RNA Pol III IgG (ELFA)	Systemic Sclerosis	5-22% [13]	RNA Pol III antibodies are present in up to 22% of patients with systemic sclerosis, particularly diffuse cutaneous scleroderma. Anti-RNA Pol III is often present in the absence of other systemic sclerosis antibodies including anti-Scl-70, anti-centromere, and anti-PM/Scl.
Anti-SSB/La IgG (ELFA)	Sjögren's Disease	39% [1]	SSB/La antibodies are highly specific for Sjögren's disease and are present in 39% of Sjögren's disease patients.

* Available as a stand alone test order.

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	Marker (method)	AVISE CTD	AVISE Lupus	SLE Monitor	SLE Prognostic	AVISE APS	AVISE Vasculitis	Associated Disease	Sensitivity	Description
ENA Markers	Anti-U1-RNP IgG (ELFA)	●						MCTD	95-99% [10]	U1RNP antibodies are highly sensitive for MCTD but are also present in 30-40% of SLE patients. The absence of anti-U1RNP antibodies is used to rule out MCTD.
	Anti-Histone IgG * (ELFA)							Drug-Induced Lupus (DIL)	95% [14]	Up to 95% of DIL and 50% of SLE patients exhibit elevated levels of histone antibodies. Histone antibodies have also been found in RA, DM, and Sjögren's disease placing added importance on clinical presentation.
RA Markers	**Marker (method)**							**Associated Disease**	**Sensitivity**	**Description**
	Anti-Cyclic Citrullinated Peptide IgG (ELFA)	●	●					Rheumatoid Arthritis (RA)	70-90% [15]	Antibodies to cyclic citrullinated peptides (CCP) aid in the diagnosis of RA. Anti-CCP antibodies are highly specific for RA.
	Anti-Carbamylated Protein (CarP) IgG * (ELISA)							RA	33% [16]	Antibodies to carbamylated proteins (CarP) serve as markers of more severe prognoses in RA, independent of anti-CCP or RF status. Studies have shown anti-CarP found in early RA associates with future erosive damage. The clinical significance of positive anti-CarP in the absence of RA has not been established.
	Rheumatoid Factor IgM & IgA (ELFA)	●						RA	70-90% [15]	Rheumatoid factor (RF) antibodies are detected in 70%-90% of patients with rheumatoid arthritis (RA). The specificity for RA improves with higher RF titers and the presence of multiple positive isotypes, particularly IgM and IgA. The detection of the IgA isotype has been associated with a more severe disease prognosis.
	Anti-RA33 IgG, IgA, IgM (ELFA)	●						RA	16-32% [17]	RA33 autoantibodies are highly specific (>95%) for RA against healthy individuals. Collectively, IgG, IgM, and IgA antibodies are present in 32% of seropositive RA patients and 16% of seronegative RA patients.
APS Markers	**Marker (method)**							**Associated Disease**	**Sensitivity**	**Description**
	Anti-β2-Gylcoprotein I IgG, IgM & IgA ** (ELFA)	●			●	●		Antiphospholipid Syndrome (APS)	45% [18]	Antibodies to beta-2 glycoprotein 1 (ß2 GP1) exhibit higher specificity than anti-cardiolipin. In 3-10% of APS patients, ß2 GP1 antibodies may be the only positive test. Positive results should be confirmed after 12 weeks to ensure persistency of antibodies. IgA ß2 GP1 antibodies are less common than IgG or IgM and can occur in isolation.
	Anti-Cardiolipin IgG, IgM & IgA ** (ELFA)	●			●	●		APS	97% [19]	Antibodies to cardiolipin are present in SLE patients (30-40%) and APS. The prevalence of anti-cardiolipin in APS is high, but the specificity is lower than other anti-phospholipid antibodies. Positive results should be confirmed after 12 weeks.
	Anti-Phosphatidylserine /Prothrombin (PS/PT) IgM & IgG (ELISA)				●	●		APS	22-37% [20]	Antibodies to PS/PT are markers for APS that have been found to significantly correlate with lupus anticoagulant (LAC).[19] Unlike LAC, anti-PS/PT testing is unaffected by anti-coagulant therapy.
Thyroid Markers	**Marker (method)**							**Associated Disease**	**Sensitivity**	**Description**
	Anti-Thyroglobulin IgG (ELFA)	●						Hashimoto's Thyroiditis & Graves' Disease	60-85% [21]	Anti-thyroglobulin antibodies are found in 60-85% of patients with Hashimoto's thyroiditis and 30-80% of patients with Graves' disease.
	Anti-Thyroid Peroxidase IgG (ELFA)	●						Hashimoto's Thyroiditis & Graves' Disease	71-97% [21]	Anti-thyroid peroxidase antibodies are found in > 90% of patients with Hashimoto's thyroiditis & 71-97% of patients with Graves' disease. Over 95% of thyroiditis patients have thyroglobulin IgG and/or thyroid peroxidase antibodies.
Vasculitis Markers	**Marker (method)**							**Associated Disease**	**Sensitivity**	**Description**
	ANCA (IFA)						●	ANCA-Associated Vasculitis	77% [22]	The c-ANCA pattern produces a granular cytoplasmic pattern with interlobular accentuation on ethanol fixed neutrophils. c-ANCA patterns are associated with necrotizing segmental glomerulonephritis and GPA. [22, 23]
									85% [22]	The p-ANCA pattern produces perinuclear staining with or without nuclear extension. The p-ANCA pattern is commonly detected in patients with MPA and about 40% of patients with Eosinophilic Granulomatosis with Polyangiitis (EGPA). [23, 24]
	Anti-PR3 IgG (CIA)						●	Granulomatosis with Polyangiitis (GPA)	81% [22]	Anti-PR3 antibodies are primarily associated with GPA and to a lesser extent, found in MPA (10%) and EGPA. [22, 24] However, anti-PR3 antibodies can also be seen in connective tissue disease, IBD, some infections, malignancy, and as a reaction to drugs. Therefore, results should be interpreted with care in light of the clinical findings and workup. [25]
	Anti-MPO IgG (CIA)						●	Microscopic Polyangiitis (MPA)	85% [22]	Anti-MPO antibodies are primarily associated with MPA and to a lesser extent, found in GPA (6%) and EGPA. [22, 24] However, anti-MPO antibodies can also be seen in connective tissue disease, inflammatory bowel disease (IBD), some infections, malignancy, and as a reaction to drugs. Therefore, results should be interpreted with care in light of the clinical findings and workup. [25]
	Anti-GBM IgG (CIA)						●	Goodpasture's Syndrome (GPS)	96% [26]	Anti-GBM antibodies are often associated with Goodpasture's disease and anti-GBM nephritis. [26] A significant proportion of patients with anti-GBM disease are also positive for ANCA.

* Available as a stand alone test order.

** IgA antibodies only available in AVISE APS and SLE Prognostic test orders.

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AVISE HCQ

A test to aid in assessing adherence to HCQ and individual exposure to HCQ as measured in whole blood.

HCQ Level	Interpretation & Consideration
Supratherapeutic (>1200 ng/mL)	Level associated with clinical efficacy. HCQ is likely absorbed effectively. However, levels >1200 ng/ml have a minimal added benefit compared to levels in the therapeutic range (750 ng/ml - 1200 ng/ml). Thus, adjusting HCQ doses to maintain blood levels in the therapeutic range may maximize efficacy while limiting toxicity.
Therapeutic (750-1200 ng/mL)	Levels associated with clinical efficacy. HCQ is likely to be absorbed effectively.
Subtherapeutic (200-<750 ng/mL)	Patient may be partially adherent to therapy. Patients with HCQ < 750 ng/mL can be at greater risk for disease flare. Thus, adjusting HCQ doses and/or discussing barriers to compliance may maximize efficacy.
Underexposed (<200 ng/mL)	Patient is likely non-adherent to HCQ therapy.

AVISE MTX

A test to aid in assessing adherence to MTX and individual exposure to active MTX metabolites in red blood cells.

MTXPG Level	Interpretation & Consideration
Therapeutic (>60 nmol/L)	Patient is metabolizing MTX effectively. Level is consistent with clinical efficacy.
Intermediate (20-60 nmol/L)	Patient may need more exposure to MTX.
Sub-therapeutic (<20 nmol/L)	Patient may not be metabolizing MTX effectively or patient may be non-adherent with therapy.

Methodology Definitions:

FC: Flow Cytometry
IFA: Immunofluorsecence Assay
ELISA: Enzyme-Linked Immunosorbent Assay
ELFA: Enzyme-Linked Fluorescence Assay
IT: Immunoturbidimetry
CIA: Chemiluminescent Immunoassay

AVISE Interpretation Guide

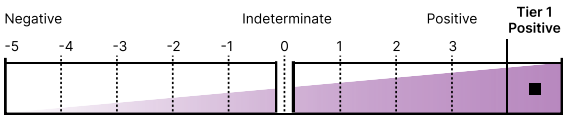
AVISE® CTD result report

Lupus index and interpretation

The AVISE Lupus algorithm and its insightful interpretation turn isolated data points into meaningful information to help rule in or rule out lupus.

Comprehensive Connective Tissue Disease Assessment | Exagen | Provider MD | Received 10/23/2024 | Reported 10/25/2024 | MRN AB123450 | DOB 01/01/1996

AVISE Lupus Result: **Tier 1 Positive**



INDEX INTERPRETATION: Tier 1 positive results are associated with an increased likelihood of SLE and are greater than 96% specific for SLE against other autoimmune CTDs. These results are driven by elevated markers that are highly specific for SLE (anti-dsDNA, anti-smith, and/or strong positive EC4d/BC4d). Results should be interpreted by a provider in conjunction with all available clinical findings.

Lupus Index Score Biomarkers	Value	Interpretation	Reference Range
+ Anti-dsDNA IgG (ELISA)	865.61 IU/mL	POSITIVE	<201 - Negative I 201-<302 - Equivocal I ≥302 - Positive

T Cell lupus result

The newly available T Cell biomarkers provide unique and unmatched diagnostic accuracy to further substantiate an SLE diagnosis when conventional markers are negative.

Anti-Scl-70 IgG (ELFA)	0.8 U/mL	Negative	<7 - Negative I 7-10 - Equivocal I >10 - Positive
Anti-Centromere Protein B (CENP) IgG (ELFA)	1.0 U/mL	Negative	<7 - Negative I 7-10 - Equivocal I >10 - Positive

T Cell Result: **Abnormal**

T Cell Biomarkers	Value	Interpretation	Reference Range
+ CB-CAP: TC4d (FC)	215 Net MFI	**POSITIVE**	<200 - Negative I ≥200 - Positive
+ T Cell autoantibody: TIgG (FC)	190 Net MFI	**POSITIVE**	<170 - Negative I ≥170 - Positive
+ T Cell autoantibody: TIgM (FC)	250 Net MFI	**POSITIVE**	<230 - Negative I ≥230 - Positive

ANA (Immunofluorescence)	Value	Interpretation	Reference Range
+ ANA by HEp-2 (IFA)			

Rheumatoid arthritis biomarkers

The inclusion of highly specific RA biomarkers aids in the early diagnosis of seronegative RA patients.

Comments:

- EC4d and TC4d are markers of … and less than 1% of patients with other autoimm… …nge, TC4d is present in 59% of SLE patients and in low percentages of patients with Sjögren's disease, spondyloarthropathies, PSA, fibromyalgia, RA, and chronic localized pain.
- TIgG and TIgM autoantibody formation against T Cell antigens is common in SLE. In the positive range, TIgG is present in 33% of SLE patients …

Rheumatoid Arthritis Biomarkers	Value	Interpretation	Reference Range
Anti-CCP IgG (ELFA)	1.4 U/mL	Negative	<7 - Negative I 7-10 - Equivocal >10 - Positive
Anti-RA33 IgG (ELFA)	1.8 U/mL	Negative	<8 - Negative I ≥8 - Positive
Anti-RA33 IgM (ELFA)	0.9 U/mL	Negative	<42 - Negative I ≥42 - Positive
Anti-RA33 IgA (ELFA)	0.6 U/mL	Negative	<5 - Negative I ≥5 - Positive
Rheumatoid Factor IgM (ELFA)	<0.6 IU/mL	Negative	<3.5 - Negative I 3.5-5 - Equivocal I >5 - Positive
Rheumatoid Factor IgA (ELFA)	1.3 IU/mL	Negative	<14 - Negative I 14-20 - Equivocal I >20 - Positive

specificity for SLE vs. healthy individuals). RA33 autoantibodies are highly specific (>95%) for RA against healthy individuals. In a cohort of 161 diagnosed RA patients (60 seropositive and 101 seronegative based anti-CCP and RF), IgG, IgM, and IgA RA33 autoantibodies were collectively present in 32% of seropositive RA patients and 16% of seronegative RA patients.

SA 1685 (11/24 v4)

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