WHITE PAPER

The critical role of the lab in enabling RA diagnosis and care

This white paper presents diagnostic insights that lab testing can provide to help you improve outcomes for your rheumatoid arthritis patients throughout the care continuum.

Inside, you'll find best practices that can help you provide patients a faster path to symptom relief:

- Identify key biomarkers for early diagnosis
- Assess disease severity
- Implement effective treatment strategies through molecular signature testing
- Monitor response to therapies and adjust as needed

Critical points of impact: diagnosis, risk stratification, therapy selection, monitoring

The critical role of the lab in enabling RA diagnosis and care

Introduction

Autoimmune rheumatic diseases (ARDs) are a diverse group of conditions that primarily affect the joints, bones, muscle, and connective tissue. Aside from that commonality, ARDs often manifest in a web of overlapping presentations that pose a long and often complicated diagnostic odyssey, compromising the quality of life for many patients. There are more than 100 forms of arthritis affecting more than 60 million Americans.[1] Rheumatoid arthritis (RA) is the most common type of autoimmune arthritis, affecting an estimated 1.3 million Americans.[2]

60M suffer from arthritis[1]

1.3M suffer from RA[2]

Advances in pharmacotherapies have evolved greatly in the past 2 decades, providing symptom relief for many patients with RA. Accurate and timely diagnosis is the key step in determining the appropriate disease-suppressing therapy to reduce joint pain, swelling, and damage and improve a patient's quality of life.[3,4] The road to the right treatment, however, is not always a straightforward process and entails highly patient-specific therapeutic planning. Considerations of the appropriate therapy, dosing, toxicity, and autoimmune response are often at the forefront of disease management. As such, laboratory testing has advanced to support rheumatologists across the continuum of RA care from diagnosis to treatment and monitoring of the disease.

Lab testing across the continuum of care

Clinical laboratory testing offers tools to aid in diagnosis, treatment selection, and monitoring of RA disease activity. The mercurial nature of autoimmune rheumatic diseases requires a care plan that is continually monitored and amended to address the patient's evolving needs and drug response. Therefore, testing is fundamental to care beyond achieving the initial diagnosis and may help to guide changes to therapies before the patient is negatively impacted by diminishing efficacy of their current treatment (Figure 1).

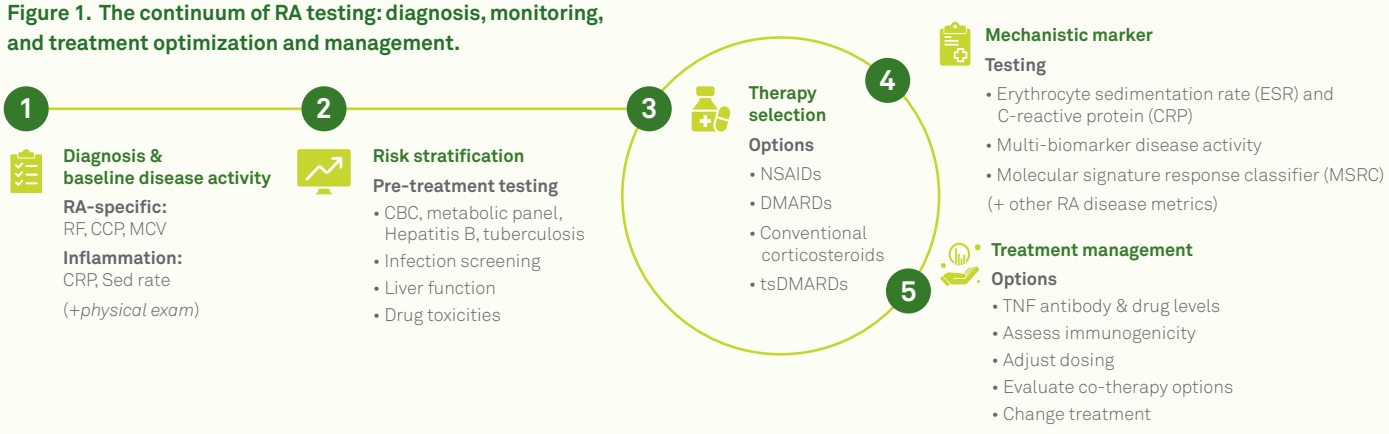
Identifying key biomarkers for earlier diagnosis

The American College of Rheumatology (ACR) last offered diagnostic guidance in 2010 (Table 1). Today, the recommendations lag laboratory advances and continue to specify markers with known limitations. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are general inflammatory markers, but are not specific to RA. The 2 markers most closely associated with RA are rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), measured as anti-cyclic citrullinated peptide (CCP). RF has low sensitivity and low specificity. CCP's sensitivity is usually higher than RF, but its chief advantage is its very high specificity.

Table 1. Who should be tested for RA? The ACR guideline for screening RA: 1 joint with definitive clinical synovitis (swelling), not explained by another disease and a total score of 6 or greater from the ACR/EULAR classification criteria for RA.

Score of ≥ 6/10 needed for "definite RA"	
Joint involvement	
1 large joint	0
2-10 large joints	1
1-3 small joints	2
4-10 small joints	3
> 10 joints (≥ 1 small joint)	5
Serology (≥ 1 test result needed)	
Negative RF *and* negative ACPA[b]	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
Acute phase reactants (≥ 1 test result needed)	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
Duration of symptoms	
< 6 weeks	0
≥ 6 weeks	1

Figure 1. The continuum of RA testing: diagnosis, monitoring, and treatment optimization and management.



Combining multiple markers for increased diagnostic accuracy

By combining tests for multiple markers, greater diagnostic accuracy may be achieved. Assessing the combination of RF and CCP antibodies provides greater sensitivity than either assay alone and is a common strategy in the clinical evaluation of suspected RA. However, seronegativity rates for RF and CCP, which can range from 28% to 44% of RA patients,[5] is a major limitation of these markers and can delay proper diagnosis and treatment. Therefore, these conventional assays alone are suboptimal for screening RA as seronegative patients may be overlooked based on the current criteria.

The past several years have seen a search for biomarkers which might increase sensitivity in order to identify the minority of RA patients who are negative for either RF or CCP. Candidates have included 14.3.3 eta,[6] antibodies to proteins with other similar post-translational modifications such as carbamylated protein,[7] antibodies to the enzyme responsible for citrullination,[8] and antibodies to specific citrullinated proteins such as collagen, fibrinogen, alpha-enolase, and vimentin.[9]

Vimentin is an intermediate filament protein found in mesenchymal cells. Antibodies to citrullinated vimentin (called anti-Sa) were among the first antibodies to specific citrullinated proteins to be identified and were discovered to be highly specific for RA.[10] However, their sensitivity (40%) was too low to be considered an additional diagnostic marker. In 2007, investigators discovered that vimentin in synovial macrophages in RA was mutated and expressed increased numbers of arginine residues, the target for the enzyme responsible for citrullination. Antibody activity in RA patients against mutated citrullinated vimentin (MCV)—as opposed to wild-type—was markedly enhanced, while maintaining high specificity (Figure 2).[11,12]

Since then, many studies have documented the diagnostic performance of the MCV antibody test.[13-17] When CCP and MCV are tested in parallel, overall sensitivity increases to 77%[18]; in early RA, the sensitivity reached 81.2% when anti-MCV and anti-CCP positive results were used as one combined criterion (Figure 3).[19]

The prevalence of serum anti-MCV in patients with early RA (78.2%, 133/170) was significantly higher than that of other rheumatologic patients and patients with infectious diseases,[19] helping to identify patients with undifferentiated arthritis who will develop RA in the future[19,20] and predict risk for progression of severe disease.[21-24]

By implementing an RA screening protocol that combines key markers, clinicians may be better enabled to make care decisions across the RA patient journey from early RA diagnosis, treatment planning, and ongoing care planning.

Figure 2: Scattergrams showing antibody reactivities against wild-type vimentin (wt) and mutated vimentin (MV) and against their citrullinated analogs (cwt and MCV, respectively), using sera from rheumatoid arthritis (RA) patients and healthy volunteers. OD = optical density; NS = not significant.[12]

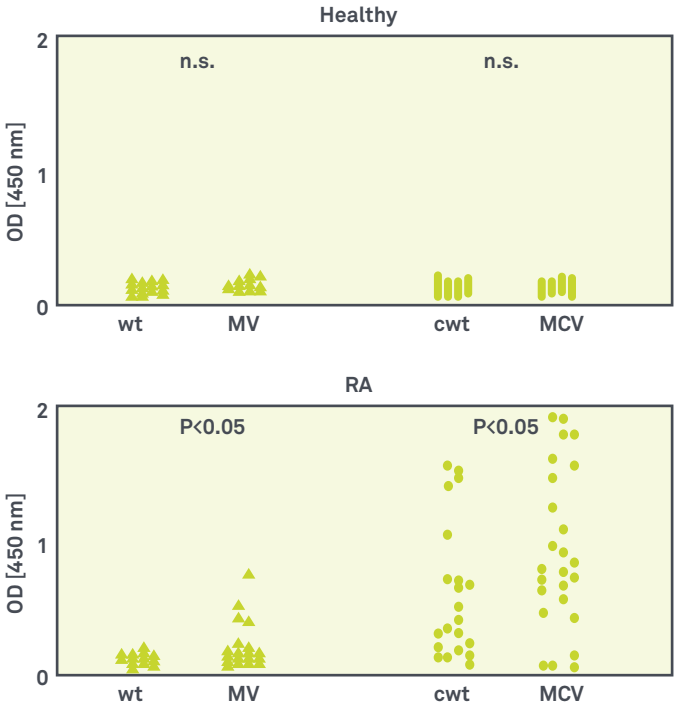
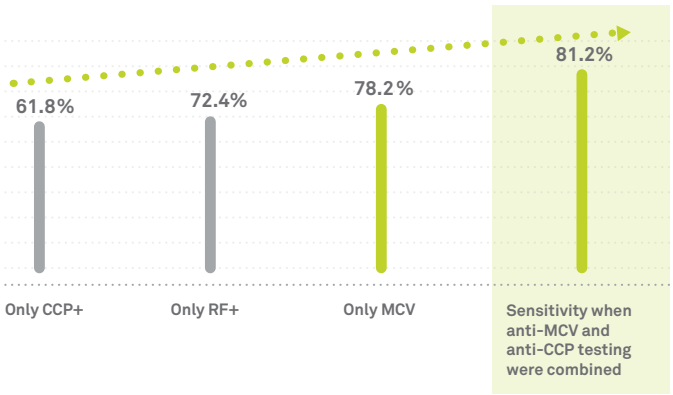


Figure 3: Cumulative benefit of RA marker detection[19]



The role of lab testing in pretreatment screening

NSAIDs, steroids, disease-modifying antirheumatic drugs (DMARDs), biologics, anti-tumor necrosis factor (TNF) drugs, and JAK inhibitors are the medications most commonly used to treat symptoms of RA. These drugs can slow the progression of RA and save the joints and other tissues from permanent damage. However, RA treatments come with well-documented risks.

Determining the potential for increased risk of infection

Corticosteroids, DMARDs, and targeted biologic therapies can be life-changing treatments for RA patients. However, these therapies suppress immune response and therefore pose greater infection risk to patients with already high infection susceptibility.[25] Biologic therapies specifically inhibit targeted molecules of the immune system to better achieve disease control, at the expense of increased risk of infections. Clinicians need to consider various risk factors when selecting the most appropriate biologic therapy for RA patients, as well as precautions and screening for specific infections such as tuberculosis, intracellular bacterial infections, chronic viral infections, hepatitis B, hepatitis C, and HIV. Because of this risk, pretherapeutic laboratory screening is recommended by the American Academy of Dermatology, American College of Gastroenterology, and the ACR.[26,27]

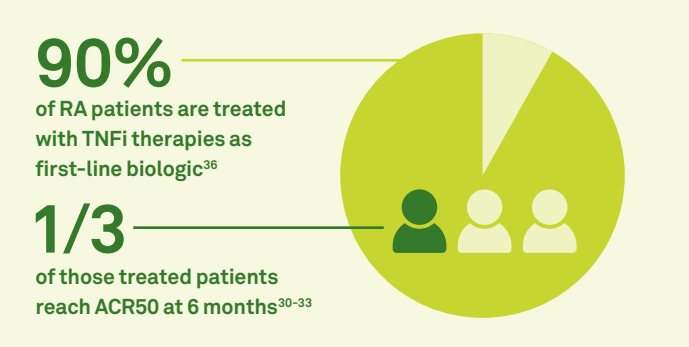
Reducing risk of toxicity

Laboratory testing may also assist physicians in avoiding adverse drug events. Patients who carry defective alleles of TPMT are more likely to experience life-threatening toxicity when they are treated with thiopurine drugs, purine antimetabolites widely used in the treatment of ARDs. The FDA-approved labels for thiopurines recommend testing for the common TPMT gene mutations (genotype) or TPMT activity (phenotype) before beginning treatment.[28] Likewise, because the DMARD methotrexate, an effective immune-system suppressant and common first-line therapy for the treatment of RA, can affect the liver, RA treatment guidelines recommend laboratory testing for liver function before initiating methotrexate treatment.[29]

Despite increased risks associated with RA therapies, many serious side effects can be reduced or prevented with prescreening testing to identify individuals for whom certain therapies will be ineffective or potentially dangerous.

Identifying the right treatment for the right patient

An ongoing challenge in RA treatment relates to forced trial-and-error in therapy selection. While up to 90% of patients with RA are treated with TNFi therapies as first-line biologic or targeted synthetic DMARD,[30,31] only one-third of patients reach ACR50 at 6 months with a biologic treatment after failing methotrexate.[30-33]



PrismRA® from Scipher Medicine is a blood-based, precision medicine, molecular signature response classifier (MSRC) that predicts inadequate response to TNFi therapy in RA. Patients with a molecular signature of inadequate response can be directed to a more appropriate therapy selection. With tailored insights to treatment response, studies indicate that patients are nearly twice as likely to reach low disease activity or remission (Table 2).

PrismRA score	Interpretive criteria
9.2	Patient may be likely to respond to a TNFi
12.4	Patient has a 10% chance of responding to a TNFi
21.5	Patient has a 5% chance of responding to a TNFi

<10.6 = no detectable molecular response signal of nonresponse to TNFi therapies
≥10.6 = high signal of inadequate response to TNFi therapies
≥18.5 = very high signal of inadequate response to TNFi therapies

Adjusting treatment plans, assessment of disease progression and therapy monitoring

Once a treatment plan is developed and initiated, laboratory testing may further aid the physician in maximizing effectiveness of RA therapeutic agents.

Assessing DMARDs response

Therapeutic response to methotrexate can vary widely among patients based on dosage and administration method.[35] However, 30% to 40% of RA patients do not adequately respond to these treatments.[36] Therefore, a test indicating whether a patient has achieved an expected therapeutic goal using a specific dosage is instrumental in ongoing treatment planning for optimal disease management. The test may also help to rule out noncompliance with prescribed therapy.

30% – 40%

of RA patients do not adequately respond to DMARDs[36]

Tailoring biologic agents

Biologic agents are biomanufactured in a living cellular system and represent another drug class that can be effectively used in the treatment of RA.[37] They are considered to be less toxic and generally regarded to be better tolerated in the human body than DMARDs. Adalimumab is a human monoclonal antibody (MAb), and infliximab is a mouse-based MAb. Because of this difference, adalimumab can be self-administered by patients at home, whereas infliximab/Inflectra® must be infused in a clinician's office and is usually combined with an antihistamine to reduce allergic response while infusing. Laboratory testing can help identify those patients who are likely to achieve a long term, stable response.[38]

Many patients, however, will not respond to an individual biologic agent and the right dosing, tailored to each individual patient, could be difficult to achieve and maintain (Table 3). Clinical research shows that dosing biologic agents for RA by weight and empiric titration is often inefficient,[39,40] leaving the physician to prescribe sequential biologics and dose levels in an iterative trial-and-error process until an effective treatment dosage can be determined. For some patients, this process can be lengthy, allowing for further joint damage and prolonging the time to relief.

To mitigate this process, therapeutic drug monitoring assays provide physiological insight to tailor biologic therapy.[41] Physicians can monitor circulating levels of biologic agents such as infliximab and adalimumab in the patient's blood and make dosing and frequency changes more rapidly than relying on the patient's symptomatic response alone (Table 3). Testing can also help differentiate noncompliance and undertreatment from other factors that may cause a lack of response.

Table 3: Incidence of nonresponse to adalimumab and infliximab for treatment of RA

Indication	Adalimumab[a,b,c]	Infliximab and Infliximab-dyyb[a,d,e]
RA[f]	Week 52: 27% (MTX-naïve)[g]	Week 30: 40%-50% (MTX-nonresponsive)[b,g]
	Week 104: 31% (MTX-naïve)[g]	Week 54: 41%-58% (MTX-nonresponsive)[b,g]
		Week 54: 34%-38% (MTX-naïve)[b,g]

ACR, American College of Rheumatology; MTX, methotrexate.

a. HUMIRA® (adalimumab). Prescribing information. AbbVie Inc; 2020. Accessed May 13, 2020. https://www.rxabbvie.com/pdf/humira.pdf

b. Study design, dosage regimens, and patient population (eg, methotrexate-naïve vs no response to methotrexate) varied by drug and disease. Ranges are presented in this table if multiple doses or trial arms were presented in the package insert. See package insert for specific information.

c. Adalimumab is also indicated for treatment of juvenile idiopathic arthritis, hidradenitis suppurativa, and uveitis. See package insert for response rates.

d. REMICADE® (infliximab). Prescribing information. Janssen Biotech Inc; 2020. Accessed June 29, 2020. http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/REMICADE-pi.pdf

e. INFLECTRA® (infliximab-dyyb). Prescribing information. Pfizer Inc; 2019. Accessed May 13, 2020. http://labeling.pfizer.com/ShowLabeling.aspx?id=9271

f. Nonresponse is defined as not meeting ACR 20 response (≥20% improvement for ACR response criteria).

g. In combination with methotrexate.

Addressing immunogenicity

One factor that may cause diminished response to treatment over time is immunogenicity.[42] The biologic agents used to treat RA are intrinsically immunogenic, as they represent complex proteins which are manufactured outside of the body. Antidrug antibodies (ADAbs) develop in up to one-third of patients on biologic therapy, making immunogenicity a primary cause of loss of efficacy observed in RA patients. When a patient produces ADAbs sufficient to suppress the effects of biologic therapies, the physician may opt for an alternate biologic agent. With careful monitoring, physicians can use a combination of strategies to optimize care including cotherapy with methotrexate,[43] titration of drug levels, and maintenance dosing (vs on-demand use) to help reduce the risk of antidrug antibody formation.

Conclusion

If left untreated or undertreated, RA results in severe joint damage leading to impaired physical function and even disability. Clinical best practice cites early identification, assessment of disease severity at diagnosis, and rapid implementation of an effective treatment strategy as key determinants of patient prognosis.[3]

RF and CCP are the 2 markers most closely associated with RA, but adding MCV to CCP can dramatically increase sensitivity.[19] As a complementary marker, MCV can enable an earlier diagnosis since antibodies can be detected earlier in the course of the disease than CCP or RF. MCV can also help identify patients with undifferentiated arthritis who may develop RA in the future,[19,20] and predict risk for progression of severe disease.[21-24]

When combined with pretreatment testing, infection screening, and analysis of liver function and drug toxicities, physicians can more confidently manage treatment across the continuum of RA care. As a result, physicians can achieve faster diagnosis, reduced therapeutic risk, optimized treatment plans, and proactive monitoring of therapy. For the patient, comprehensive RA testing ensures cost-effective care with effective dosing and a faster path to symptom relief.

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