RHEUMATOID ARTHRITIS
Rheumatoid arthritis

Rheumatoid arthritis (RA) affects an estimated 1.5 million people in the United States. RA is the most common type of autoimmune arthritis. Treatments have improved greatly and help many of those affected. For most people with RA, early diagnosis and treatment can control joint pain and swelling, and lessen joint damage. LabCorp offers a variety of tests to aid in diagnosis, management of treatment and monitoring of disease activity.
Single-Source Solution for the Rheumatology Specialist

LabCorp offers a comprehensive testing menu and numerous service benefits to support the needs of a rheumatology practice:

- Broad capabilities in autoimmune testing
- Specialized assays for treatment monitoring
- Multiple connectivity options
- More than 1900 patient service centers nationwide
- Extensive network of managed care health plans
- Experienced medical affairs professionals are available for consultation and educational programs
- LabCorp offers a dedicated hotline for biologic drug monitoring
  - Biologic Monitoring Hotline: 844-225-8877

Monitor Disease Activity

Physical Exam
Vectra DA (Monitor)

Treatment Monitoring

- Thiopurine Metabolites
- MTX Polyglutamates
- Biologic Drug Concentration and Antibody Testing (DoseASSURE™)

Treatment Management

- Quantify active drug levels
- Identify immunogenicity
- Adjust dosing and frequency
- Consider co-therapy
- Switch Treatment

Responder
Monitor progress
Adjust dosing if indicated
RA Diagnosis

Early diagnosis of RA is important because it has been recognized that early initiation of disease-suppressing therapy may improve clinical outcomes and reduce the accrual of joint damage and disability. LabCorp offers three RA-specific markers that, when used in combination, provide industry leading sensitivity as well as early diagnosis of RA.

Anti-CCP 3.1

- LabCorp’s Anti-CCP 3.1 offers greater sensitivity than earlier CCP tests
  - Enhanced sensitivity is achieved by utilizing both IgG and IgA antibodies
  - Anti-CCP 3.1 provides a sensitivity of 70.3% and specificity of 97.8%
  - Anti-CCP 3.1, when used in combination with RF, provides greater sensitivity than RF alone
  - Anti-CCP 3.1 has been shown to correctly identify 83% of RA patients who were found to be RF negative
  - Anti-CCP 3.1 is the first assay approved for early detection of RA
  - Improved detection within 2 years of onset

14-3-3 eta

- The 14-3-3 eta protein is a joint-derived, proinflammatory mediator that is implicated in the joint erosion process and pathogenesis of RA
  - Positive serum 14-3-3 eta levels are associated with higher rates of joint damage as measured by radiographic assessments using the Sharp/van der Heijde Score
  - Serum testing shows that 14-3-3 eta is elevated in both early and established RA
  - 14-3-3 eta is highly specific for RA. Serum 14-3-3 eta may be especially helpful in identifying patients with early RA, as it provides a 15% incremental benefit to the diagnostic sensitivity of markers including, Rheumatoid Arthritis (RA) Factor and Cyclic Citrullinated Peptide (CCP) Antibodies
  - A higher level of 14-3-3ŋ also helps to identify RA patients who are most likely to exhibit rapid progression and need earlier, tailored therapy

Profiles

LabCorp offers the following profiles to aid in the diagnosis of RA.

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Test No</th>
</tr>
</thead>
<tbody>
<tr>
<td>RheumAssure</td>
<td>504509</td>
</tr>
<tr>
<td>Profile includes:* Anti-CCP 3.1, Rheumatoid Arthritis (RA) Factor and 14.3.3 eta</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid Arthritis (RA) Profile</td>
<td>164065</td>
</tr>
<tr>
<td>Profile includes:* Anti-CCP 3.1, Rheumatoid Arthritis (RA) Factor</td>
<td></td>
</tr>
</tbody>
</table>

*Individual components may be ordered separately.
Crescendo Bioscience’s test, Vectra® DA (Test no. 819290), is available for ordering through LabCorp. Vectra DA assesses disease activity in adult rheumatoid arthritis (RA) patients. It provides a score, ranging from 1 to 100, that assesses RA disease activity, and is used to categorize the activity as low, moderate or high. This quantitative method can be used over time to track the progression of disease activity within RA patients. No kits are necessary for this test. Vectra DA is available for physicians to order through the standard LabCorp ordering process and collection can take place at LabCorp patient service centers. Additionally, reports will be delivered through the standard results delivery process for LabCorp.

Please note that LabCorp contracts do not apply as Crescendo Bioscience will continue to perform testing and billing for Vectra DA.
Monitoring Methotrexate
The reaction to methotrexate can vary widely among rheumatoid arthritis patients. Data suggests that the process of MTX polyglutamation is a function of the dosage level and administration method. It has been found that 30% to 40% of rheumatoid arthritis patients do not adequately respond to methotrexate treatment. A test indicating whether or not a patient has achieved an expected therapeutic level on a specific dosage can be useful in ongoing patient management.

Methotrexate Polyglutamates (MTXpgsRA) Test
• It is considered important to work to attain dose optimization when treating patients on methotrexate.
• Testing may be ordered at any time during therapy and should be conducted at least 36 hours after last dose of methotrexate.
• The report for MTXpgsRA provides the measurement of each polyglutamate (1-5) and shares detailed information that can assist in result interpretation and treatment planning.

Thiopurine-related Testing
Thiopurine related testing, including genetic and metabolic activity, may be used to identify patients who may be at risk for drug toxicity and to assess dosage, and to maximize treatment effectiveness.

TPMT Activity Test and TPMT Genetic Test
Due to potential toxicity that can occur even with standard Thiopurine dosages in patient with TPMT enzyme deficiency, the FDA-approved label recommends consideration for testing for the common TPMT gene mutations (genotype) or TPMT activity (phenotype) before beginning treatment.

TPMT Enzyme Activity Test
• Utilize prior to treatment as a screen for low TPMT activity
• Interpretive reports support initial dosing decisions
• TPMT Activity directly measures red blood cell thiopurine S-methyltransferase activity and may detect clinically relevant mutations not detected in the TPMT Genetic Test

TPMT Genotyping
• TPMT genetic testing has a clinical sensitivity of approximately 95% for TPMT mutations # *2, *3A, *3B, and *3C and is not sensitive to red blood cell transfusion or environmental factors that can impact results for TPMT Activity

Thiopurine Metabolites Test
• Utilize during treatment to help reach and maintain therapeutic goal
• Assists with evaluating unresponsive patients
• Monitors responsive patients to avoid potential toxicity
• Drug concentrations reported for 6-TG (6-thioguanine) and 6-MMP (6-methylmercaptopurine)
Monitoring Biologics — *DoseASSURE™* Portfolio

Therapeutic drug monitoring for biologics is a valuable tool to evaluate dose and tailor dose adjustments to your individual patient.\(^{15-19}\) Dosing by weight and empiric dose adjustment may be inefficient and suboptimal.\(^{16,19}\) *DoseASSURE™*, LabCorp’s portfolio of biologics monitoring assays, may help physicians optimize biological therapy using a personalized, patient-specific approach by:

- Aiding in titrating doses and adjusting frequency to maximize effectiveness\(^{15,16}\)
- Help differentiate non-compliance and under-treatment from other causes of lack of response.\(^{17}\)
- Assisting in preventing and managing loss of response due to immunogenicity\(^{15,18}\)
- Minimizing cost to patient by avoiding unhelpful dose escalation\(^{19}\)
- Predicting which patients are likely to retain long-term response\(^{20}\)

Clinical efficacy in RA has been shown to correspond with serum concentrations of adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab, and ustekinumab.\(^{18,21-25,36}\)

### Immunogenicity Testing (Anti-drug Antibody Level)

- As many as one third of RA patients on biological therapy may develop anti-drug antibodies.\(^{29,30}\)
- Anti-drug antibodies can adversely affect the amount of drug in the body.\(^{15,29-31}\)
- Co-therapy with methotrexate, sufficient drug levels, and maintenance dosing (vs. episodic or on-demand use) reduce the risk of anti-drug antibody formation.\(^{29-34}\)

### Drug Normal half-life Proposed Target Ranges for Trough Concentrations \(^{§}\) Other clinical data on Trough Concentrations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Normal half-life</th>
<th>Proposed Target Ranges for Trough Concentrations (^{§})</th>
<th>Other clinical data on Trough Concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>Approx. 2 weeks</td>
<td>5 - 8 ug/mL in RA(^{21}); 5 - 8 mg/L in PA(^{26}); 3.5 – 7.0 mg/L in psoriasis(^{27})</td>
<td>A definitive target range has yet to be determined.</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>Approx. 2 weeks</td>
<td>&gt;23 µg/mL corresponded to better EULAR response rates.(^{36})</td>
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<tr>
<td>Etanercept</td>
<td>3 – 5.5 days</td>
<td>&gt; 3.1 ug/mL (at 3 months predicted response at 6 months in RA.)(^{28})</td>
<td>In RA, good responders had higher levels (median 3.8 mg/L, 2.5 – 5.2) compared to non-responders (2.8 mg/L, 1.3 - 3.9).(^{23}) In AS, clinical responders (ASDAS) had higher median levels (median 3.8 mg/L, 2.5 – 5.2) than non-responders (2.3 mg/L, 1.2 – 3.4).(^{20})</td>
</tr>
<tr>
<td>Golimumab</td>
<td>Approx. 2 weeks</td>
<td>No consensus on clinical recommendation for RA</td>
<td>In RA, higher levels (median 3.4 ug/mL) were associated with a greater rate of clinical response (ACR20).(^{24})</td>
</tr>
<tr>
<td>Infliximab</td>
<td>7.7 to 9.5 days</td>
<td>&lt; 2 ug/mL: low and ≥ 8 ug/mL: high in RA(^{16})</td>
<td>In RA, responders had higher levels (median 3.6 mg/L, 1.4 – 8.2) than non-responders (0.5 mg/L, 0.2 – 2.2).(^{21})</td>
</tr>
<tr>
<td>Rituximab</td>
<td>18 days (5.2-77.5 days)</td>
<td>No consensus on clinical recommendation for RA</td>
<td></td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>Approx. 3 weeks</td>
<td>A definitive target range has yet to be determined</td>
<td>In psoriasis, PASI 50 responders had higher trough concentrations than non-responders.(^{35})</td>
</tr>
</tbody>
</table>

\(^{§}\)Note: These targets concentrations were those used in landmark studies and do not necessarily translate into general recommendations for individual patients. Please see referenced literature for more details.

### Treatment Management

LabCorp’s variety of test options provide physicians information that may assist in treatment management decisions.

Treatment decisions based on quantification of active drug levels, and the identification of immunogenicity can assist physicians with the following decisions:

- Adjustment of dose and frequency
- Consideration of co-therapy
- Treatment change based on patient response
References
4. QUANTA Lite™ CCP 3.1 IgG/IgA ELISA [directional insert]. INOVA Diagnostics, Inc; October 2009. Revision 2.