New 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
- Identifying lack of response due to non-compliance or under-treatment
- Assisting in preventing and managing loss of response due to immunogenicity
- Predicting which patients are likely to retain long-term response
- Minimizing cost to patient by avoiding unhelpful dose escalation
- Avoiding overtreatment in low disease activity cases where tapering down is desirable

### LabCorp Biologic Tests provide both drug concentration (TDM) & anti-drug antibody (immunogenicity)

#### Therapeutic Drug Monitoring (TDM)

- Biologics have variable pharmacokinetics.
- Dosing by weight and empiric dose adjustment may be inefficient and suboptimal.
- Clinical efficacy in RA has been shown to correspond with serum concentrations of infliximab, adalimumab, etanercept, golimumab and rituximab.
- TDM for biologics is a valuable tool to evaluate doses and to tailor dose adjustments to your individual patient.
- TDM can help differentiate non-compliance and under-treatment from other causes of lack of response.
- Personalized treatment using TDM has been shown to improve both clinical and cost-effectiveness in RA.

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

- All biologics have the potential to induce an antibody-mediated immune response.
- As many as one third of RA patients on biological therapy may develop anti-drug antibodies.
- Anti-drug antibodies may appear as early as 2 weeks or as late as 3 years after the first infusion.
- Co-therapy with methotrexate, sufficient drug levels, and maintenance dosing (vs. episodic or on-demand use) reduce the risk of anti-drug antibody formation.
- Anti-drug antibodies can adversely affect the amount of drug in the body. Therefore, concomitant measurement of anti-drug antibodies is an important adjunct to TDM for biologics.

<table>
<thead>
<tr>
<th>Biologic Drug Name</th>
<th>Primary Target</th>
<th>*Clinical Indications</th>
<th>LabCorp® Test</th>
<th>LabCorp® Test #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>TNF</td>
<td>RA, PA, PP, AS, CD, UC</td>
<td>Infliximab Concentration and Anti-Infliximab antibody (Serial Monitor)**</td>
<td>503870</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>TNF</td>
<td>RA, JIA, PA, PP, AS, CD, UC</td>
<td>Adalimumab Concentration and Anti-Adalimumab Antibody (Serial Monitor)</td>
<td>503890</td>
</tr>
<tr>
<td>Etanercept</td>
<td>TNF</td>
<td>RA, JIA, PA, PP, AS, CD, UC</td>
<td>Etanercept Concentration and Anti-Etanercept Antibody Levels (Serial Monitor)</td>
<td>504245</td>
</tr>
<tr>
<td>Golimumab</td>
<td>TNF</td>
<td>RA, PA, AS, UC</td>
<td>Golimumab Concentration and Anti-Golimumab Antibody</td>
<td>504340</td>
</tr>
<tr>
<td>Rituximab</td>
<td>CD20</td>
<td>RA, NHL, CLL</td>
<td>Rituximab Drug Concentration and Anti-Rituximab Antibody Levels</td>
<td>504355</td>
</tr>
</tbody>
</table>


** Published validation study, Marini JC, et al. Comparisons of Serum Infliximab and Antibodies-to-Infliximab Tests Used in Inflammatory Bowel Disease Clinical Trials of Remicade® AAPS Journal 2016. DOI: 10.1208/s12248-016-9981-3
Interpreting Drug Concentrations

- Higher drug trough levels have been correlated with clinical improvement as well as to higher rates of response and remission in rheumatic diseases.1-7
- A consensus has yet to be reached about target ranges and maximally effective concentrations.1

Optimal drug concentration depends on the disease and the desired therapeutic endpoint.

<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>Infliximab</td>
<td>7.7 to 9.5 days</td>
<td>&lt; 2 ug/mL: low and ≥ 8 ug/mL: high in RA2</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).2</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Approx. 2 weeks</td>
<td>5 - 8 ug/mL in RA; 5 - 8 mg/L in PA;1,15 3.5 – 7.0 mg/L in psoriasis20</td>
<td>In RA, higher levels (median 3.4 ug/mL) were associated with a greater rate of clinical response (ACR20).6</td>
</tr>
<tr>
<td>Golimumab</td>
<td>Approx. 2 weeks</td>
<td>No consensus on clinical recommendation for RA</td>
<td>In RA, responders had higher levels (median 3.8 mg/L, 2.5 – 5.2) compared to non-responders (2.9 mg/L, 1.3 – 3.9).9 In AS, clinical responders (ASDAS) had higher median levels (3.8 mg/L, 2.5 – 5.2) than non-responders (2.3 mg/L, 1.2 – 3.4);21</td>
</tr>
<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)21</td>
<td></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>
</tbody>
</table>

§Note: These target 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.

When & where to collect blood on my patients?

- The timing of sample collection is important because the drug concentration will change during the dosing interval.
- The trough concentration (TC) is measured at the least variable time in the dosing interval, just before the next dose (same day to within < 7 days depending on the drug’s normal half-life).
- During induction and maintenance phases, trough collections are usually recommended because target ranges are defined using TC.
- Blood can be drawn at any of LabCorp’s 1700 patient service centers located nationwide.

Additional RA and Treatment-Related Testing

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Drug or Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.3.3 ETA/Rheumatoid Arthritis (504550)</td>
<td>Rheumatoid Arthritis (RA) Factor (006502)</td>
</tr>
<tr>
<td>C-Reactive Protein (CRP), Quantitative (006627)</td>
<td>Rheumatoid Arthritis (RA) Profile (164065)</td>
</tr>
<tr>
<td>Complete Blood Count With Differential (005009)</td>
<td>Sedimentation Rate, Modified Westergren (005215)</td>
</tr>
<tr>
<td>Cyclic Citrullinated Peptide (CCP) Antibodies, IgA, IgG, ELISA (164914)</td>
<td>Thiopurine Metabolites (503800)</td>
</tr>
<tr>
<td>Hepatitis B Virus (HBV) Evaluation Profile (037215)</td>
<td>Thiopurine Methyltransferase (TPMT), Enzyme Activity, Erythrocytes (510750)</td>
</tr>
<tr>
<td>Metabolic Panel (14), Comprehensive (322000)</td>
<td>Thiopurine Methyltransferase (TPMT) Genotyping (504142)</td>
</tr>
<tr>
<td>Methotrexate Polyglutamates (504104)</td>
<td>Vecstar® DA Disease Activity (819290)</td>
</tr>
<tr>
<td>QuantIFERON®-TB Gold (182873)</td>
<td></td>
</tr>
</tbody>
</table>

References