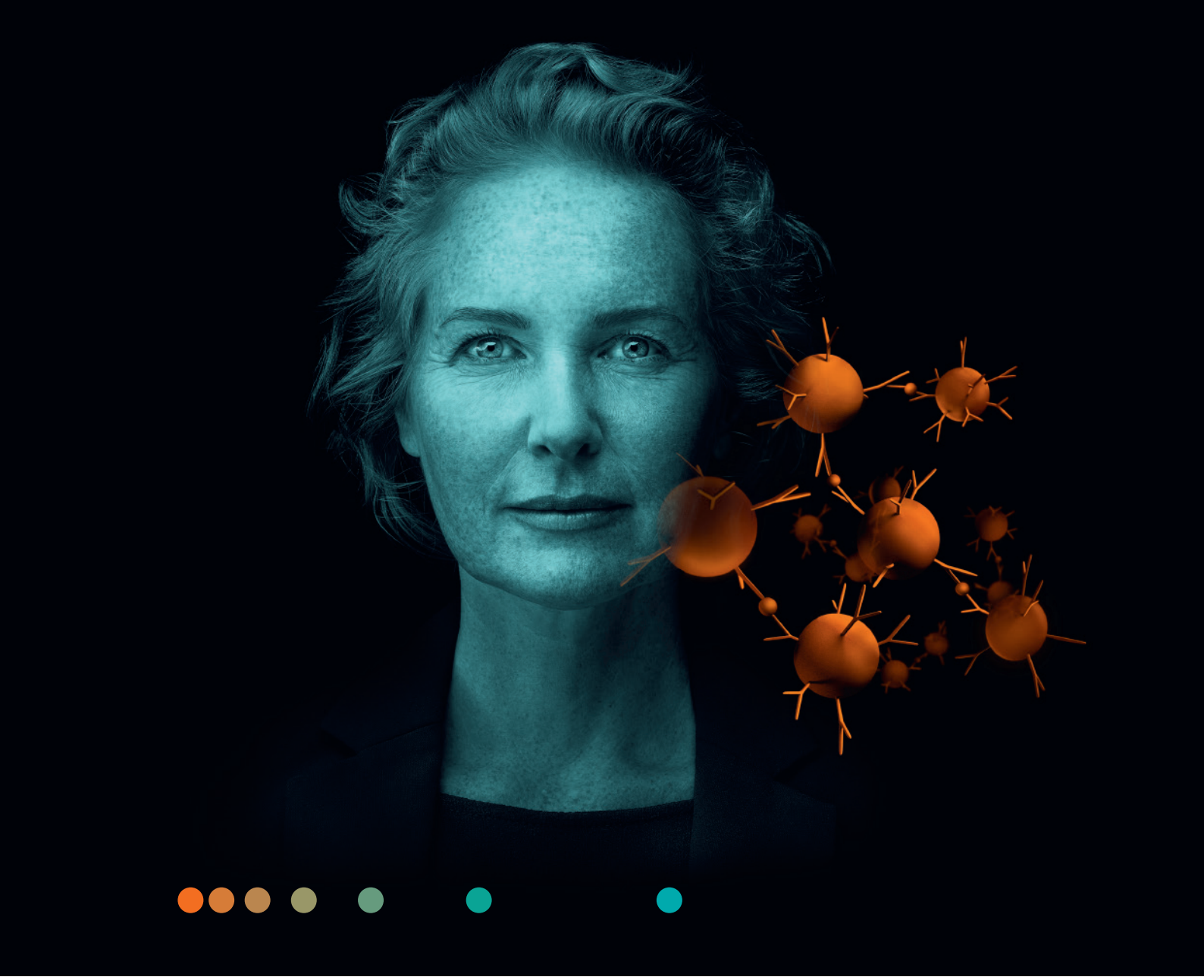

N Latex aTNFα (TNFα Inhibitor) Assay

An automated, cost-effective, and easily accessible assay for monitoring the effectiveness of therapeutic anti-inflammatory medication regimens

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SIEMENS Healthineers

TNF-alpha Inhibitor Drugs: An Effective but Challenging Therapy for Inflammatory Diseases

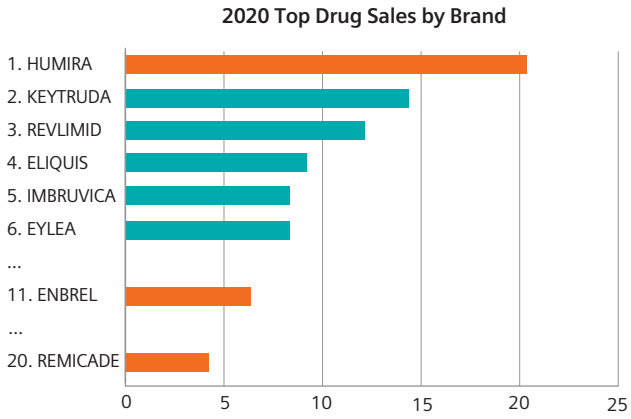
Millions of patients globally suffer from rheumatoid arthritis, inflammatory bowel disease, psoriasis, or ankylosing spondylitis.

While there's no cure available for these diseases, the development of biologicals has helped to improve therapy. Tumor necrosis factor-alpha (TNFα) antagonists became a cornerstone in treatment and are extensively used in clinical settings to treat inflammation-associated disorders.

Well-established drugs (see Figure 1) employ TNFα antagonists to help reduce inflammatory responses by targeting both membrane-bound and soluble TNFα to reduce TNFα activity. Different biologicals are used in TNFα inhibitor drugs: Adalimumab (ADA), infliximab (INF), and etanercept (ETA) are most commonly used, followed by recently developed agents such as certolizumab pegol and golimumab.

While the introduction of these agents improved patient management and can be very effective, the therapy often has to be complemented by other drugs, depending on the specific disease and its severity. TNFα-inhibitor treatments provide positive therapeutic effects; however, they are also associated with high costs and patient burden due to regular subcutaneous injections as well as potential dose-dependent side effects.

Therapeutic failure (primary or secondary loss of response) is also common and has been attributed to inadequate serum concentrations of the drug or formation of anti-drug antibodies.[4] Therapeutic drug monitoring (TDM) can therefore be an effective tool for the interpretation of loss of response to certain drugs and to monitor and adjust dosage for optimized exposure. Dose-reduction strategies are frequently discussed to achieve cost-effectiveness, since therapy is costly and puts a burden on healthcare budgets.[5,6]



Humira is the top-selling drug in 2020, with cancer drugs and anticoagulants recently taking over top positions. The trend towards use of TNFα inhibitors (orange) still continues, with more biosimilars competing with established brands entering the market.

Figure 1. List of top-selling drugs in 2020 in billion US$. Data from https://www.pharmadigicoach.com/top-selling-drugs-by-2020-sales/.

Worldwide, millions of people suffer from chronic inflammatory diseases:

Rheumatoid arthritis
~14 million[1]

Inflammatory bowel disease
~7 million[2]

Psoriasis
~125 million[3]

Why Therapeutic Drug Monitoring for Biologic Agents Is Imperative

The use of biologicals designed from monoclonal antibodies, such as TNFα inhibitors, has expanded exponentially. Despite their effectiveness and safety, continuous administration of these drugs may be associated with an undesirable anti-drug antibody (Ab complex) response, reducing the efficacy of the biologicals and eventually leading to adverse immune reactions. Therefore, the effectiveness of these therapeutic drugs can be hampered.

Up to one-third of patients with Crohn's disease or ulcerative colitis show primary non-response to biologic therapies, and up to 50% of patients stop therapy for either secondary loss of response or a serious adverse event.[7] Secondary loss of response occurs most frequently within 2–3 years after initiation of treatment (Figure 2). Loss of response is often associated with subtherapeutic drug serum levels that can be caused by Ab complex formation. But the molecular landscape of Ab complex formation is not fully understood, and many patients do not have detectable anti-drug antibody levels. Subtherapeutic drug levels can be associated with significantly higher disease activity. Conversely, overexposure is likewise not desirable. Therefore, it is important that patients be treated by maintaining the desired therapeutic drug concentration.

Another challenge for TDM of TNFα inhibitors might be the limited availability of testing options on automated, random-access immunoassay platforms. Current methods include enzyme-linked immunosorbent assay (ELISA), chemiluminescence immunoassay (CLIA), and liquid chromatography-tandem mass spectrometry (LC-MS/MS), which might not be available in every lab. These methods might also suffer from long turnaround times, the need to batch samples because single measurements are uneconomical, and extensive hands-on time for lab staff.

Many practical recommendations for the use of TNFα inhibitors have been published to support clinicians in decision making. TNFα inhibitor measurement is considered appropriate for:

- Reactive testing in patients with loss of response
- Proactive testing in patients before a loss of response is noted
- Testing in responders for all TNFα inhibitors at the end of induction
- Testing at least once during maintenance for patients on all TNFα inhibitors
- Testing for all TNFα inhibitors in patients with confirmed secondary loss of response

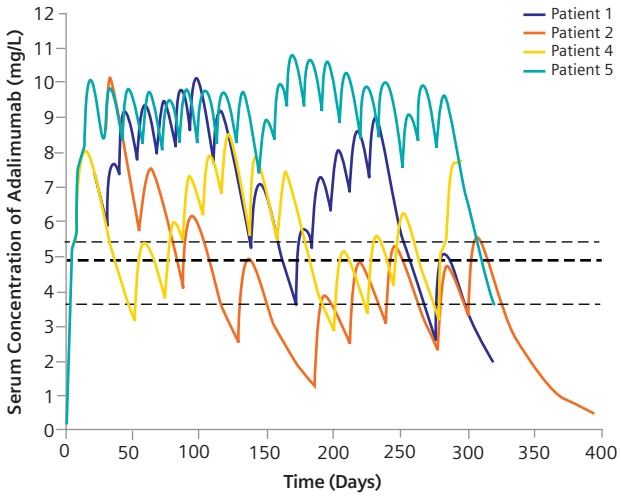
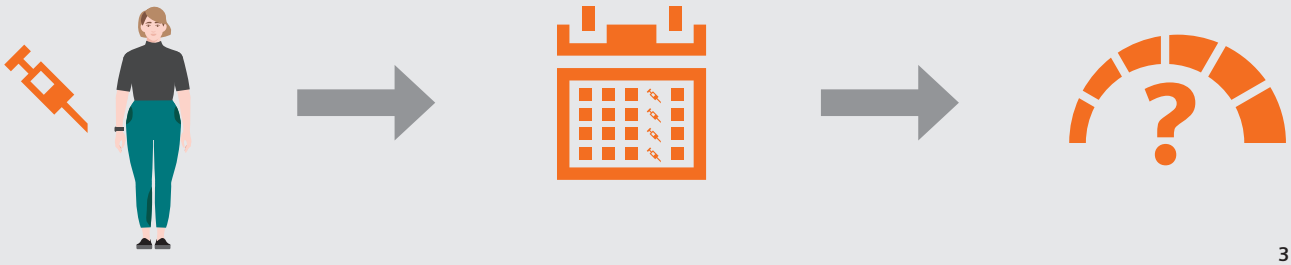


Figure 2. Serum concentration of adalimumab over time for patients whose serum levels dropped below the therapeutic threshold. Graphic adapted from Morrison A, et al. 2015.[8]

TNF-alpha inhibitor drugs have become a commonly used therapy for treatment of inflammatory diseases. Without lab testing, the level of response in patients undergoing therapy remains unclear.



Optimizing Individual Therapeutic Dosage Regimens Supports Improved Disease-state Management and Reduction of Healthcare Costs

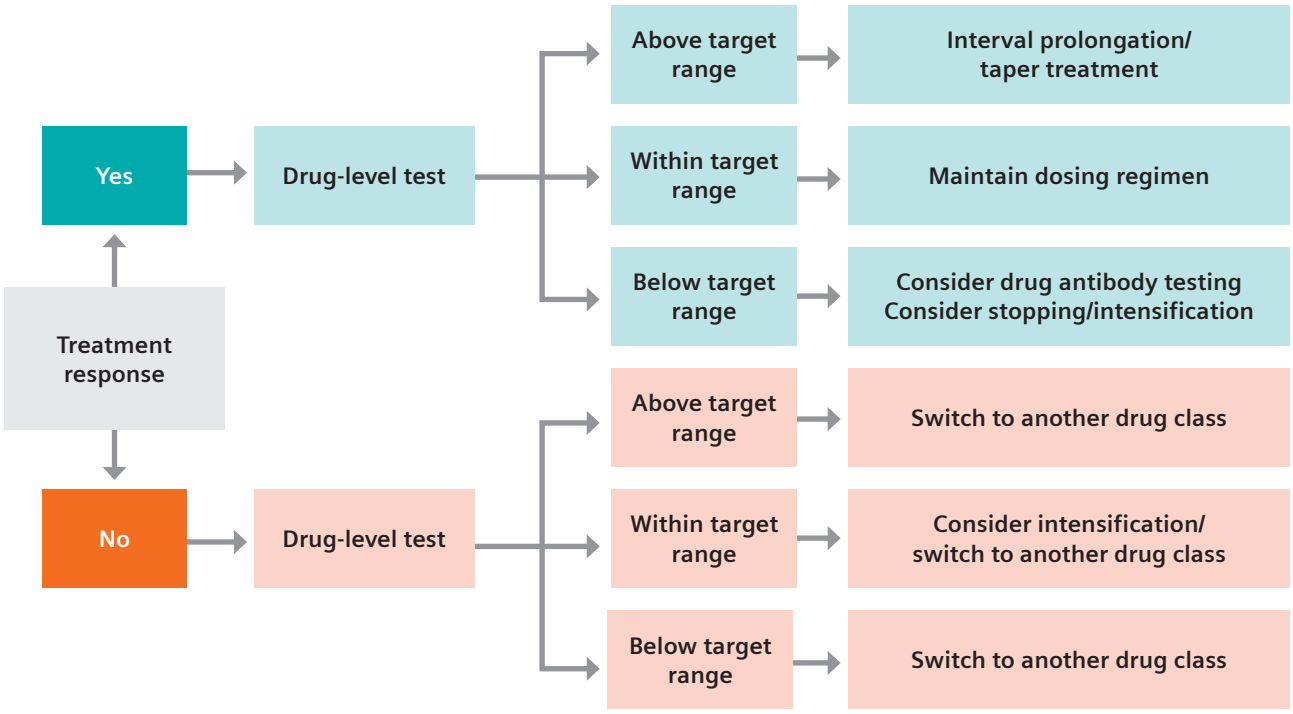


Figure 3. Generic TDM algorithm.

Therapeutic drug monitoring of TNFα inhibitor drugs is more than quantifying a patient's drug concentration in serum: It also provides insights into the response to and effectiveness of anti-inflammatory medication. Biologicals such as adalimumab, infliximab, and etanercept are in clinical use for treatment for rheumatoid arthritis (RA), while adalimumab and infliximab are most commonly used in clinical settings to treat inflammatory bowel disease (IBD), such as Crohn's disease or ulcerative colitis. A further clinical area for use of TNFα inhibitors is psoriasis (especially psoriatic arthritis). The significant number of primary and secondary non-responders, whose disease does not respond to the drug at all or stops responding at a later stage of treatment, has led to the development of many practical recommendations.

Treatment strategies for the management of RA patients with biologicals were published by the European League Against Rheumatism (EULAR) starting in 2010, with the latest update in 2019.[9] For IBD, several guidelines or consensus statements for TDM are available describing scenarios when TDM should be performed.[7,10,11]

Overall, it seems appropriate to order drug or drug antibody concentration testing in responders, during maintenance, in primary non-responders, and in patients with confirmed secondary loss of response and who are becoming resistant (refractory) to the specific drug. The optimization of individual therapeutic dosage regimens for improved personalized patient management and therapy has been discussed in multiple publications, leading to proposed TDM algorithms as shown in Figure 3. Patients should always receive the optimal dosage, since serum drug concentrations correlate with clinical response, clinical remission, and mucosal healing in patients with IBD.

Monitoring serum drug level with TNFα inhibitor assays can therefore support making faster and more accurate clinical decisions about adjusting the drug regimen.

Cost-effectiveness of TDM

Insights into response and effectiveness of anti-inflammatory medication with adalimumab, infliximab, or etanercept by using TDM in combination with published clinical recommendations can improve patient management and clinical outcomes. In addition to its clinical benefits, the cost-effectiveness of TDM has been investigated. Dose-reduction strategies are commonly discussed to achieve cost effectiveness, since TNFα inhibitor therapy is costly and puts a burden on healthcare budgets.

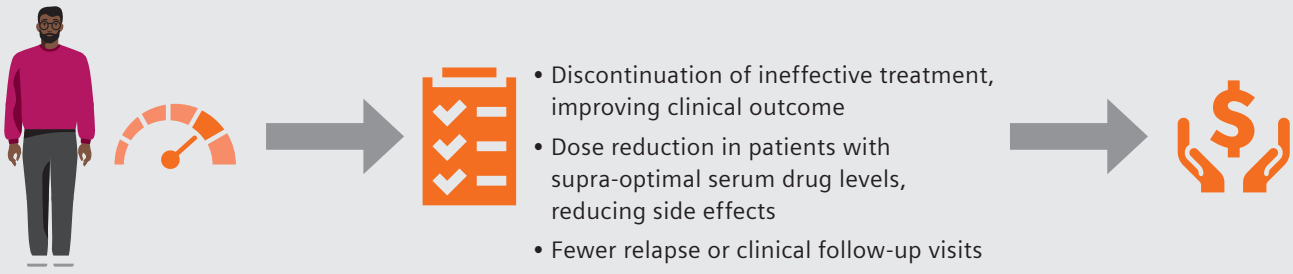
Several randomized studies and modeling approaches using Markov or other models have shown significant overall cost savings, despite additional costs for lab testing.[12] When looking at a single patient base, avoiding ineffective treatment was estimated to provide cost savings of more than €3000 per non-responder in just 12 weeks.[6] Other studies used virtual cohorts to estimate high-level savings and found cost reductions of more than €130 000 000 within 5 years in a cohort of 10 000 patients.[13]

Studies using virtual cohorts to estimate high-level savings found potential cost reductions of more than €130 000 000 within 5 years for a cohort of 10 000 patients.[13]

While current test methods, such as ELISA or POC tests, already provide sensitive and efficient TDM, the new N Latex aTNFα assay from Siemens Healthineers offers a cost-effective option with fully automated, random-access quantification of adalimumab, infliximab, and etanercept using just one reagent for all three biologicals, plus individual packaging and ordering options for economical testing.

- **With lab testing calculated at €200 for drug-level and antibody testing, only two to five non-optimal clinical decisions per 100 patients led to cost savings.[14]**
- **Lab tests costing as much as €2000 per test could still benefit from a TDM-based strategy.[13]**

While insight into drug-level responses supports improved patient outcomes, it also has the potential to reduce overall healthcare costs related to TNF-alpha inhibitor drug therapies.



- Discontinuation of ineffective treatment, improving clinical outcome
- Dose reduction in patients with supra-optimal serum drug levels, reducing side effects
- Fewer relapse or clinical follow-up visits

N Latex aTNFα Assay: Flexible Assay. Few Steps. Fast Results.

An automated, cost-effective, and easily accessible assay for monitoring the effectiveness of therapeutic anti-inflammatory medication regimens

An easy-to-use, automated assay for TNFα inhibitor determination

The N Latex aTNFα assay enables easy, cost-effective access to therapeutic drug monitoring in serum and EDTA plasma samples for adalimumab (ADA), infliximab (INF), and etanercept (ETA) for personalized treatment of patients with rheumatoid arthritis and inflammatory bowel disease.

Fewer steps and faster results

The N Latex aTNFα assay runs on Atellica® NEPH 630 and BN™ Systems from Siemens Healthineers and can be requested as a single, ad hoc test. Unlike other commercially available ELISA testing solutions, testing on plasma protein analyzers from Siemens Healthineers does not require batching. Integrating anti-TNF-alpha testing in your lab helps to broaden clinical insights, avoid send-outs, and enable faster time to result.

Flexible 3-in-1 solution supports testing for multiple drugs with just one reagent

- One reagent kit for three applications
- Individual packaging and consumable ordering options for ADA, INF, and ETA for cost-effective testing
- Option to efficiently measure just one sample without waste of testing capacity
- 26 tests/vial* enables testing even with low throughput and helps avoid costly send-outs

This flexible assay is designed to determine ADA, INF, and ETA concentrations using just one reagent kit in combination with selective calibrators and controls. Latex-enhanced particles form aggregates with TNFα that correlate to the amount of TNFα inhibitors in the sample. Drug concentration in the sample is measured based on the calibrator(s) employed.

N Latex aTNFα assay for the quantification of:		
Adalimumab	Infliximab	Etanercept

This 3-in-1 solution not only allows less hands-on time, but helps reduce handling, material, and ordering complexity.

Offered along with the broadest plasma proteins menu† for a comprehensive diagnostic picture

Dedicated to improving outcomes for labs and patients, Siemens Healthineers is among the first suppliers to offer an automated, random-access immunoassay for anti-TNFα inhibitor testing. This makes therapeutic drug monitoring accessible to any-sized lab. The assay is offered in conjunction with the industry's broadest plasma protein testing portfolio for a comprehensive disease-state picture, without the need for a dedicated TDM testing platform.

*Based on typical reagent consumption defined by the assay protocols. Individual number of tests per unit may vary. Automated redilutions in case of very high or low drug concentrations in the sample may increase reagent consumption.

†As of 01/2022.

The N Latex aTNFα assay runs on Atellica NEPH 630 and BN Systems and produces results in just 7 to 9 minutes. Test results correlate well with ELISA testing methods (Figure 4).

Contact your Siemens Healthineers representative today to upgrade your testing with the N Latex aTNFα assay and achieve improved clinical and economical outcomes in therapeutic drug monitoring.

High correlation with established ELISA assays (Figure 4)

- Optimized for sensitive nephelometric technology for confidence in results
- NIBSC-standardized determination for ADA, INF, and ETA
- High lot-to-lot consistency due to use of monoclonal antibodies

Consolidated, random-access testing for a streamlined workflow and fast results

- Fully automated, random-access immunoassay with few manual steps required
- Testing on demand: no need to batch or collect samples
- Automated recognition of all assay components by active barcode identification
- Time to result just 7–9 minutes
- Six-week calibration curve stability and up to 2-week onboard storage of reagents
- Option to include testing in a laboratory automation setup with the BN II System

Robust performance across all parameters

Broad initial measuring range covers the majority of samples with one measurement.

	Initial Measuring Range (mg/L)	Recommended Therapeutic Reference Range[6,15-18] (mg/L)
Adalimumab	0.90–15.0	5–8 (5–12 in IBD)
Infliximab	0.90–15.0	3–7
Etanercept	0.45–7.5	>1.5

Correlation of N Latex aTNFα assay to ELISA methods: scatter plots with Passing-Bablok regression (internal data)

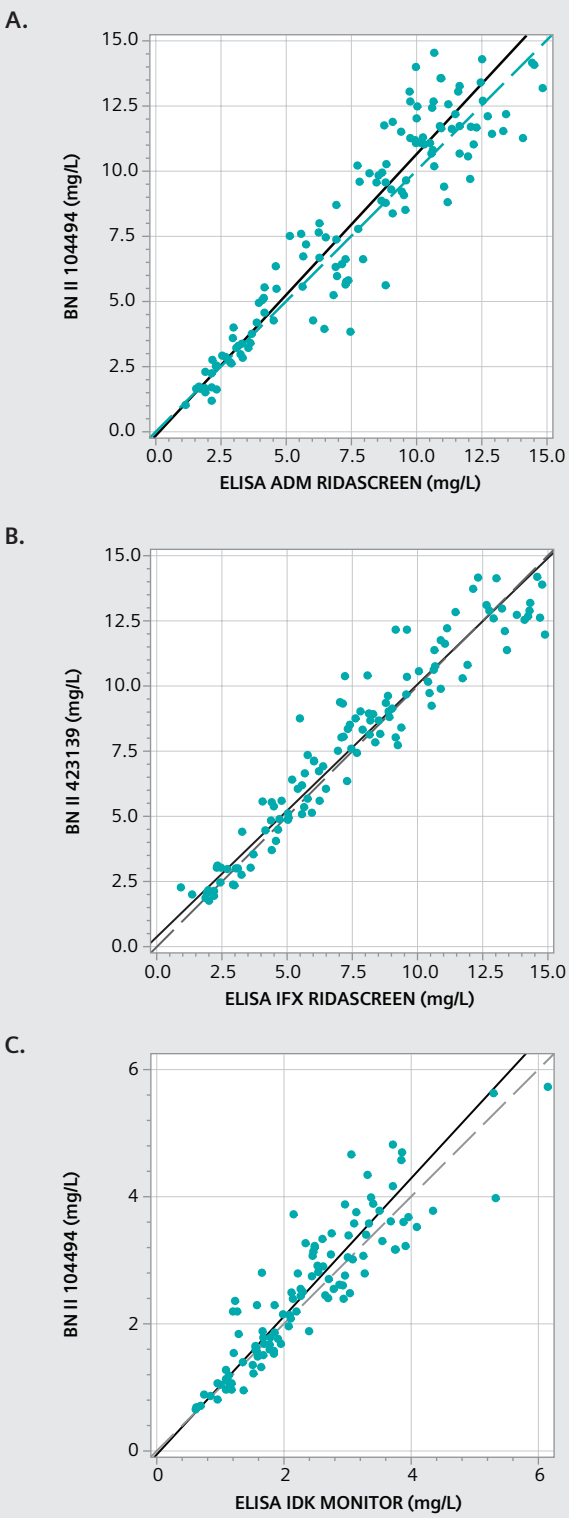


Figure 4. Method comparison according to CLSI EP09-A3 using N Latex aTNFα assay on a BN II System for adalimumab (A) and infliximab (B) vs. RIDASCREEN ADM/IFX Monitoring ELISA kits, and etanercept (C) vs. IDK MONITOR Etanercept drug-level ELISA kit.

At Siemens Healthineers, we pioneer breakthroughs in healthcare. For everyone. Everywhere. By constantly bringing breakthrough innovations to market, we enable healthcare professionals to deliver high-quality care, leading to the best possible outcome for patients.

Our portfolio, spanning from in-vitro and in-vivo diagnostics to image-guided therapy and innovative cancer care, is crucial for clinical decision-making and treatment pathways. With our strengths in patient twinning, precision therapy, as well as digital, data, and artificial intelligence (AI), we are well positioned to take on the biggest challenges in healthcare. We will continue to build on these strengths to help fight the world's most threatening diseases, improving the quality of outcomes, and enabling access to care.

We are a team of 66 000 highly dedicated employees across more than 70 countries passionately pushing the boundaries of what's possible in healthcare to help improve people's lives around the world.

Product availability may vary from country to country and is subject to varying regulatory requirements. Please contact your local representative for availability.

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