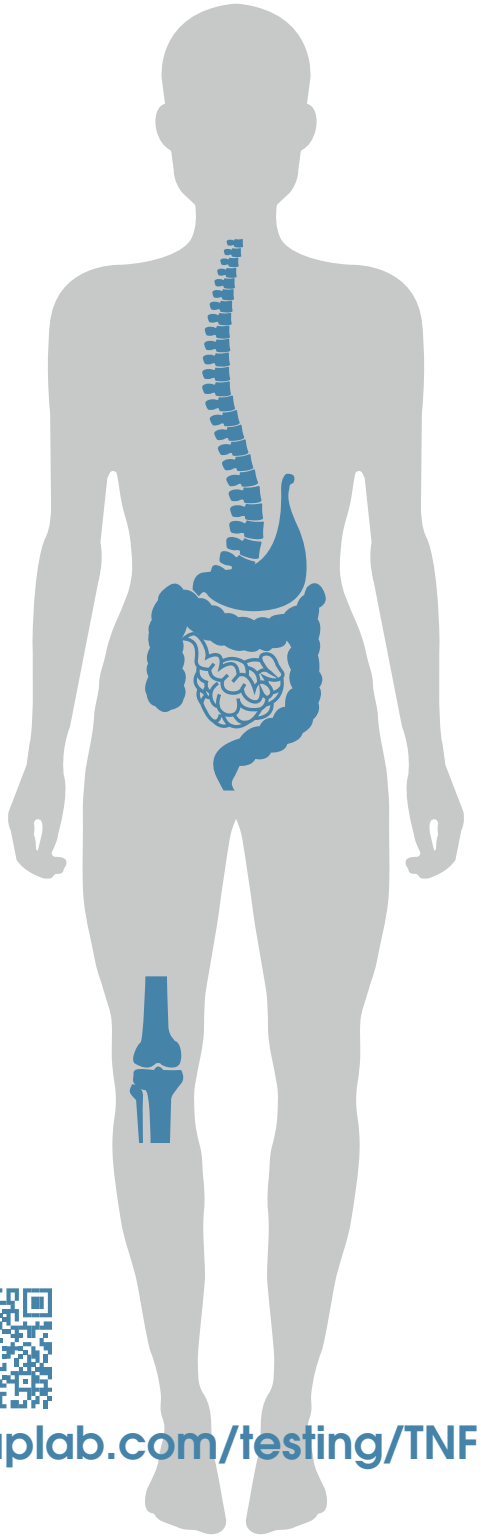

aruplab.com/testing/TNF

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A nonprofit enterprise of the University of Utah and its Department of Pathology

BD-CS-023, Rev 7, September 2021

TNF Antagonists

Testing at ARUP Laboratories

ARUP LABORATORIES

Monitoring the concentration of tumor necrosis factor (TNF) antagonist drugs and detecting the development of antidrug antibodies (ADAs) enables physicians to optimize patient treatment over time. The test results help physicians understand underlying causes of suboptimal outcomes, make informed therapy choices, and provide more effective treatment to their patients. The use of TNF antagonists has revolutionized the treatment of patients with several noninfectious inflammatory disorders, including Crohn disease and ulcerative colitis.

50%

of patients suffering from autoimmune and chronic inflammatory disorders experience treatment failure.

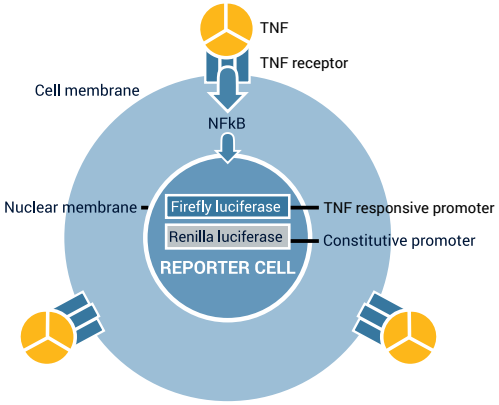
There are different approaches to managing patients with treatment failure in response to TNF antagonists; one approach is to monitor drug levels and ADAs. A new guideline from the American Gastroenterological Association on therapeutic drug monitoring in inflammatory bowel disease recommends that physicians should perform reactive therapeutic drug monitoring to guide changes in TNF antagonist therapy.[1]

Current methods for ADA detection are complicated by the fact that most TNF antagonists are antibodies and by the complexity of measuring antibodies against antibodies in nonfunctional binding assays. More importantly, all non-ARUP methods fail to differentiate binding from neutralizing ADAs.

ARUP's TNF antagonist drug and neutralizing antibody assays are cell-based bioassays that measure the ability of a drug to inhibit TNF. The assays also detect the presence of antibodies that neutralize drug activity. Emergence of these neutralizing antibodies in a patient leads to treatment failure. Other methods detect ADAs that bind to the drug, but unlike ARUP's assays, these methods are not able to distinguish whether the antibodies neutralize drug activity or not.

How ARUP's Test Works

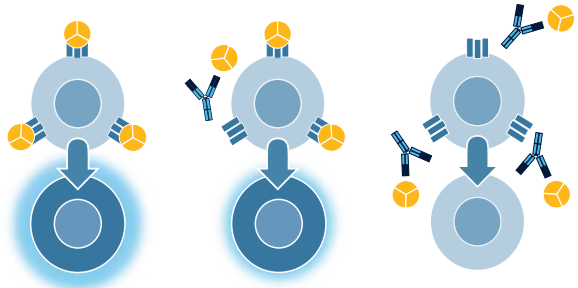
This functional reporter gene assay uses the principles of iLite technology (licensed by Euro Diagnostica).



Reporter cells carry a TNF-inducible, NFκB-regulated firefly luciferase reporter gene construct. When TNF is added to the cells, the reporter gene turns on and generates firefly luciferase, which is measured by a luminometer. Results of firefly luciferase expression are normalized relative to the expression of the renilla luciferase gene, which is carried by the same reporter cell under the control of a constitutive promoter.

Drug Measurement

Serum of a patient taking a TNF antagonist drug is mixed with TNF and added to the cells. If the drug is present, it will block the activity of TNF, decreasing luminescence. Serum concentration of a biologically active TNF antagonist drug can be calculated using a calibration curve.

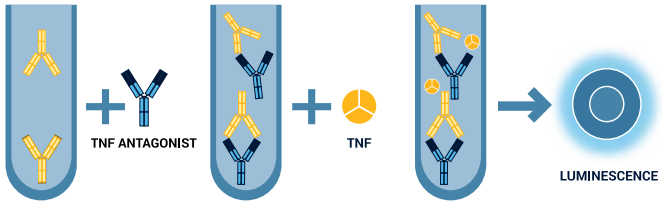


NO DRUG—HIGH LUMINESCENCE

LOW DRUG—MODERATE LUMINESCENCE

HIGH DRUG—NO LUMINESCENCE

Antibody Detection



Some patients develop antibodies to the drug. In the presence of neutralizing antibodies, the reporter gene is turned on despite the presence of exogenous drug in the assay. The antibody titer is obtained by identifying the dilution point of a patient's serum at which blocking of the drug activity is no longer observed.

Laboratory Testing

ARUP Test Code and Name	
2011248	Adalimumab Activity and Neutralizing Antibody
2013605	Adalimumab Activity with Reflex to Antibody
2008320	Infliximab or Biosimilar Activity and Neutralizing Antibody
2013612	Infliximab or Biosimilar Activity with Reflex to Antibody

The functional reporter gene assays were clinically validated for diagnosing and monitoring TNF antagonist treatment failure.

Currently, the ARUP assays are the only clinical assays available for the detection of biologically active TNF antagonist drugs and ADAs with drug-neutralizing function, as recommended by the FDA.

The ARUP cell-based assay is inherently more reflective of the in vivo environment in tissue and circulation in which TNF antagonist drugs are believed to function. The assay can easily be adapted for all known anti-TNF drugs.