

## What is 14-3-3η?

14-3-3η (eta) is normally a ubiquitous intracellular protein with critical life-sustaining functions. In RA, it is pathologically expressed in the extracellular space, through an exosomal-mediated process, where it can be measured in blood by a standard ELISA test in a clinical laboratory. 14-3-3η's extracellular presence mechanistically drives up the expression of inflammatory factors such as TNFα, IL-6, MCP-1 as well as joint damage factors such as MMP1/3 and RANKL. Stimulation of cells, in vitro, with increasing concentrations of 14-3-3η leads to a dose-dependent increase in inflammatory and joint damage factors. These effects are induced by 14-3-3η's selective activation of key intracellular pathways.

## Clinical Data

The 14-3-3η protein is a biomarker for RA. It is produced by joints and it plays a biologic role in the joint erosion process. Blood levels are elevated in patients with RA, but not in other diseases including psoriasis, osteoporosis, gout, ulcerative colitis, type 1 diabetes, systemic lupus erythematosus, Crohn's disease, primary Sjögren syndrome, scleroderma, and multiple sclerosis. Patients with Erosive Psoriatic Arthritis may be positive. A positive test indicates that the patient should be considered for referral to a rheumatologist, prior to the onset of significant joint damage. A positive JOINTstat™ test early in disease also marks high joint damage risk, and therefore, along with other clinical indicators, would signal to a rheumatologist how aggressively to manage the patient. Studies to date have shown that 14-3-3η:

- When positive (>0.19 ng/ml), provides a 5-50 times greater likelihood of having RA versus non-RA.
- Is positive in patients with joint pain who develop RA within 5 years of symptom onset.
- At high levels (>0.80 ug/L) is an indicator of RA that will lead to more joint damage over 3 years.
- At lower levels (<0.40 ug/L or negative in RA diagnosed patients) is an indicator of a higher likelihood of response to RA therapy.
- Decreasing levels with treatment or over time indicate a better disease outcome.
- Overall, RA patients who are negative or who have low levels (<0.40 ug/L) have a more favourable outcome.

One in three RA patients are missed by the sensitivity measures of RF or anti-CCP; 14-3-3η improves diagnostic sensitivity to 81%. 96% of healthy individuals are negative for 14-3-3η. JOINTstat™ (14-3-3η) testing improves early RA diagnosis, which along with prompt referral and appropriate treatment can significantly improve patient outcomes.

## Clinical Availability

- In the United States, 14-3-3η testing has been available through Quest Diagnostics either as a stand-alone test or with RF and anti-CCP in an RA diagnostic panel called IdentRA™ since October 2013.
- In Canada, LifeLabs Medical Laboratory Services has launched 14-3-3η as JOINTstat™, which has been available since December 2014. In BC, healthcare providers must indicate JOINTstat™ under the section "Other tests" of the standard requisition form. In the rest of Canada, JOINTstat™ requires a separate requisition form.
- The 14-3-3η test is Health Canada approved, CE marked for clinical use in Europe and is FDA CLIA regulated in the US.

## References

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