Transforming Health Management

The 14-3-3η Biomarker for Rheumatoid Arthritis Diagnosis, Prognosis and Monitoring

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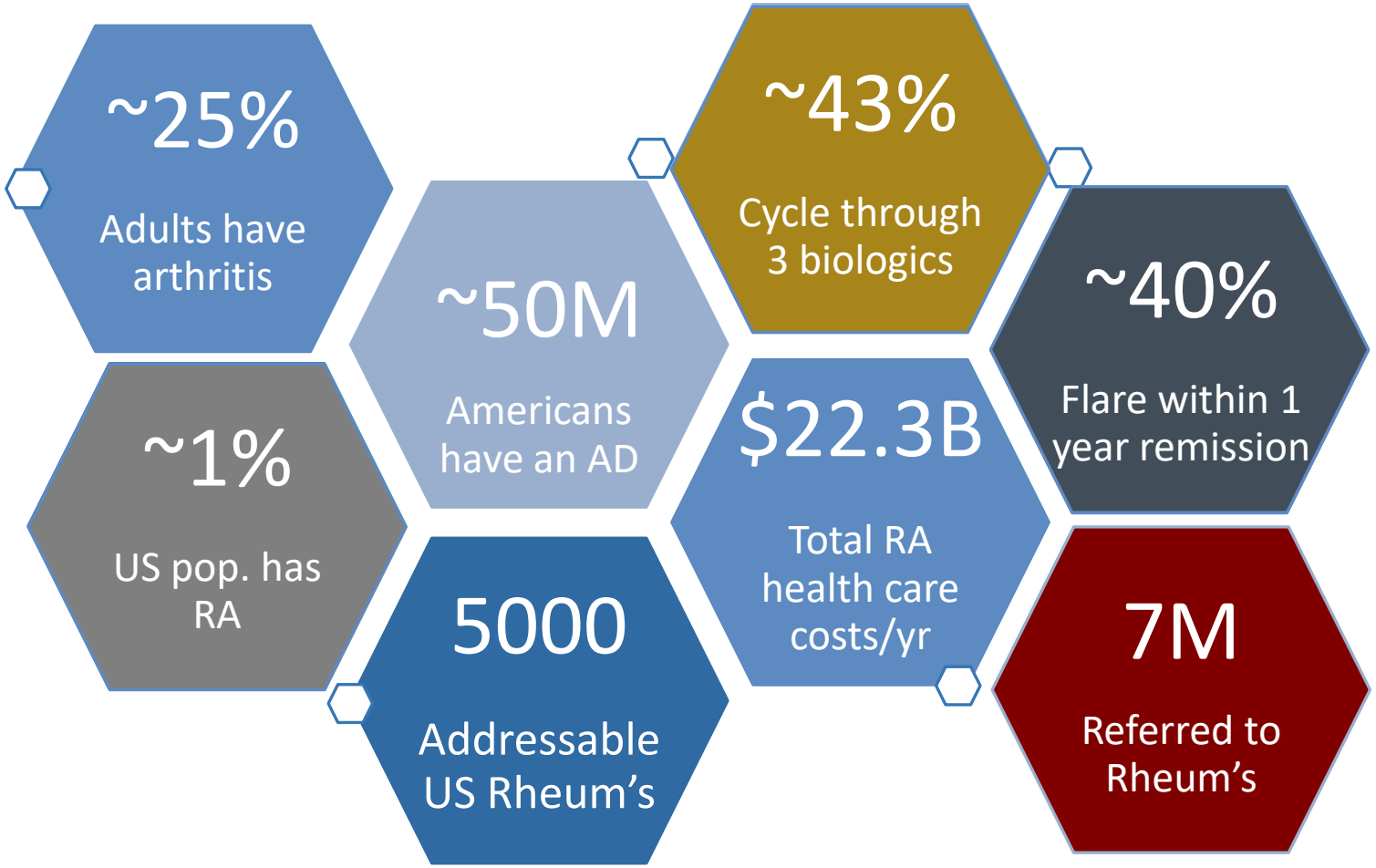
Market Overview

Unmet needs in Rheumatoid Arthritis patient management

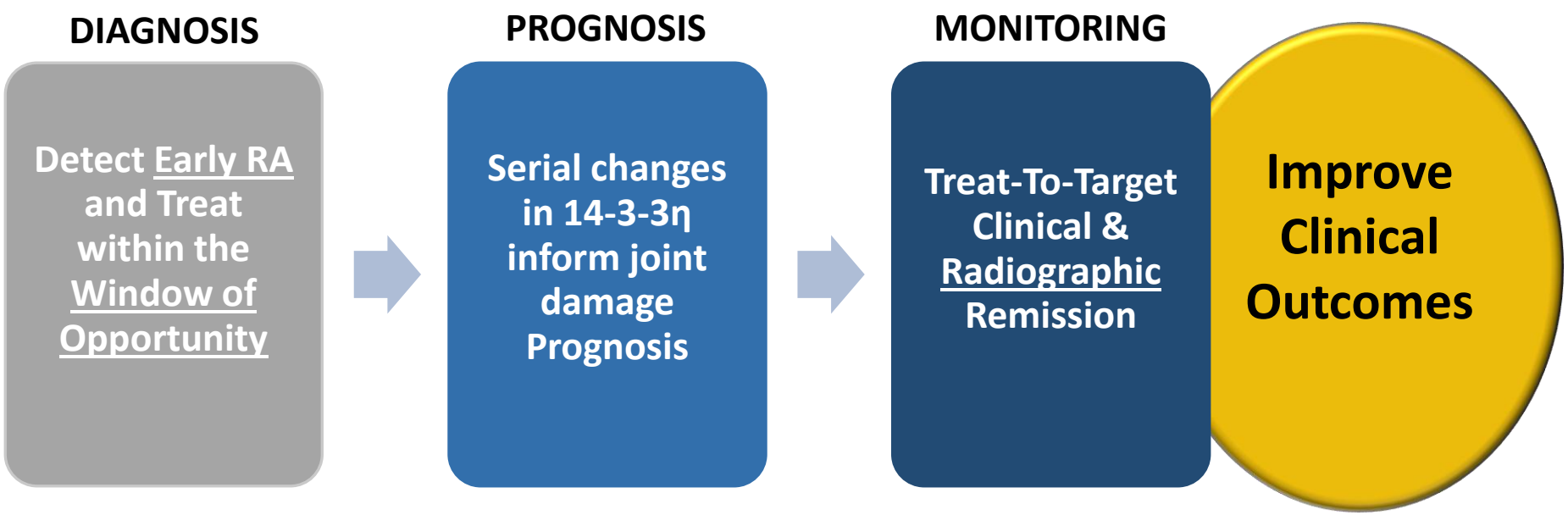


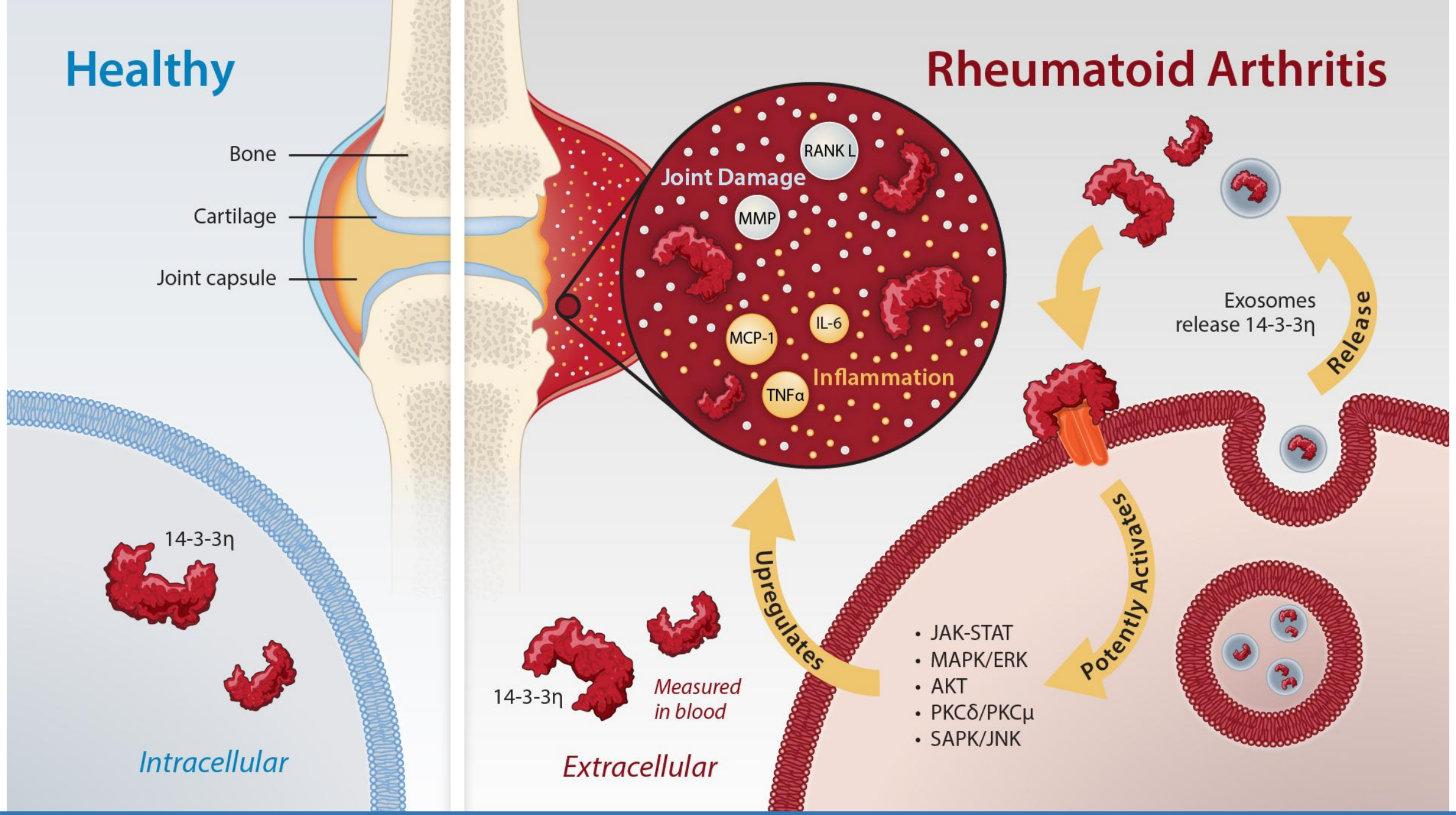
Various market reports

14-3-3η Assists with RA Patient Management

A multi-faceted blood test for diagnosis and prognosis, and monitoring of RA

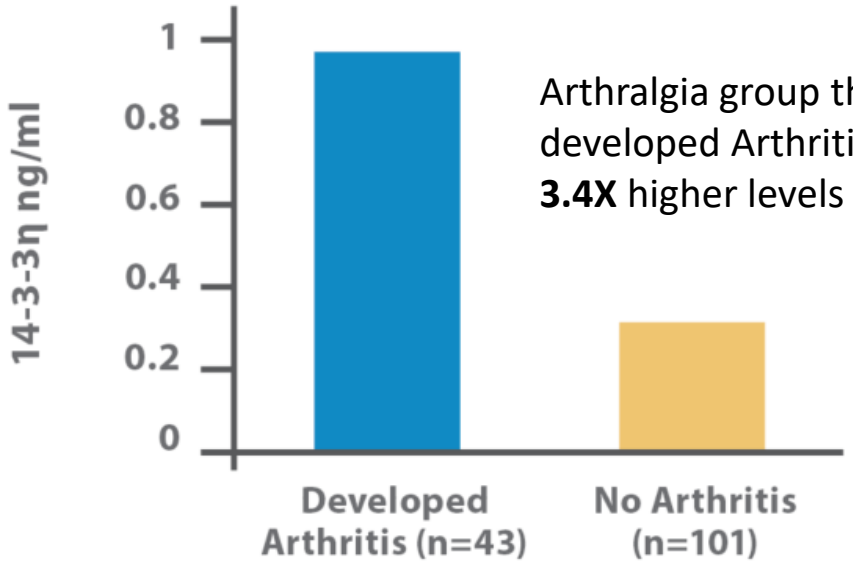
Mechanistic and modifiable biomarker: From pre-RA to remission




Healthy
Rheumatoid Arthritis
Bone
Cartilage
Joint capsule
RANK L
Joint Damage
MMP
MCP-1
IL-6
Inflammation
TNFα
Exosomes
release 14-3-3η
Release
14-3-3η
Intracellular
14-3-3η
Measured
in blood
Extracellular
Upregulates
Potently Activates
• JAK-STAT
• MAPK/ERK
• AKT
• PKCδ/PKCμ
• SAPK/JNK

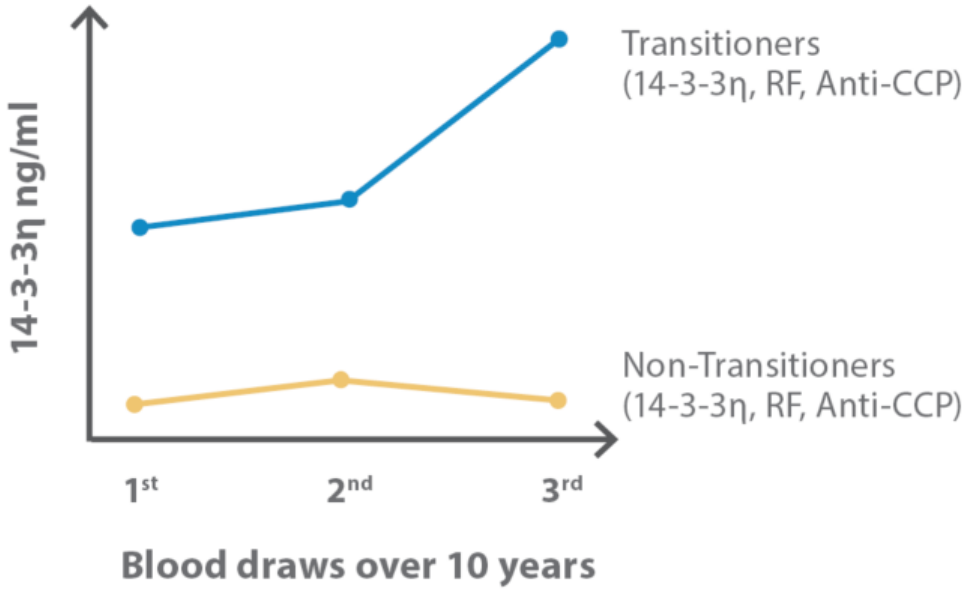
Moving Upstream: Who's at Risk for RA

Identify patients even pre-disease



Arthralgia group that developed Arthritis had **3.4X** higher levels

14-3-3η predictor of imminent RA



References:
Arthralgia Data
First Degree Relatives

Diagnostic Value of 14-3-3η

RA Panel (n=331)	14-3-3η Additional Diagnostic Benefit
Anti-CCP2+	**37%**
Rheumatoid Factor (RF)+	24%
RF+ and/or Anti-CCP2+	15%

- **14-3-3η highest sensitivity singular biomarker for early RA**
- **Complements RF and anti-CCP**
- **Captures significant portion of seronegative RA**
- **Earlier and more accurate diagnosis (6-12 weeks of symptom onset)**

Combining all 3 increases diagnostic sensitivity to 78% in early RA and 96% in established RA

14-3-3η identifies 21% of early RA and 67% of established RA patients seronegative for anti-CCP and/or RF

Reference:
Carrier 2016
Naides 2015

Identify At-Risk and RA Patients Early and Accurately

14-3-3η a novel mechanistic biomarker, **predicts** RA development in patients with **joint pain** (arthralgia) and assists with **early** diagnosis

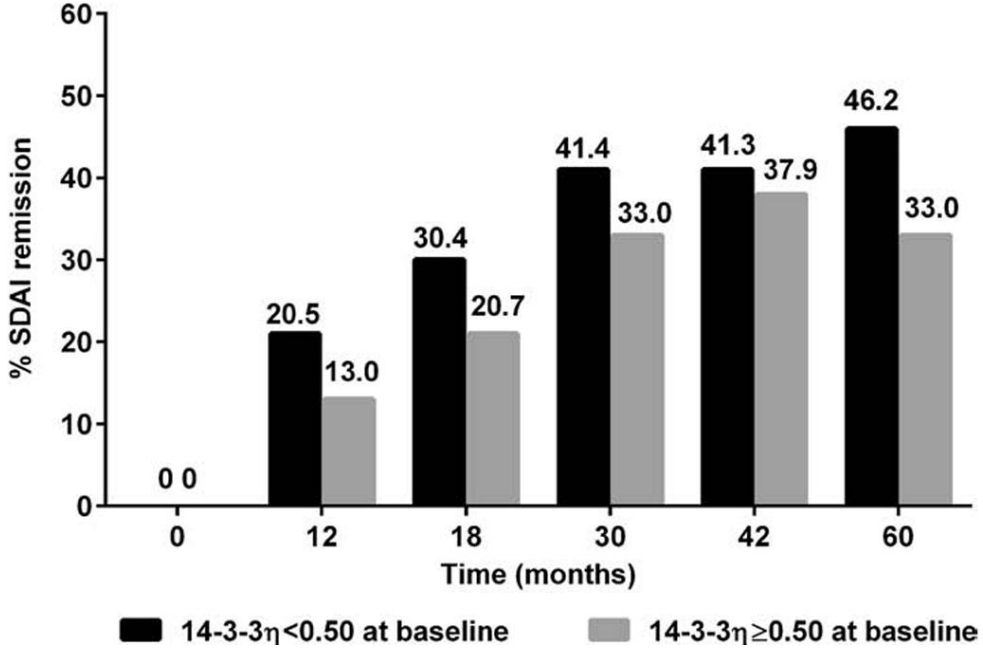
14-3-3η positive status can detect disease at a very early stage and assist with referral within 6-12 weeks of symptom onset

Identify people at risk of developing RA and follow them before any joint damage progression occurs

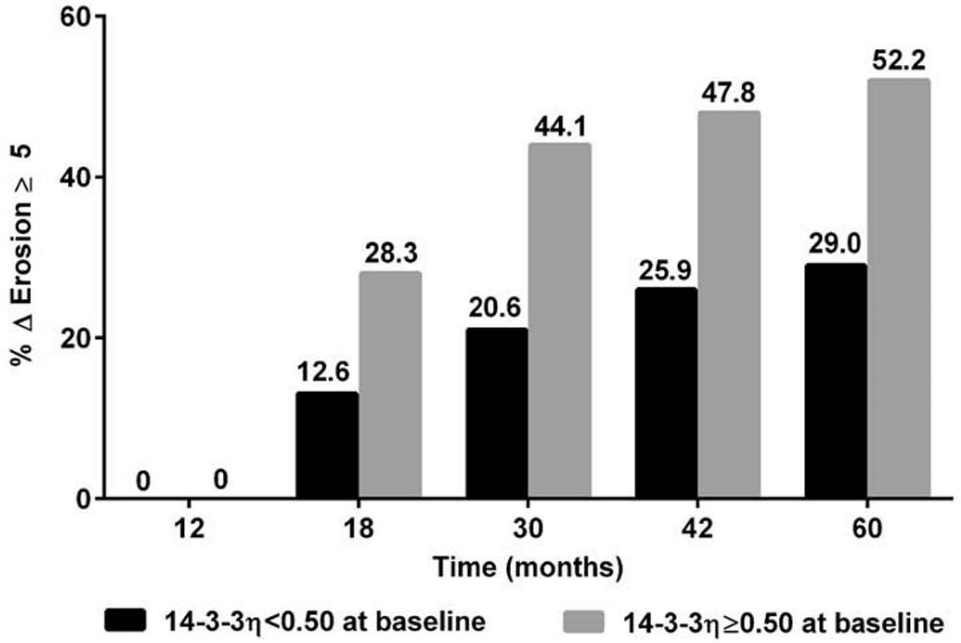
Prevent disability and irreversible joint damage

Baseline 14-3-3η is a predictor of joint damage

Remission is lower is patients with elevated baseline 14-3-3η



Erosive progression is higher in patients with elevated baseline 14-3-3η



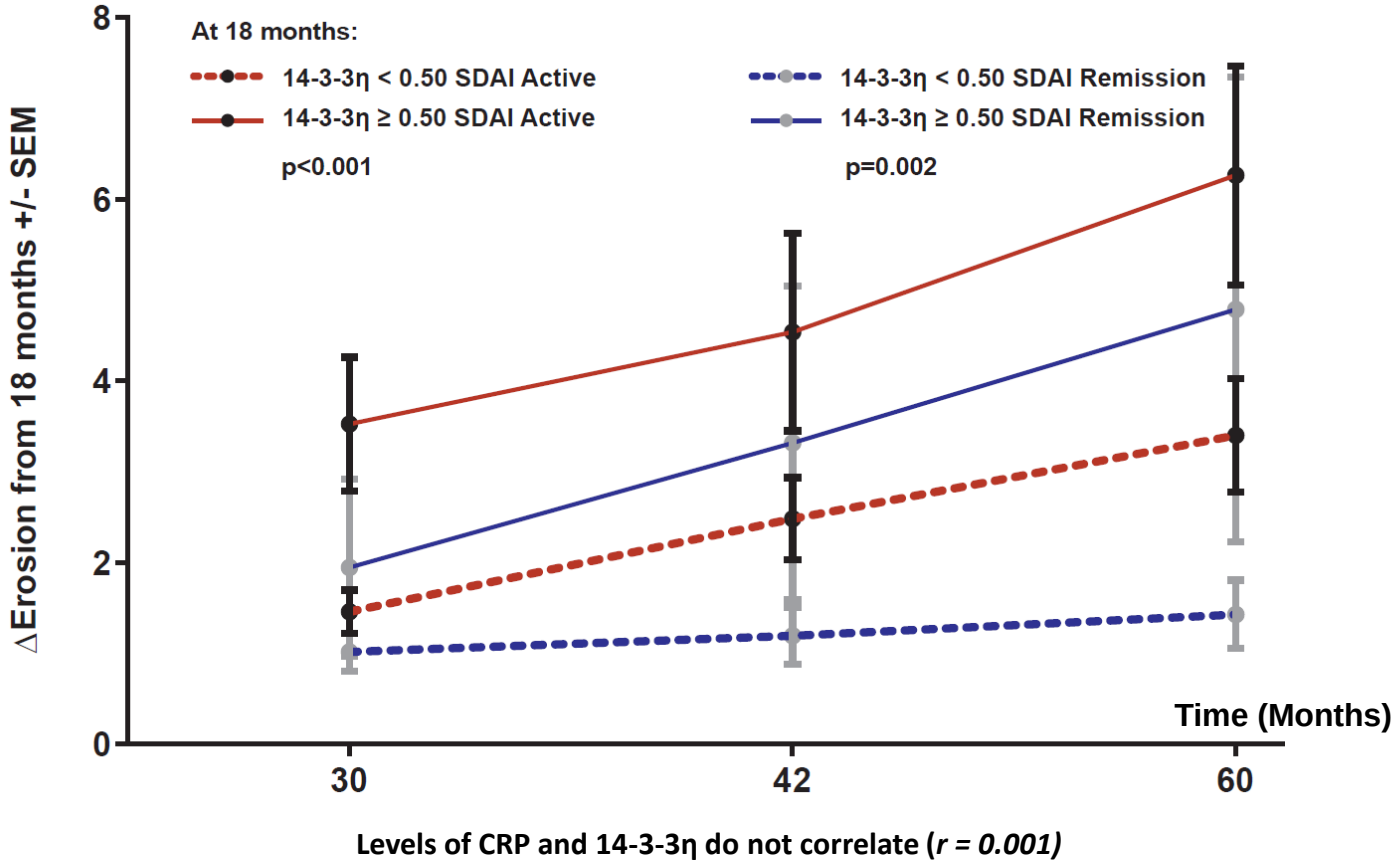
References:
Carrier 2016

Uncouple Inflammation and Joint Damage

Erosive damage progression is significantly higher in patients with 14-3-3η ≥ 0.50 ng/mL at 18 mos

CRP = Inflammation

14-3-3eta = Joint Damage

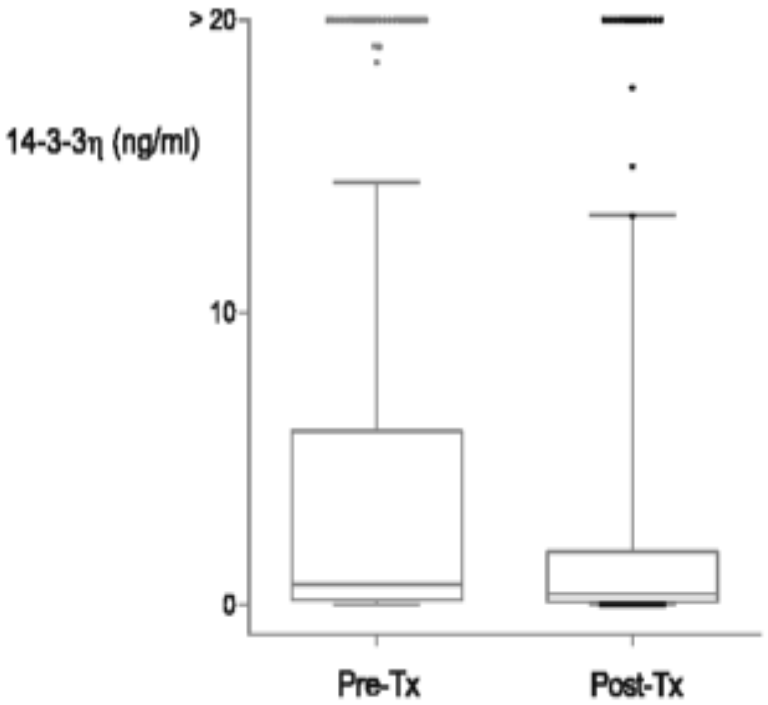


Levels of CRP and 14-3-3η do not correlate (*r = 0.001)*

References:
[14-3-3η & CRP Predictor of Flare]

14-3-3η should be combined with all CRP requisitions

Treat-to-Target Strategies & Tight Treatment Control



n = 149

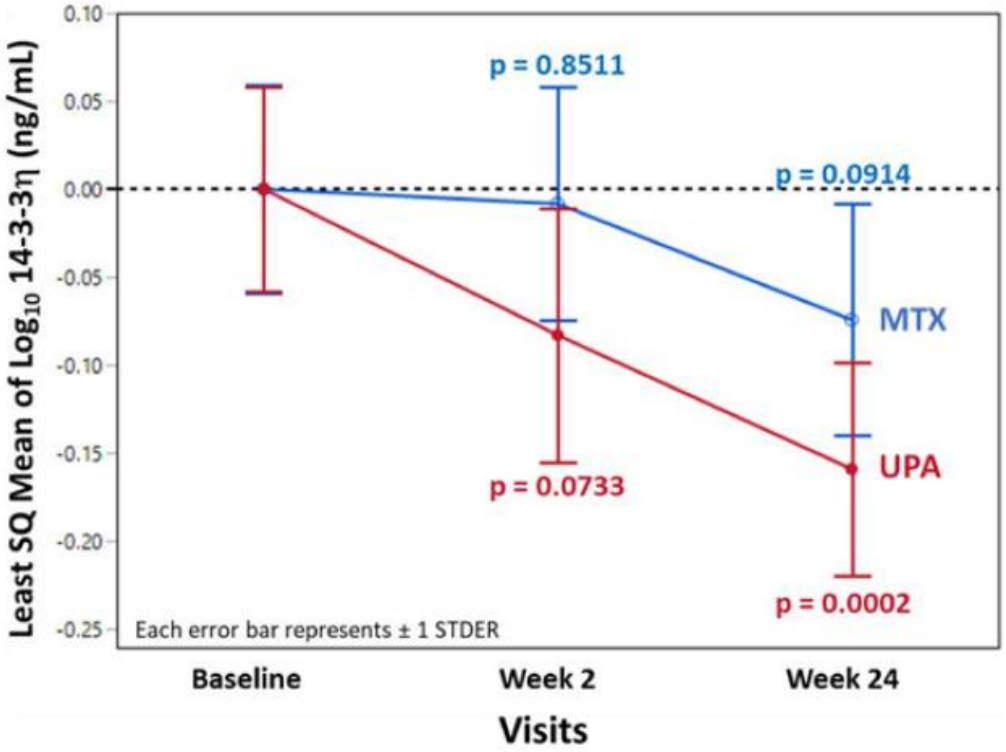
Patients who remain or become 14-3-3η negative post-treatment have the best improvement in disease activity score

Decrease in 14-3-3η levels highly correlates with improvements in DAS-ESR *(r=0.50),* DAS-CRP *(r = 0.46) & ESR (r=0.36)*

Monitor Patient Response:
14-3-3η, CRP & ESR

References:
Response to Tofacitinib
Response to Tocilizumab

14-3-3η Monitoring is Agnostic to Treatment Type



n = 200

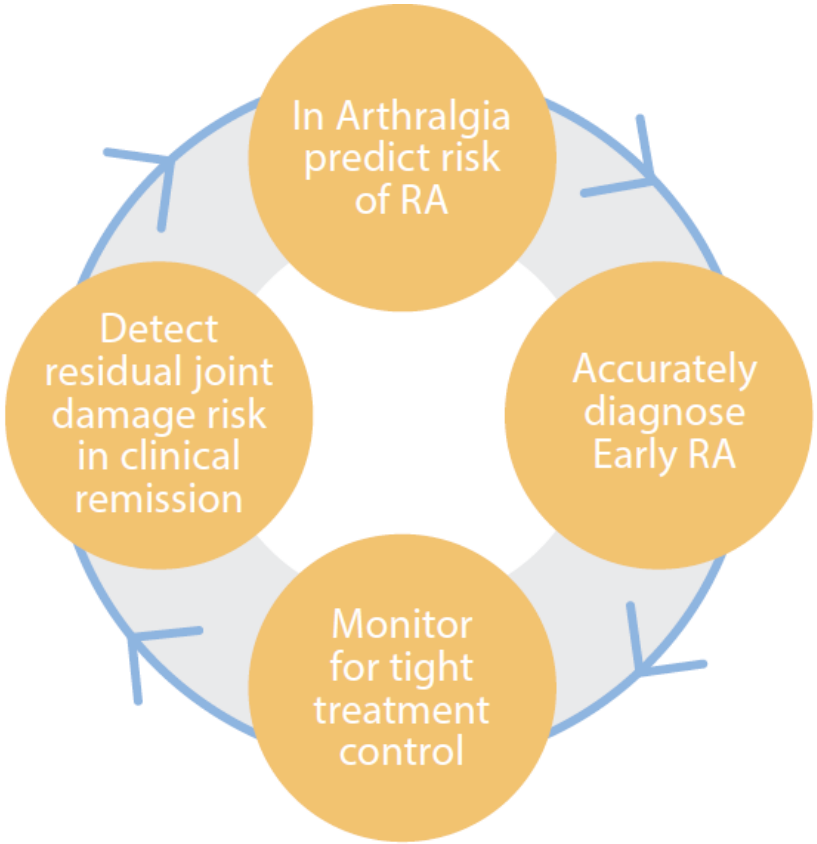
UPA = Upadacitinib (JAK 1 Inhibitor)
MTX = Methotrexate

Decrease in 14-3-3η levels with MTX or UPA treatment correlates with improvements in disease activity (CDAI 0.264, DASCRP 0.267, SDAI 0.267)

14-3-3η assists with monitoring patient response to various treatments

References:
Sornasse 2020

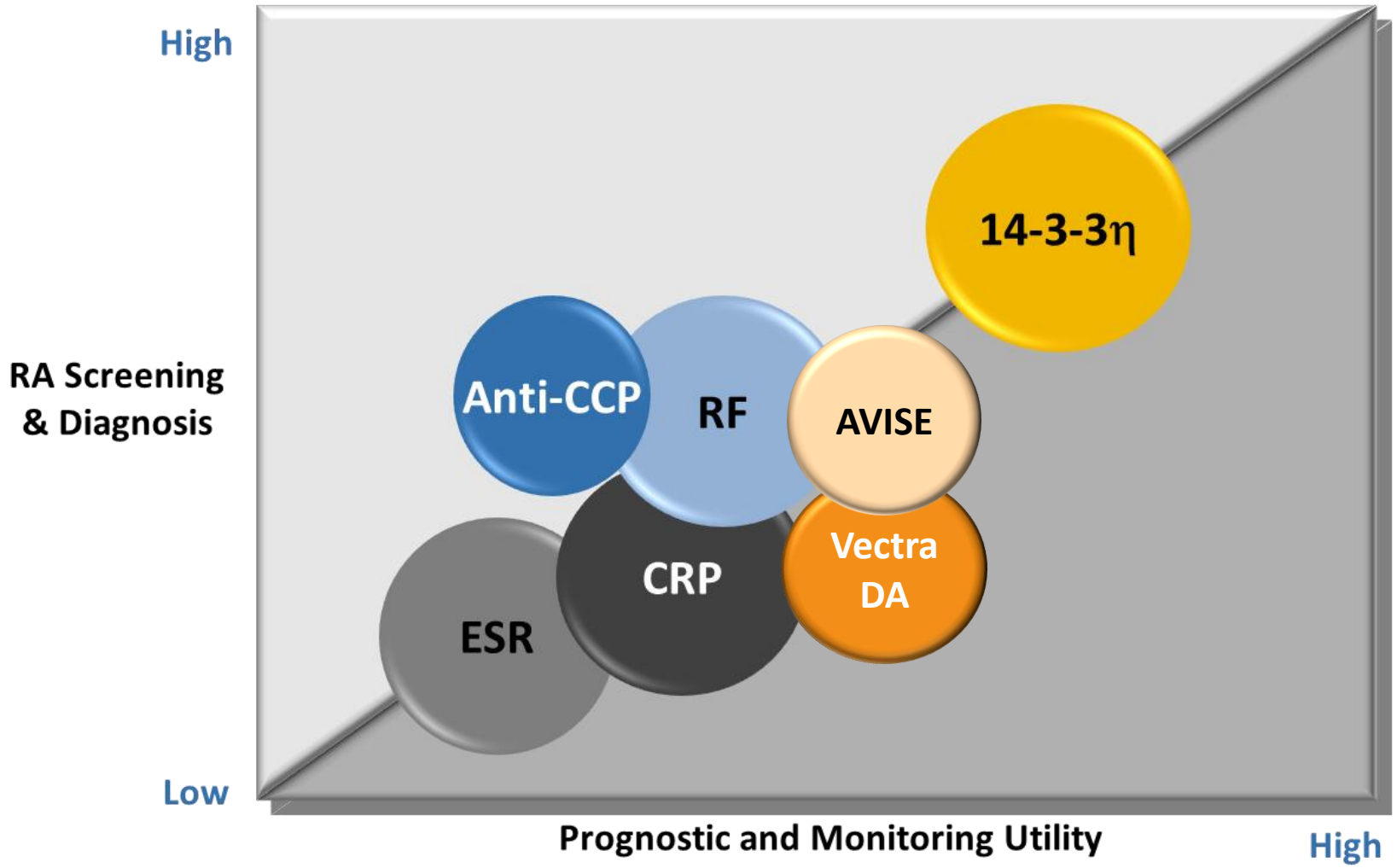
14-3-3η is a mechanistic biomarker of **joint damage** that is directly involved in the **pathogenesis** of RA and improves the diagnosis rate when added to RF and Anti-CCP



- Identify patients in **pre-clinical** phase of arthritis
- **Positive** serum levels associated with increased risk of joint damage
- Identify patients most likely to **rapidly progress** and need earlier, tailored therapy
- Monitor patient **response** to therapy

AugureX

14-3-3η Independently informs joint damage progression and is modifiable over the course of disease



High Impact 14-3-3η Publications

RHEUMATOLOGY AND IMMUNOLOGY RESEARCH

Review • DOI: 10.2478/rir-2021-0012 • 2(2) • 2021 • 87–90

The role of 14-3-3 η as a biomarker in rheumatoid arthritis

Serum 14-3-3η is a Novel Marker that Co
Current Serological Measurements to Enh
Detection of Patients with Rheumatoid Ar

Walter P. Maksymowych, Stanley J. Naides
Dirkjan van Schaardenburg, Maarten Boers
Paul-P. Tak, Mark C. Genovese, Michael E.
Rania W. Abolhosn, Joanna M. Popov, Kari

A prospective cohort study of 14-3-3η in ACPA and/or RF-positive patients with arthralgia

van Beers-Tas *et al. Arthritis Research & Therapy* (2016)

Marian H. van Beers-Tas[1*], Anthony Marotta[2], Maarten Boers[3,4], Walter P. Maksymowych[5] and Dirkjan van Sch

14-3-3η: a novel

W.P. Maksymo

14-3-3η is a novel mediator
pathogenesis of rh
damage

Walter P
Yuan Gu

14-3-3η Autoantil
Rheumatoid Arth

Serum 14-3-3η level is associated with s
and clinical outcomes of rheumatoid ar
its pretreatment level is predictive of DA
remission with tocilizumab

Serum levels of 14-3-3η protein supplement C-reactive protein and rheumatoid arthritis-associated antibodies to predict clinical and radiographic outcomes in a prospective cohort of patients with recent-onset inflammatory polyarthritis

Carrier *et al. Arthritis Researc*

Carrier[1], Anthony Marotta[2], Artur J. de Brum-Fernandes[1,3], Patrick Liang[1,3], Ariel Masetto[1,3], Ménard[4], Walter P. Maksymowych[5] and Gilles Boire[1,3,6*]

Decrease in 14-3-3η protein levels is correlated with improvement in disease activity in patients with rheumatoid arthritis treated with Tofacitinib

O. Shovman[a,b,c,d], B. Gilburd[a], A. Watad[b], H. Amital[a,b,d], P. Langevitz[c,d], N.L. Bragazzi[e], M. Adawi[f], D. Perez[a], M. Lidar[c,d], I. Katz[a,d], M. Blank[a,d], N.K. Biln[g], A. Marotta[g], Y. Shoenfeld[a,d,h,*]

"Seronegative" Rheumatoid Arthritis

J Rheumatol 2015;42:10; doi:10.3899

NTHONY MAROTTA

14-3-3η Scientific & Clinical Validation

10+ years of peer-reviewed studies

RISK OF RA DEVELOPMENT

- 1st Degree Relatives
- Arthralgia to RA

2015
Serum 14-3-3eta Are Elevated in Indigenous North Americans with Rheumatoid Arthritis and May Predict Imminent Synovitis in Their at-Risk First Degree Relatives

2016
A prospective cohort study of 14-3-3η in ACPA and/or RF-positive patients with arthralgia

RA & SLE PATIENT PROFILING & DIAGNOSIS

- Seropositivity & Risk
- Changes Over Time

2014
14-3-3η is a Novel Mediator Associated with the Pathogenesis of Rheumatoid Arthritis and Joint Damage

Serum 14-3-3η is a Novel Marker that Complements Current Serological Measurements to Enhance Detection of Patients with Rheumatoid Arthritis

2018
The Diagnostic Value of 14-3-3η Protein Levels in Patients with Rheumatoid Arthritis

2020
Serum 14-3-3η Protein is Associated with Clinical and Serologic Features of Sjögren's Syndrome in Patients with Systemic Lupus Erythematosus: A Cross-Sectional Analysis

JOINT DAMAGE PROGNOSIS

- Radiographic Progression
- CRP Independence

2016
Serum levels of 14-3-3η protein supplement C-reactive protein and rheumatoid arthritis-associated antibodies to predict clinical and radiographic outcomes in a prospective cohort of patients with recent-onset inflammatory polyarthritis

2020
Impending radiographic erosive progression over the following year in a cohort of consecutive patients with inflammatory polyarthritis: prediction by serum biomarkers

TREATMENT DECISIONS

- Remission Maintenance
- Treatment Choices

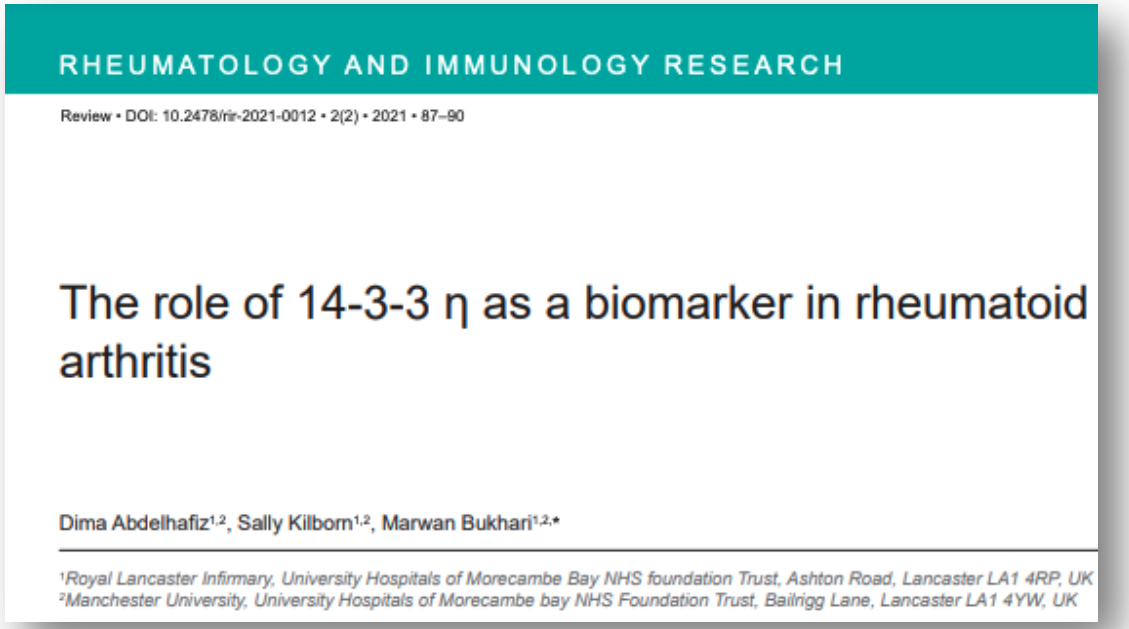
2015
Serum 14-3-3η Level is Associated with Severity and Clinical Outcomes of Rheumatoid Arthritis, and its Pretreatment Level is Predictive of DAS28 Remission with Tocilizumab

2019
Decrease in 14-3-3η Protein Levels is Correlated with Improvement in Disease Activity in Patients with Rheumatoid Arthritis Treated with Tofacitinib

2020
Correlation of Plasma 14-3-3η Levels with Disease Activity Measures in Methotrexate-Naïve RA Patients Treated with Upadacitinib Monotherapy in the Select-Early Phase 3 Study

14-3-3η's importance in the continuum of care

Substantive evidence from recent Literature Review (2021)



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Review • DOI: 10.2478/rir-2021-0012 • 2(2) • 2021 • 87–90

The role of 14-3-3 η as a biomarker in rheumatoid arthritis

Dima Abdelhafiz[1,2], Sally Kilborn[1,2], Marwan Bukhari[1,2,*]

[1]Royal Lancaster Infirmary, University Hospitals of Morecambe Bay NHS foundation Trust, Ashton Road, Lancaster LA1 4RP, UK
[2]Manchester University, University Hospitals of Morecambe bay NHS Foundation Trust, Bailrigg Lane, Lancaster LA1 4YW, UK

- 14-3-3η helps to assess the **veracity of the diagnosis** and **severity of *Early* RA.**
- Can be **combined with existing markers** to stratify patients to more effective treatments
- **Welcome addition** for an HCP's diagnostic and treatment strategy

Test Ordering

Covered by CMS and most insurance carriers

Quest Diagnostics

- Standalone 14-3-3η: **91455**
- IdentRA Panels 2/4: 91472/92812

LabCorp

- Standalone 14-3-3η: **504550**
- RheumAssure Panel: 504509

Questions?

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