

Biomarkers as tools for Precision Medicine in Rheumatoid Arthritis

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12th International Autoimmunity Seminar, Vilnius

What is Precision Medicine?



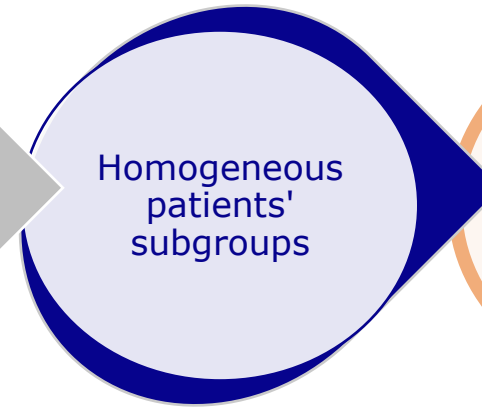
"Doctors have always recognized that **every patient is unique**, and doctors have always tried to **tailor** their treatments as best they can to individuals. [...] What if matching a cancer cure to our genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our **temperature [biomarker]**?"

Barack Obama, January 30, 2015

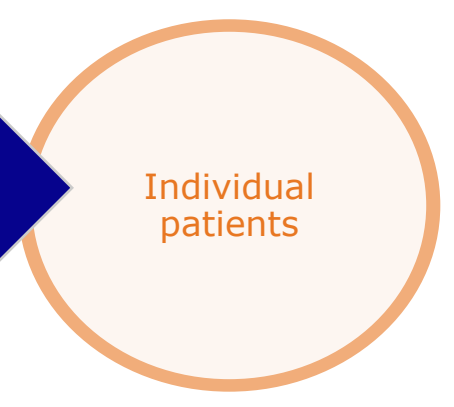
Traditional Medicine



Stratified Medicine



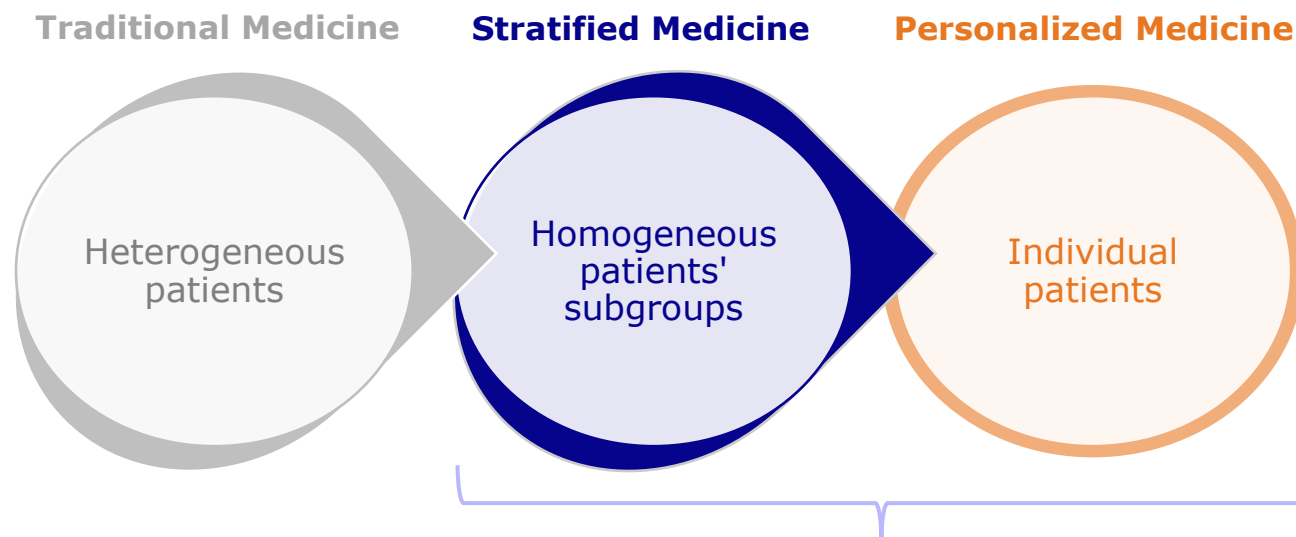
Personalized Medicine



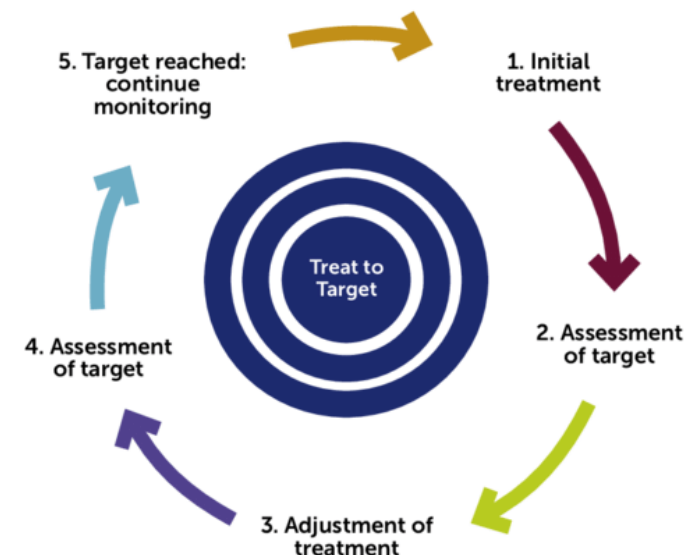
Innovative approach based on specialized diagnosis, and patient stratification using **autoantibody laboratory results** in combination with other data, and **digital decision support solutions**, to support tailoring of disease management and treatment for autoimmune conditions

March R, Schott C. *Per Med.* 2017;**14**:463-466. Fritzler MJ, et al. *Front Immunol.* 2018;**9**:2682:30505311. Mahler M. *Elsevier* 2021, ISBN:9780128202395.

Treat-to-Target



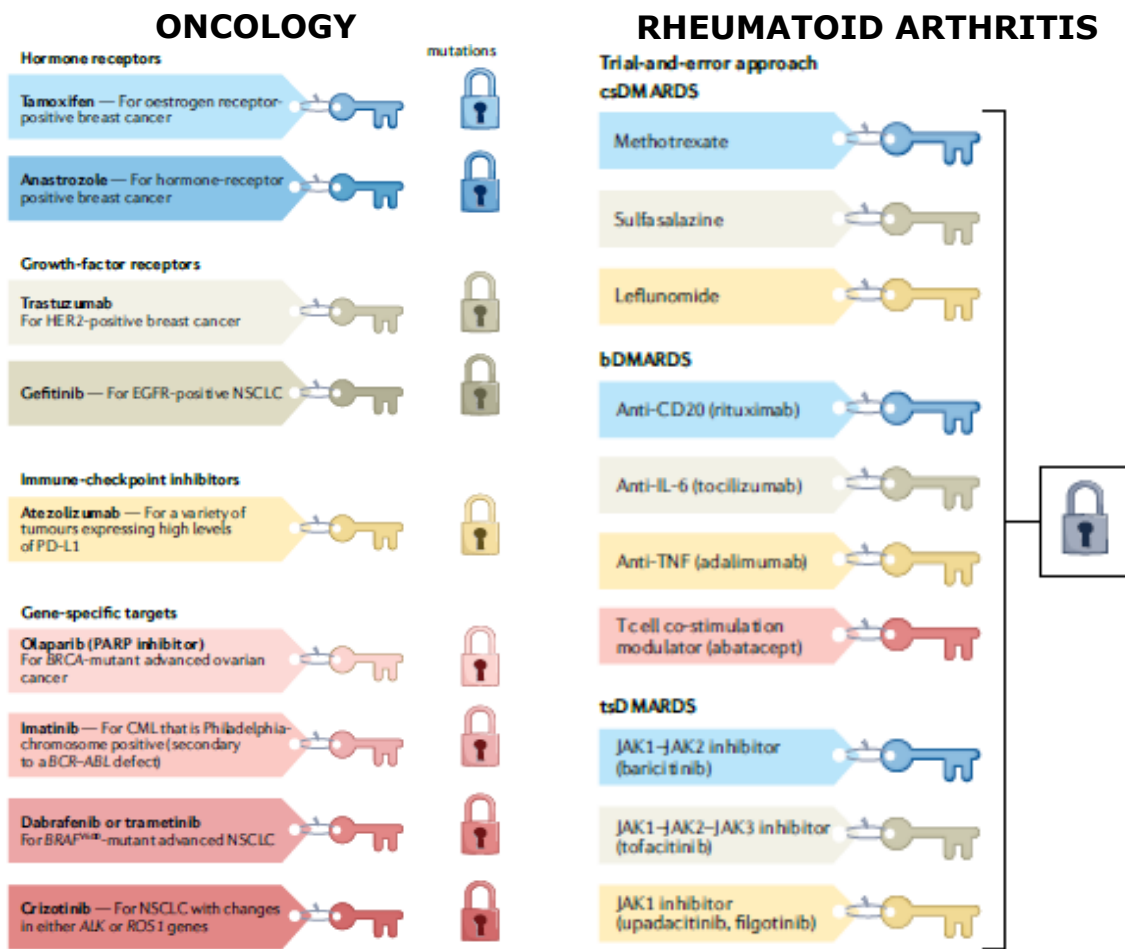
Treat-to-Target (T2T): Therapeutic strategy that involves setting specific, measurable treatment **goals, tailored** to a patient's unique **biological, clinical and biomarker profile**, and continuously **monitoring and adjusting** the therapeutic strategy to achieve those goals



- **Patient-centered approach**
- **Personalized treatment goals**
- **Dynamic and regular monitoring**
- **Treatment adjustment**

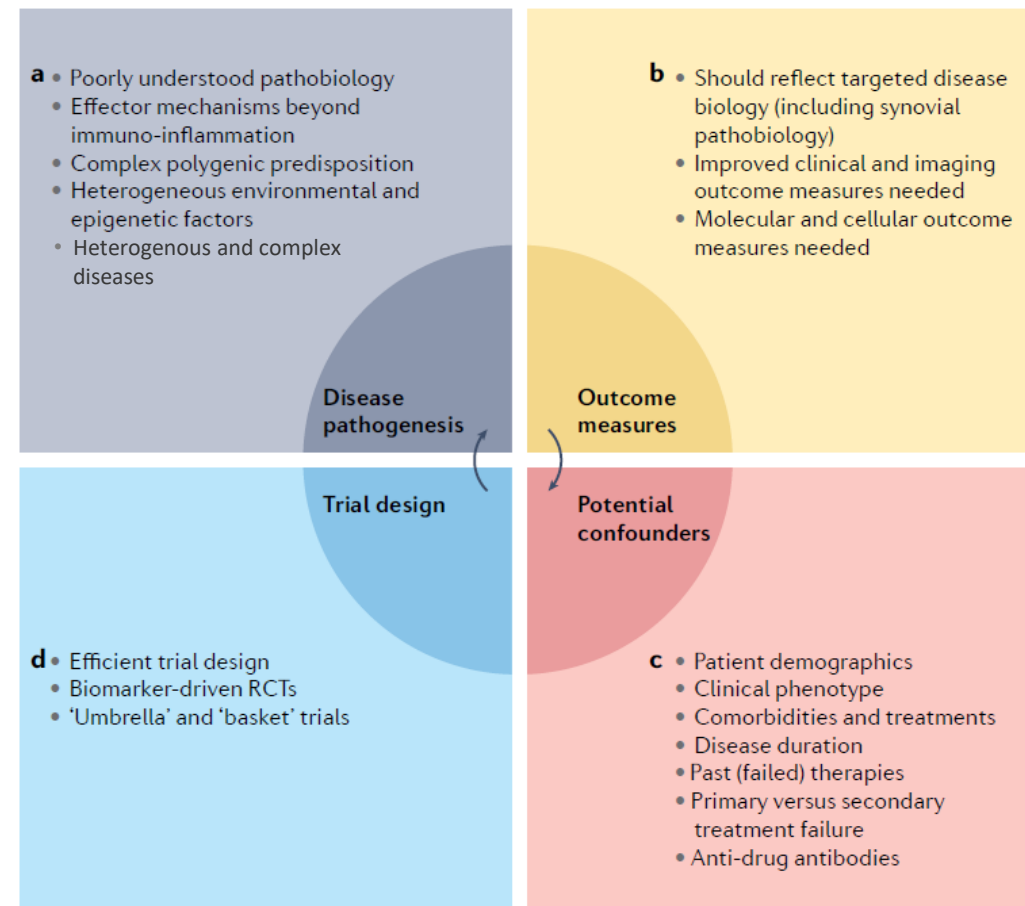
March R, Schott C. *Per Med.* 2017;**14**:463-466. Fritzler MJ, et al. *Front Immunol.* 2018;**9**:2682:30505311. Mahler M. *Elsevier* 2021, ISBN:9780128202395.

Towards Precision Medicine in Autoimmunity



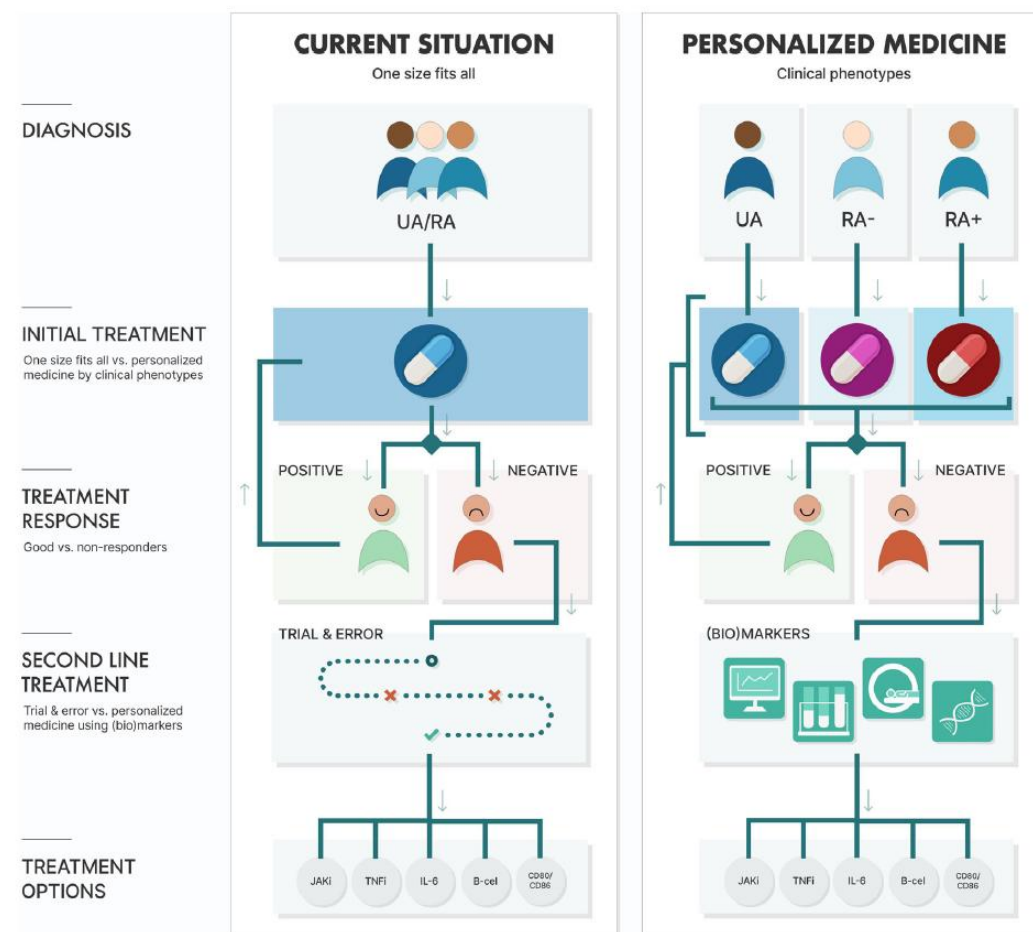
Modified from Lin CMA, Cooles FAH, Isaacs JD. *Nat Rev Rheumatol.* 2022;18:725-733.

Drivers of the precision gap in SARs

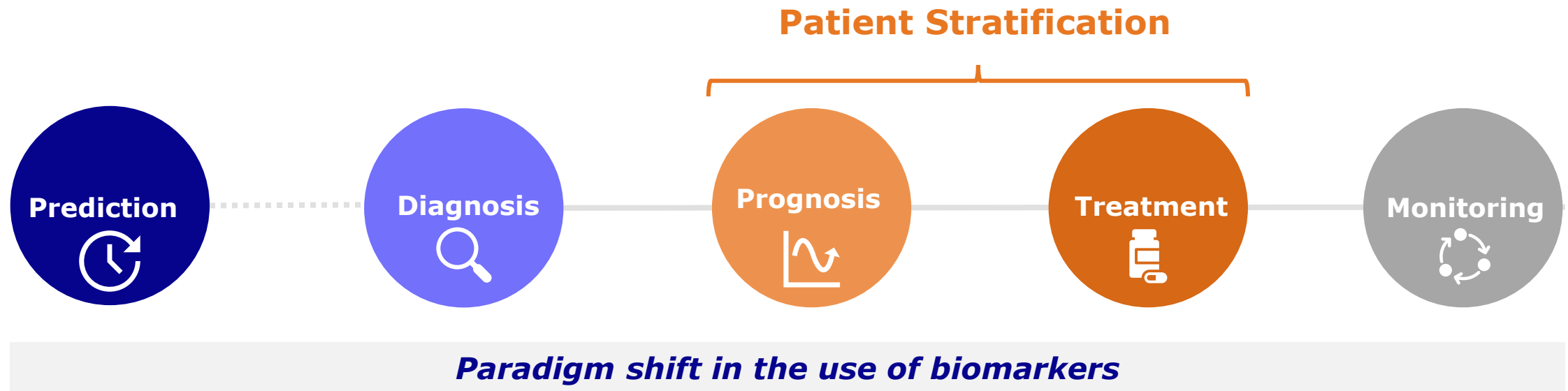


Precision Medicine in RA: Why the Time Is Now

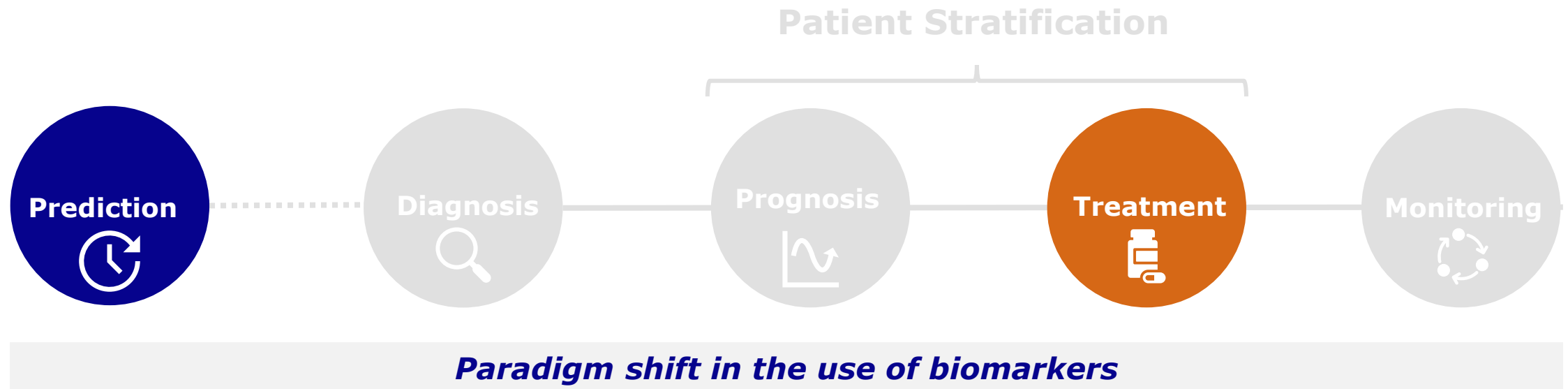
- Increasing knowledge of **pathophysiology**
- Availability of **biomarkers** and advancement in understanding their clinical utility and pathogenic roles
- Advancement in the understanding of **pre-disease** and early diagnosis, and the “**window of opportunity**”
- Improvement of patient care based on **patient stratification** and biomarker profiling
- **New treatments** based on novel MoA
- “Trial-error” → “**Treat-to-Target**”



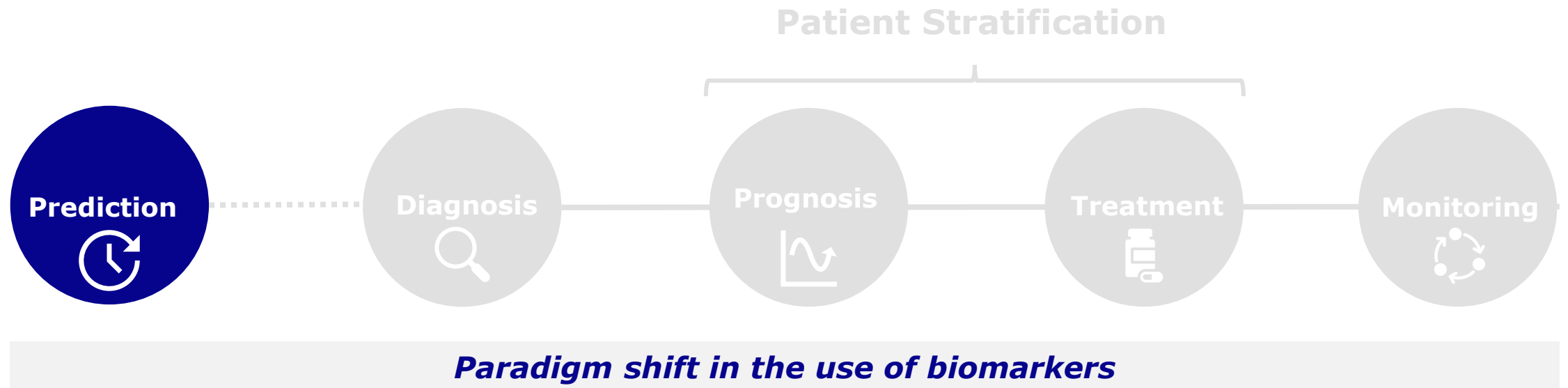
Precision Medicine in RA: Why the Time Is Now



Precision Medicine in RA: Why the Time Is Now



Precision Medicine in RA: Why the Time Is Now



Prediction

1. Prediction + <i>Prevention</i> are a clinical priority	• From theoretical model to clinical application • Clinicians' challenge of managing preclinical RA stages
2. Biomarkers are central to prediction models	• ACPA + RF + others • Increasing knowledge on timing of appearance and evolution of autoantibodies
3. Prevention trials are underway but no proven strategy yet	• Multiple clinical trials exploring preventive interventions (immunomodulatory therapies and lifestyle-based strategies); no proven preventive treatments yet
4. AI is enhancing predictive accuracy	• Integration of genetic, serologic, and clinical data to predict RA onset and therapeutic response
5. Patient education and stakeholder engagement are crucial	• Informed patients and engaged healthcare providers • Importance of educating individuals undergoing predictive testing and involving stakeholders in designing care pathways

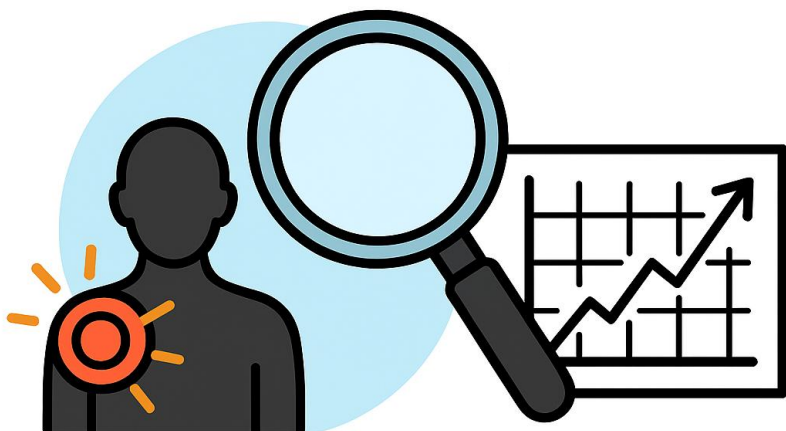
Prediction

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Prediction

1. Prediction + Prevention are a clinical priority

- Clinicians now actively managing patients in preclinical stages - those with musculoskeletal symptoms, autoantibody positivity or familial risk
- Growing recognition of the “window of opportunity” for early intervention in pre- or early RA
- How to approach RA prevention is a major contemporary challenge in rheumatology, with important implications for the other autoimmune diseases



Should we aim for personalized prevention in individuals at risk of RA?

“Advances in the treatment of RA have taught us that “one size does not fit all” and personalized treatment is now the agreed goal. This lesson should be applied to RA prevention.” - Mankia K, Emery P

Mankia K, Emery P. *Int J Rheum Dis.* 2021;**24**:621-622.

Prediction

1. Prediction + Prevention are a clinical priority

2025 EULAR/ACR risk stratification criteria for RA development

- Risk stratification method for people presenting with arthralgia considered to be at risk of RA
- Criteria for arthralgia patients in secondary care at risk (clinically suspect arthralgia) to progress to chronic RA
- High weight of ACPA
- Instrumental in preventing RA

Box EULAR/ACR risk stratification criteria (after simplification) for individuals with arthralgia at risk for RA, to be used in presence or absence of imaging

Target population (who should be tested?): persons with arthralgia in secondary care without clinical arthritis with the arthralgia not better explained by another disease/condition		
Clinical and serologic characteristics		Score
Morning stiffness ^a	0-30 min	0
	30-60 min	2
	30-60 min	4
Patient-reported joint swelling ^b	No	0
	Yes	4
Difficulty making a fist ^c	No	0
	Yes	5
Increased CRP ^d	No	0
	Yes	1
RF ^e	Negative	0
	Low-positive	2
	High-positive	4
ACPA ^e	Negative	0
	Low-positive	4
	High-positive	8
Clinical and serologic sum score		... See Figure 2 for risk
Imaging characteristics if also MRI		
Tenosynovitis flexors wrist ^f	Absent	0
	Present	6
Tenosynovitis extensors wrist ^g	Absent	0
	Present	2
Tenosynovitis extensors MCPs ^h	Absent	0
	Present	5
Tenosynovitis extensors MTPs ⁱ	Absent	0
	Present	3
Subscore MRI		...
Clinical, serologic, and imaging sum score		... See Figure 2 for risk

van Steenberg HW, et al. *Ann Rheum Dis*. 2025;S0003-4967:00076-7

Prediction

1. Prediction + Prevention are a clinical priority

The Rheumatologist[®]

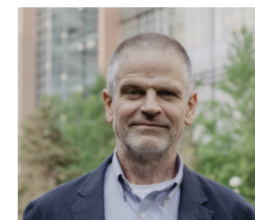
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rheumatologists and rheumatology professionals

AMERICAN COLLEGE
of RHEUMATOLOGY
Empowering Rheumatology Professionals

New Diagnostic Code R76.81 Can Be Used to Identify Those at Risk of Developing RA

Carina Stanton | July 22, 2025

Clinicians can benefit from this new code because R76.81 will facilitate more accurate determination of the at-risk state in medical records. Researchers, too, can benefit because the new code can be tracked to identify at-risk individuals in electronic medical records as well as other medical databases, supporting the ability to study the at-risk RA period, Dr. Deane explains. In his research, he is excited for this new investigative opportunity and what it can do. “When we have approved preventive interventions for RA, having this code in place will help us identify the individuals who we can approach to implement prevention,” he says.

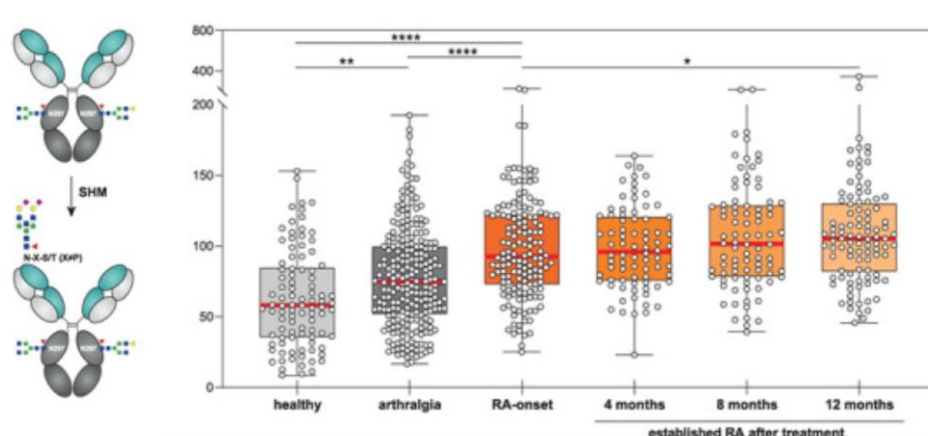


Dr. Deane

Prediction

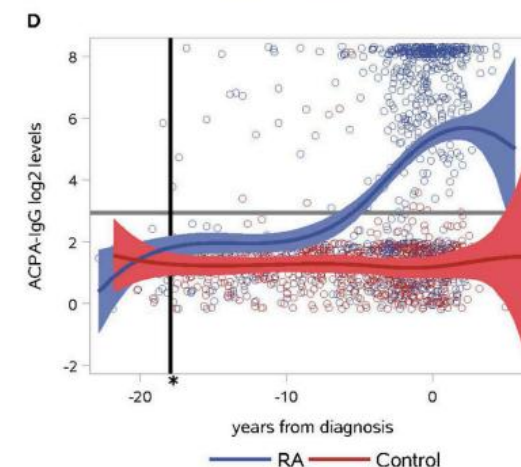
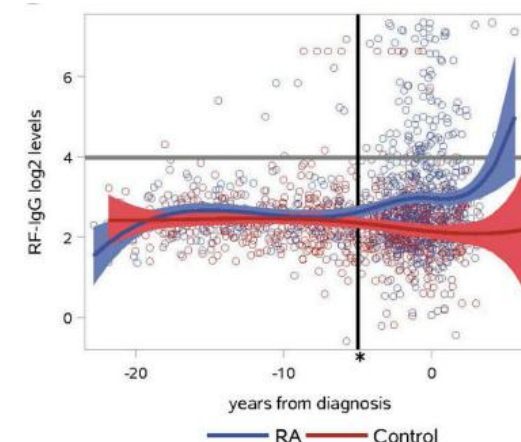
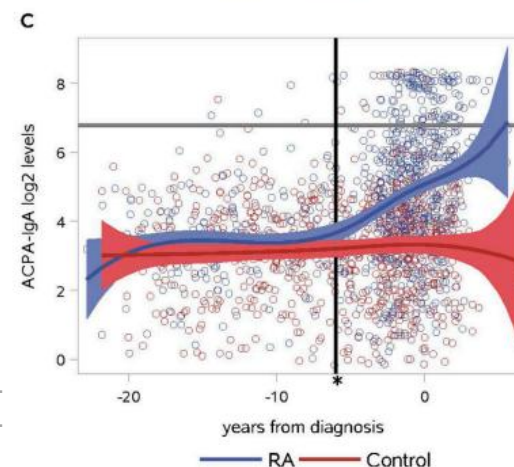
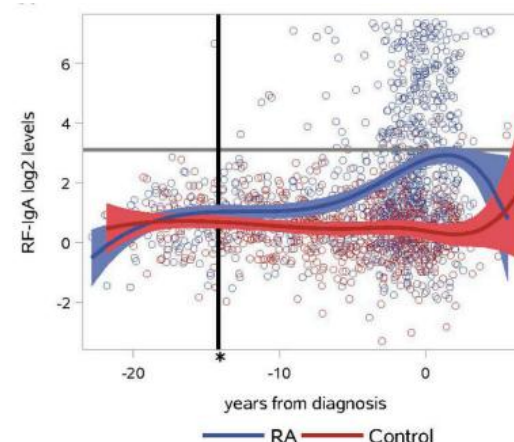
2. Biomarkers are central to prediction models – ACPA + RF

- The presence of ACPA and/or RF is associated with the development of RA in banked blood studies and in clinic settings where subjects present with joint symptoms
- Biomarkers present years prior to RA diagnosis



Kelmenson LB, et al. *Arthritis Rheumatol.* 2020;**72**:251-261.

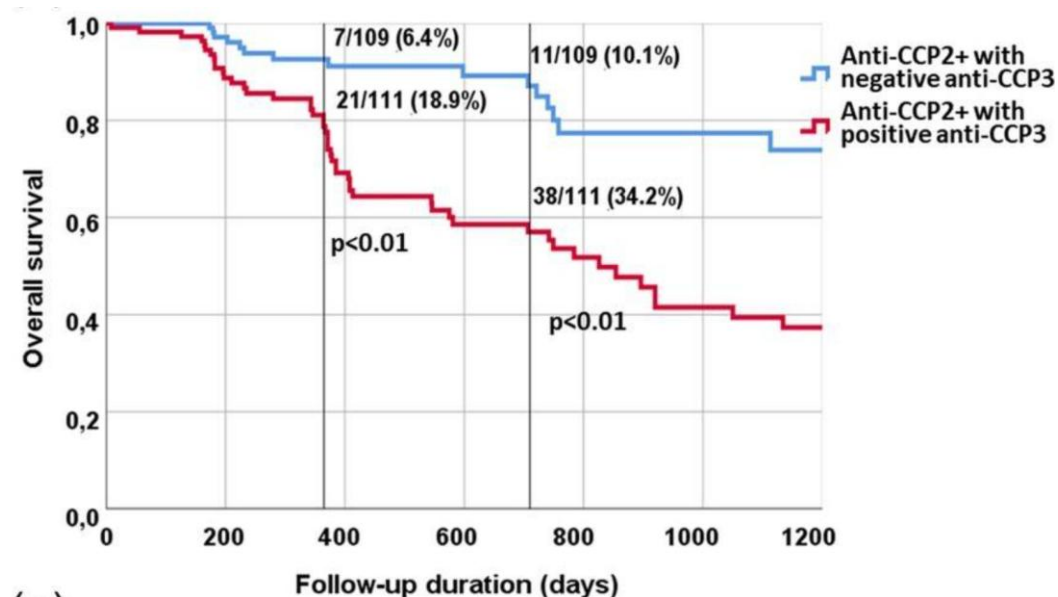
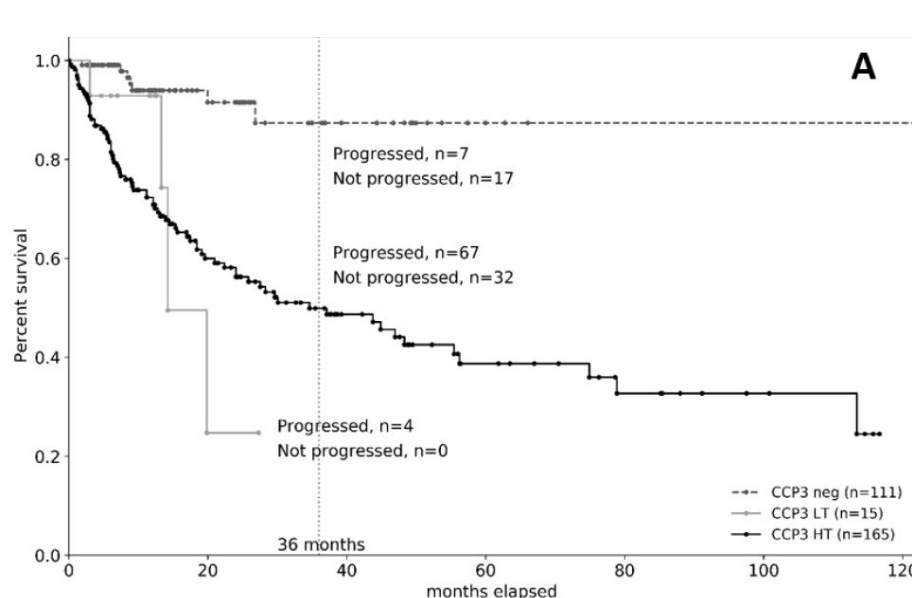
Kissel T et al. *Arthritis Rheumatol.* 2022;**74**:1147-1158.



Prediction

2. Biomarkers are central to prediction models – ACPA + RF

- Anti-CCP assays differ to an extent that may be meaningful in diagnosing RA in patients with IA
- Anti-CCP3 improve prediction of clinical arthritis in both anti-CCP2+ and - at-risk individuals
 - Anti-CCP2&3+ (high): increased incidence of developing IA within 3 years (39 → 48%)
 - Anti-CCP2+ (high) & anti-CCP3-: decreased incidence of developing IA (39 → 10%)



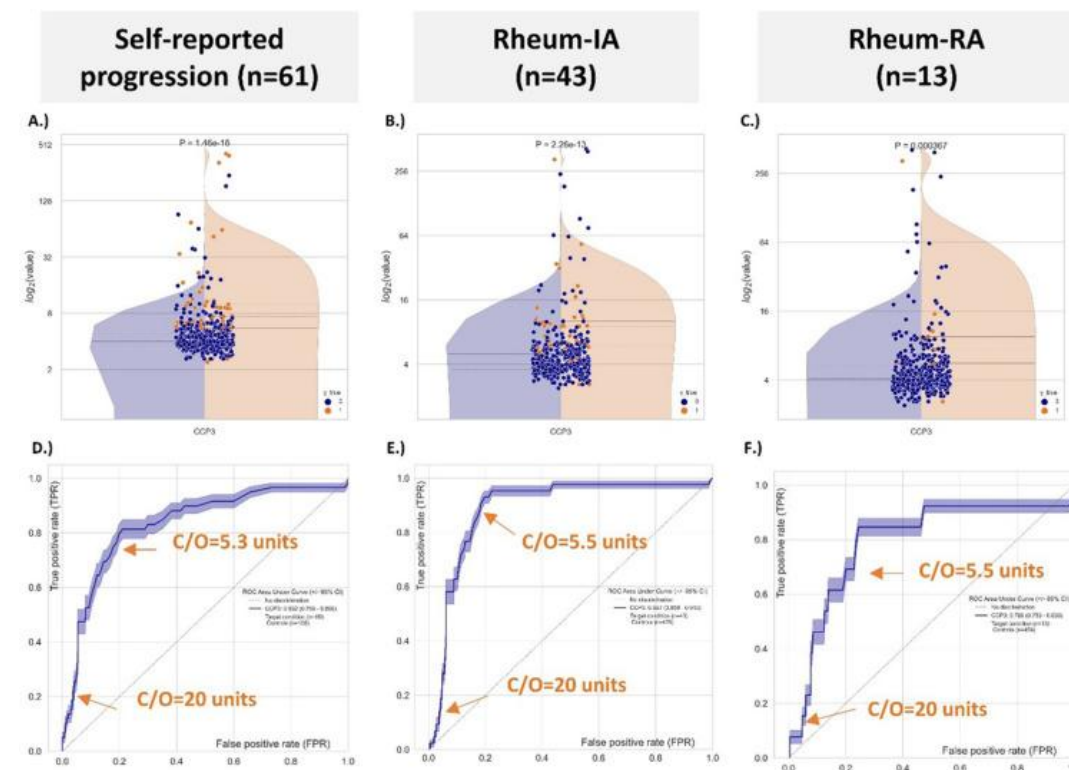
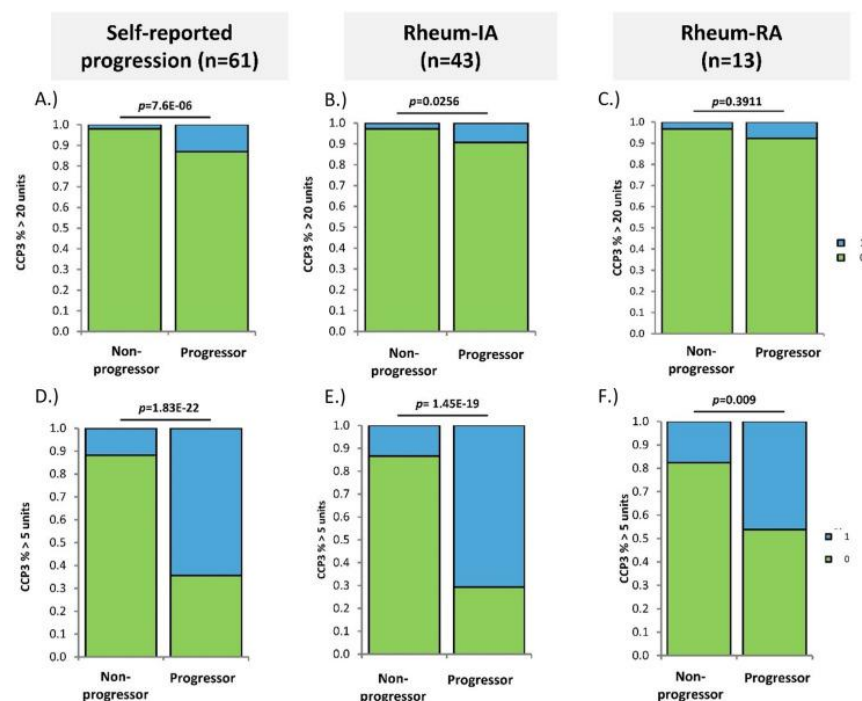
Di Matteo, A. *Arthritis Rheumatol.* 2020;**72**:1820-1828. Di Matteo A. et al. *Rheumatology.* 2022;**61**:3192–3200.

Prediction

2. Biomarkers are central to prediction models – ACPA + RF

- Anti-CCP3 testing could improve the prediction of IA development in anti-CCP2-negative individuals with new musculoskeletal symptoms
- Need for cut-off optimization for RA prediction?

Impact of anti-CCP3 antibody levels in predicting progression to IA



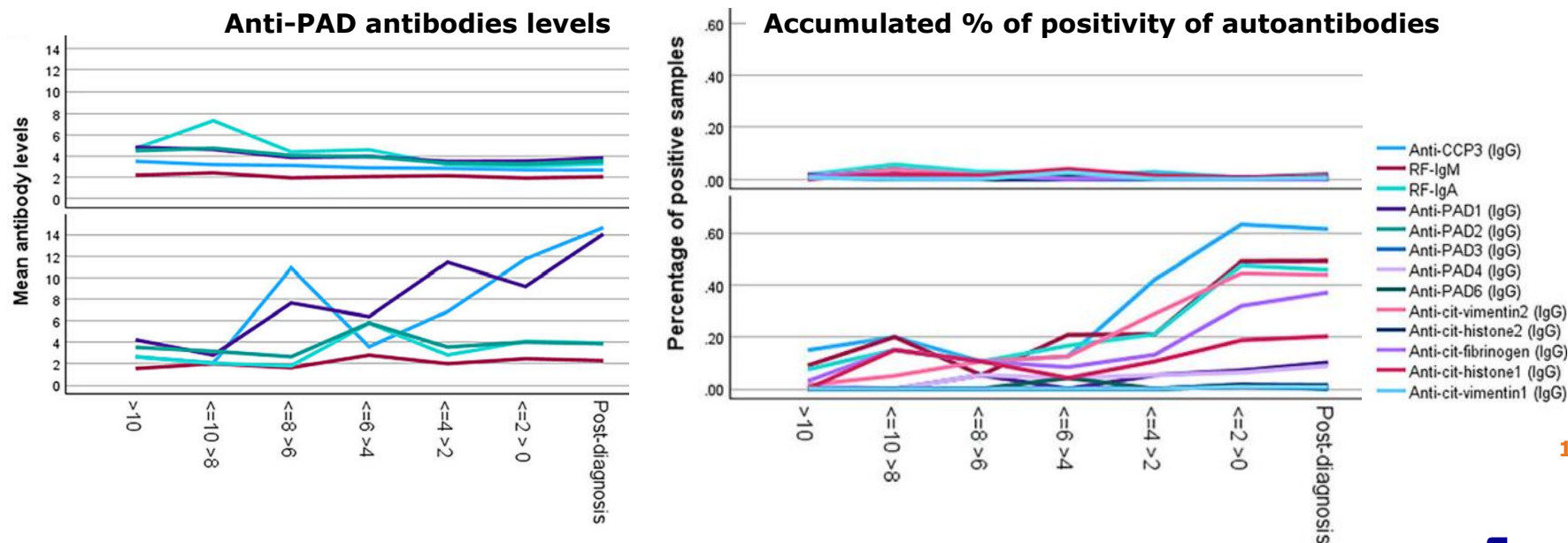
Di Matteo A, et al. *RMD Open*. 2024;10:e003927.

Prediction

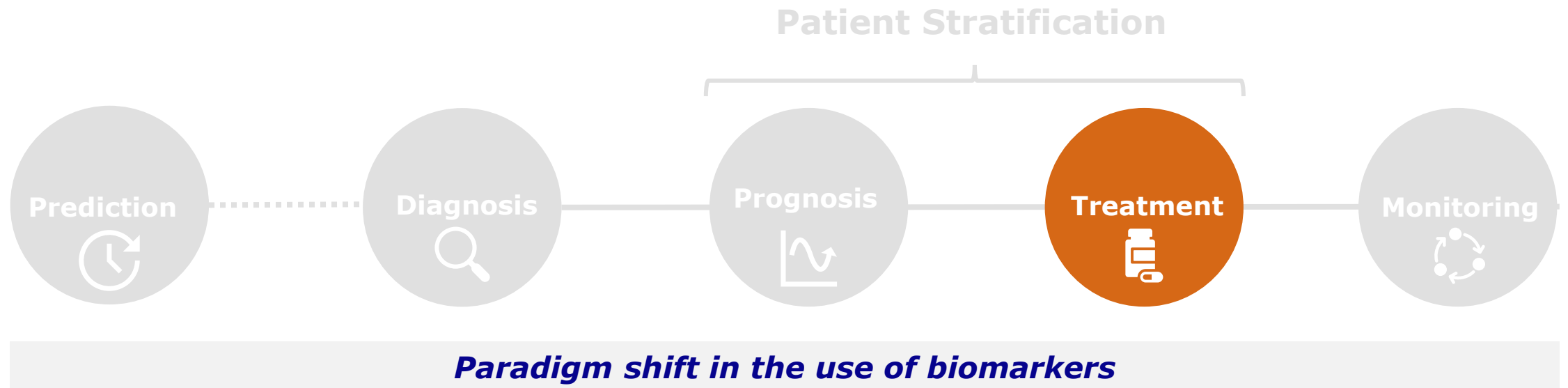
2. Biomarkers are central to prediction models – Anti-PAD antibodies

- Multiple autoab present in pre-RA and increase in positivity as the time of RA diagnosis approaches
- Anti-PAD1 and 4 IgG are present in pre-RA → Anti-PAD1 levels are significantly different between RA and controls 10 years before diagnosis
- Combinations of autoantibodies based on anti-CCP3 and the anti-PADs classify a sample as being closer to the time of RA diagnosis

Kolfenbach JR, et al. *Arthritis Rheum.* 2010;**62**:2633-9.
Goff SH, et al. *ACR Open Rheumatol.* 2024;**6**:587-597.



Precision Medicine in RA: Why the Time Is Now



Treat-to-Target

Where are we today?

- 2010 recommendations to inform patients, rheumatologists and other stakeholders about strategies to reach optimal outcomes of RA based on evidence and expert opinion
- Some elements of T2T are widely used, full implementation uncommon
- Knowledge gaps: how to select the right target for each patient, how often to assess if the target has been achieved and the selection of each subsequent therapy in an evidence-based manner

Box 1 Recommendations

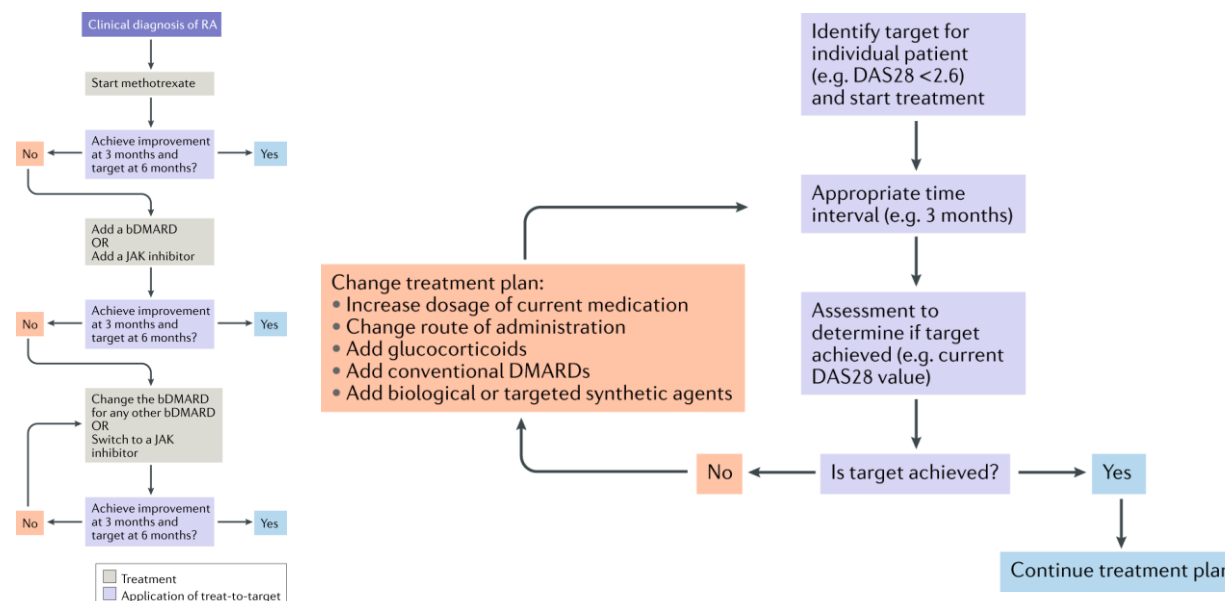
Overarching principles

- The treatment of rheumatoid arthritis must be based on a shared decision between patient and rheumatologist.
- The primary goal of treating the patient with rheumatoid arthritis is to maximise long-term health-related quality of life through control of symptoms, prevention of structural damage, normalisation of function and social participation.
- Abrogation of inflammation is the most important way to achieve these goals.
- Treatment to target by measuring disease activity and adjusting therapy accordingly optimises outcomes in rheumatoid arthritis.

10 recommendations on treating rheumatoid arthritis to target based on both evidence and expert opinion:

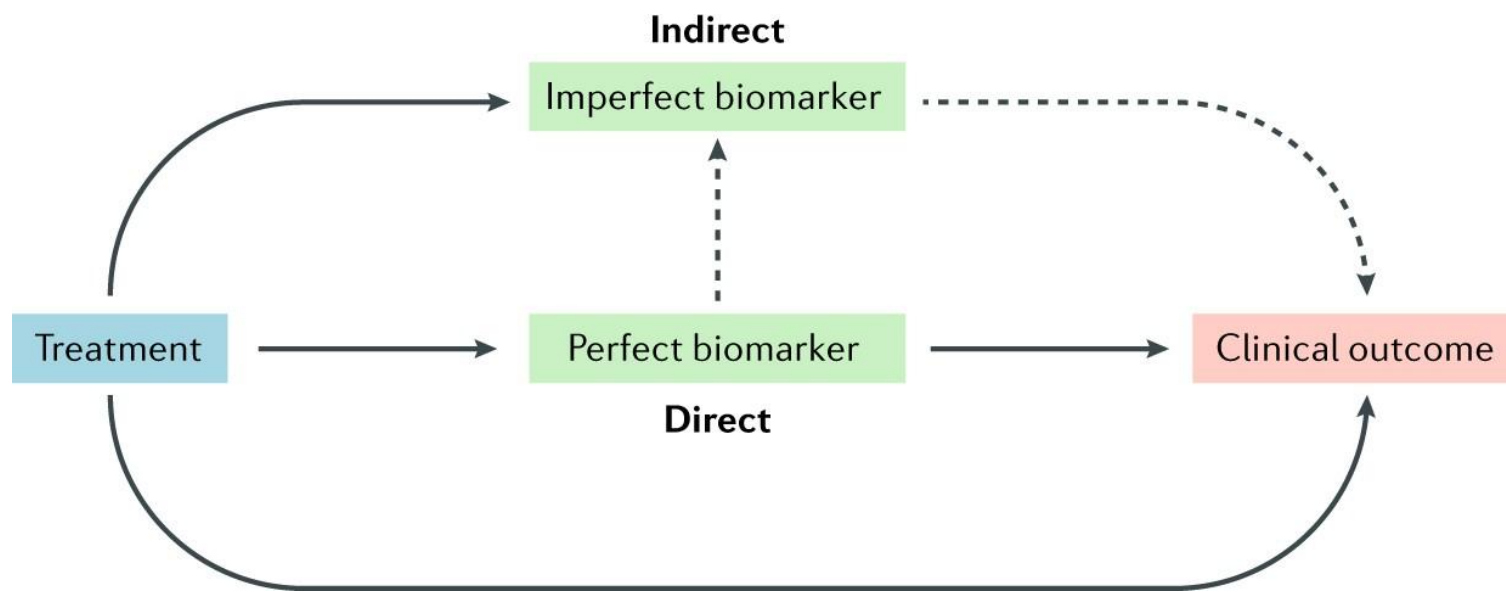
- The primary target for treatment of rheumatoid arthritis should be a state of clinical remission.
- Clinical remission is defined as the absence of signs and symptoms of significant inflammatory disease activity.
- While remission should be a clear target, based on available evidence low disease activity may be an acceptable alternative therapeutic goal, particularly in established long-standing disease.
- Until the desired treatment target is reached, drug therapy should be adjusted at least every 3 months.
- Measures of disease activity must be obtained and documented regularly, as frequently as monthly for patients with high/moderate disease activity or less frequently (such as every 3–6 months) for patients in sustained low disease activity or remission.
- The use of validated composite measures of disease activity, which include joint assessments, is needed in routine clinical practice to guide treatment decisions.
- Structural changes and functional impairment should be considered when making clinical decisions, in addition to assessing composite measures of disease activity.
- The desired treatment target should be maintained throughout the remaining course of the disease.
- The choice of the (composite) measure of disease activity and the level of the target value may be influenced by consideration of co-morbidities, patient factors and drug-related risks.
- The patient has to be appropriately informed about the treatment target and the strategy planned to reach this target under the supervision of the rheumatologist.

van Vollenhoven, R. *Nat Rev Rheumatol* 2019;**15**,180–186.
Smolen JS, et al. *Ann Rheum Dis*. 2010;**69**:631-7.



Treat-to-Target

Biomarkers for prediction of treatment response



Kraus, V.B. *Nat Rev Rheumatol* 2018;14,354–362.

Treat-to-Target

Biomarkers for prediction of treatment response

RF	ACPA
- RF levels decrease with treatment response - RF can be useful for predicting response to therapy with anti-TNF agents - RF positivity possibly predicts better clinical response in those receiving rituximab and tocilizumab	- Aggressive treatment with higher MTX dosing or triple therapy may be beneficial for ACPA RA - ACPA positivity cases possibly response to tocilizumab, rituximab, abatacept and tofacitinib better than those negative of ACPA
Anti-CarP	Anti-PAD4
Abatacept seem beneficial for those positive for anti-CarP antibodies	<u>TNFi</u>: anti-PAD4+ had an increased radiographic progression and a persistently high DAS28 <u>In failure of MTX monotherapy</u>: anti-PAD4+ had a more favorable response to Tx escalation to triple DMARD therapy or MTX+TNF inhibitor <u>GM-CSF receptor blockade</u>: better treatment response of anti-PAD4 negative patients <u>TOFA/ADA + MTX</u>: Differences in treatment response outcomes according to anti-PAD4 antibody status in early and established RA - Prediction of <u>abatacept</u> response in combination with anti-CCP + anti-CarP

Wu, C.-Y. et al. *Int. J. Mol. Sci.* 2021;**22**:686. Santos-Moreno P, et al. *Medicine (Baltimore)*. 2019;**98**:e14181. Mikuls TR, et al. *Arthritis Rheum.* 2004;**50**:3776-82. Kumar R, et al. *Clin Exp Rheumatol.* 2021;**39**:91-97. Halvorsen EH, et al. *Ann Rheum Dis.* 2009;**68**:249-52. Darrah E, et al. *Arthritis Rheumatol.* 2019;**71**:696-702. Grant E, et al. [Abstract]. *Arthritis Rheumatol.* 2016;**68**(suppl 10). Cappelli LC, et al. *ACR Open Rheumatol.* 2024;**6**:81-90. Floris, A., et al. *Arthritis Res Ther.* 2025;**27**:9. Kumar R, et al. *Clin Exp Rheumatol.* 2021;**39**:91-97

Treat-to-Target

Biomarkers for prediction of treatment response

- RA antibodies show significant interaction effects with the response to anti-TNF therapy
- Potential of approaches based on **multiple antibodies** as biomarkers for anti-TNF response in RA

Table 2 Association results for RA antibody interactions with anti-TNF response

Antibody pair	Regression coefficient (95%CI), P-value		
	Interaction effect	Antibody #1 main effect	Antibody #2 main effect
#1: Anti-CCP #2: RF	2.74 (1.20,4.26), P = 0.00068	−1.21 (−2.14, −0.28), P = 0.012	−2.24 (−3.57, −0.91), P = 0.0013
#1: RF #2: Anti-PAD4	− 2.7e-4 (−7.5e-4,1.9e-4), P = 0.25	0.17 (− 0.89,1.21), P = 0.75	1.9e-4 (− 2.1e-4,5.9e-4), P = 0.34
#1: Anti-PAD4 #2: Anti-CarP	−1.3e-6 (− 2.20−6,3.8e-6), P = 0.0062	2.2e-4 (− 3.6e-5,4.8e-4), P = 0.090	1.3e-3 (9.6e-5,2.5e-3), P = 0.035
#1: Anti-CCP #2: Anti-PAD4	−2.5e-4 (− 7.5e-4,2.5e-4), P = 0.33	0.12 (− 0.94,1.18), P = 0.83	1.8e-4 (− 2.6e-4,6.2e-4), P = 0.41
#1: Anti-CCP #2: Anti-CarP	8.9e-4 (−8.9e-4,2.7e-3), P = 0.32	−0.45 (− 1.38,0.48), P = 0.34	−8.4e-4 (− 2.5e-3,7.9e-4), P = 0.31
#1: RF #2: Anti-CarP	−5.39e-4 (− 3.1e-3,1.9e-3), P = 0.67	− 0.17 (− 0.99,0.65), P = 0.67	3.87e-3 (− 2e-3,2.8e-3), P = 0.75

Julià, A., et al. *BMC Musculoskelet Disord* 2021;**22**:372.

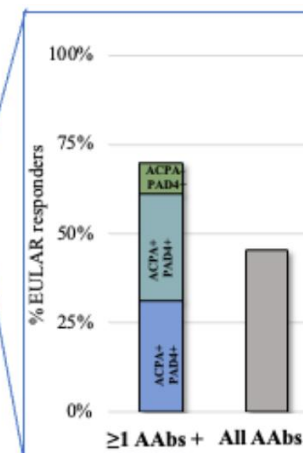
Treat-to-Target

Biomarkers for prediction of treatment response

- Prediction of abatacept response of anti-CCP + anti-PAD4 + anti-CarP

Performance of assessment of autoantibodies combinations in predicting achievement of EULAR response at 6 months from abatacept initiation

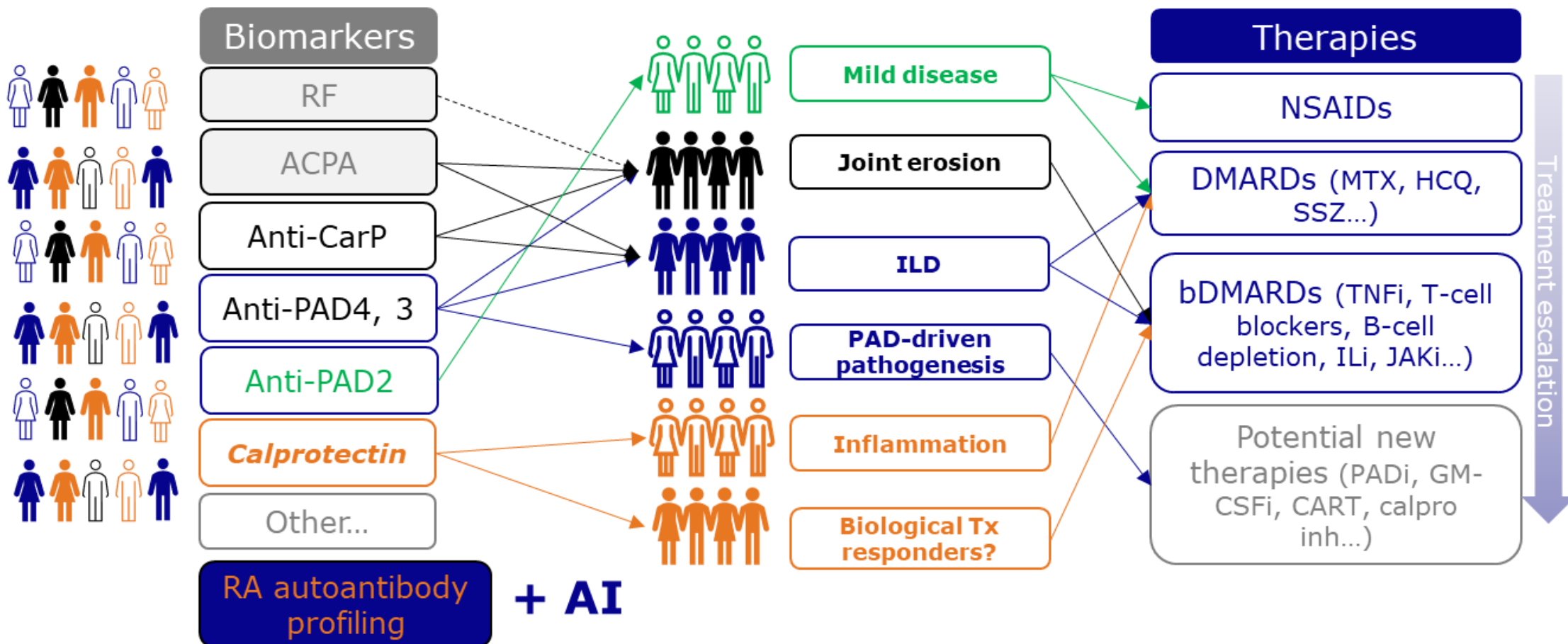
Assessed AAbs combinations	N (%) of EULAR responders			Logistic regression		
	At least one AAb +	All AAbs -	Delta	OR (95%CI)	adjOR (95%CI)	p
RF and/or ACPA + vs double -	62 (66.0%)	vs 16 (59.3%)	6.7%	1.5 (0.6 to 3.9)		0.522
RF and/or aPAD4 + vs double -	43 (67.2%)	vs 12 (50.0%)	17.2%	2.8 (0.9 to 8.3)		0.138
RF and/or aCarP + vs double -	63 (66.3%)	vs 15 (57.7%)	8.6%	1.8 (0.7 to 4.6)		0.416
ACPA and/or PAD4 + vs double -	65 (69.9%)	vs 13 (46.4%)	23.5%	3.5 (1.3 to 9.1)	2.7 (1.1 to 6.4)	0.026
ACPA and/or CarP + vs double -	61 (67.0%)	vs 17 (56.7%)	10.3%	2.0 (0.8 to 4.5)		0.304
PAD4 and/or CarP + vs double -	43 (65.2%)	vs 35 (63.6%)	1.6%	1.2 (0.5 to 2.7)		0.862
RF and/or ACPA and/or aPAD4 + vs double -	68 (68.0%)	vs 10 (47.6%)	20.4%	2.3 (0.9 to 6.1)		0.081
RF and/or ACPA and/or aCarP + vs double -	65 (65.7%)	vs 13 (59.1%)	6.6%	1.6 (0.6 to 4.7)		0.561
RF and/or aPAD4 and/or aCarP + vs double -	68 (67.3%)	vs 10 (50.0%)	17.3%	2.8 (0.9 to 8.3)		0.139
ACPA and/or aPAD4 and/or aCarP + vs double -	67 (68.4%)	vs 11 (47.8%)	20.6%	2.4 (0.9 to 5.9)		0.068
RF and/or ACPA and/or aPAD4 and/or aCarP + vs double -	70 (67.3%)	vs 8 (47.1%)	20.2%	3.4 (1.0 to 10.8)		0.106



Floris, A., et al. *Arthritis Res Ther.* 2025;27:9.

Treat-to-Target

Biomarkers for prediction of treatment response



Treat-to-Target

New treatment avenues

1

Growing interest from **pharmaceutical companies** in immune-mediated diseases and Autoimmunity

2

From trial-error to **T2T** leveraging **biomarkers profiles** for prediction of treatment response

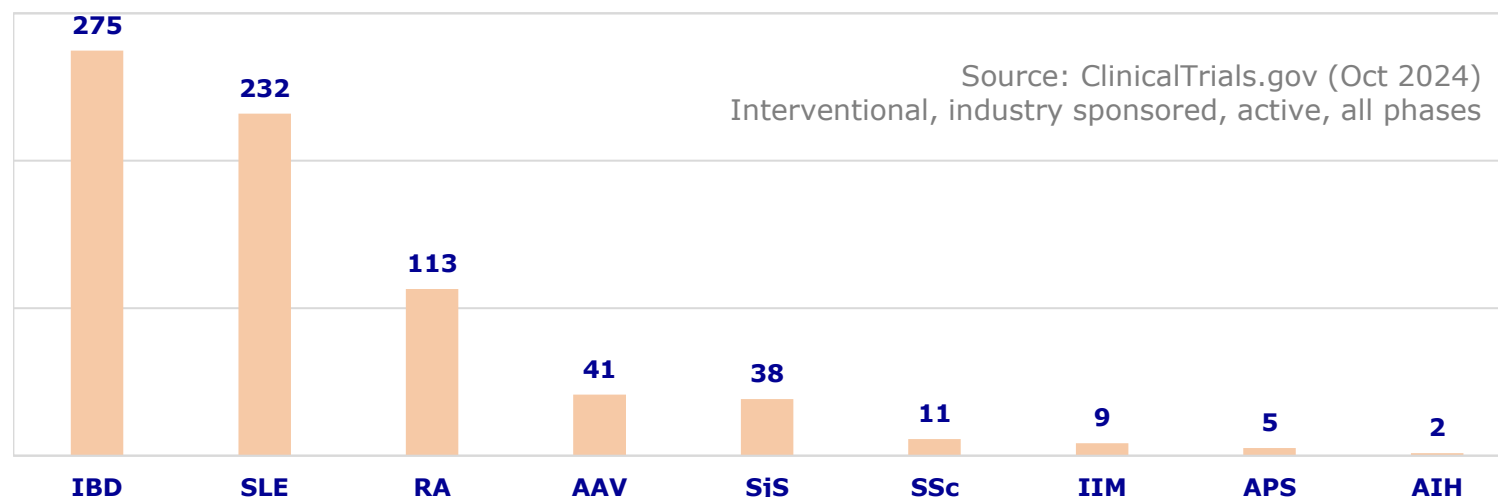
3

Opportunities for biomarkers in all phases of **drug development**. Importance of early introduction.

4

Two important concepts from a **regulatory standpoint**: companion vs complementary diagnostics

Clinical Trials in Autoimmunity

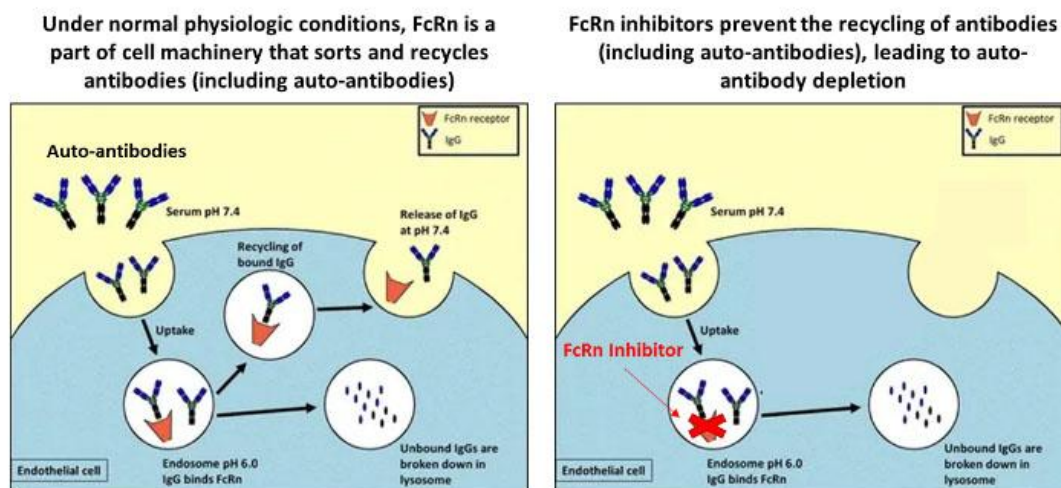


- **Autoantibodies widely used in clinical trials today** for patient selection (inclusion criteria), patient stratification, and/or outcome measures
- Perceived by pharma as a **tool to accelerate drug development** because they provide insights into the biological mechanisms of diseases and the effects of treatments

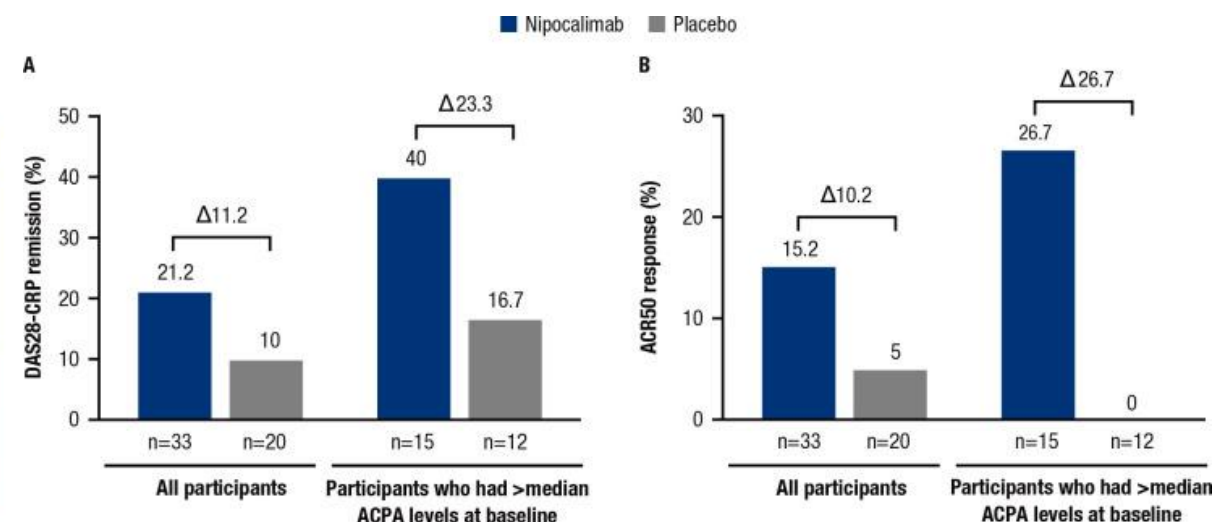
Treat-to-Target

New treatment avenues: 1. FcRn inhibitors

- Designed to lower serum IgG levels by selectively blocking the neonatal Fc receptor (FcRn)
- Efficacy benefits in participants with moderate to severe active RA, with greater benefit in participants with a higher baseline ACPA



Chadha, G.S., Morris, M.E. Curr Pharmacol Rep 2016;2:45–56.

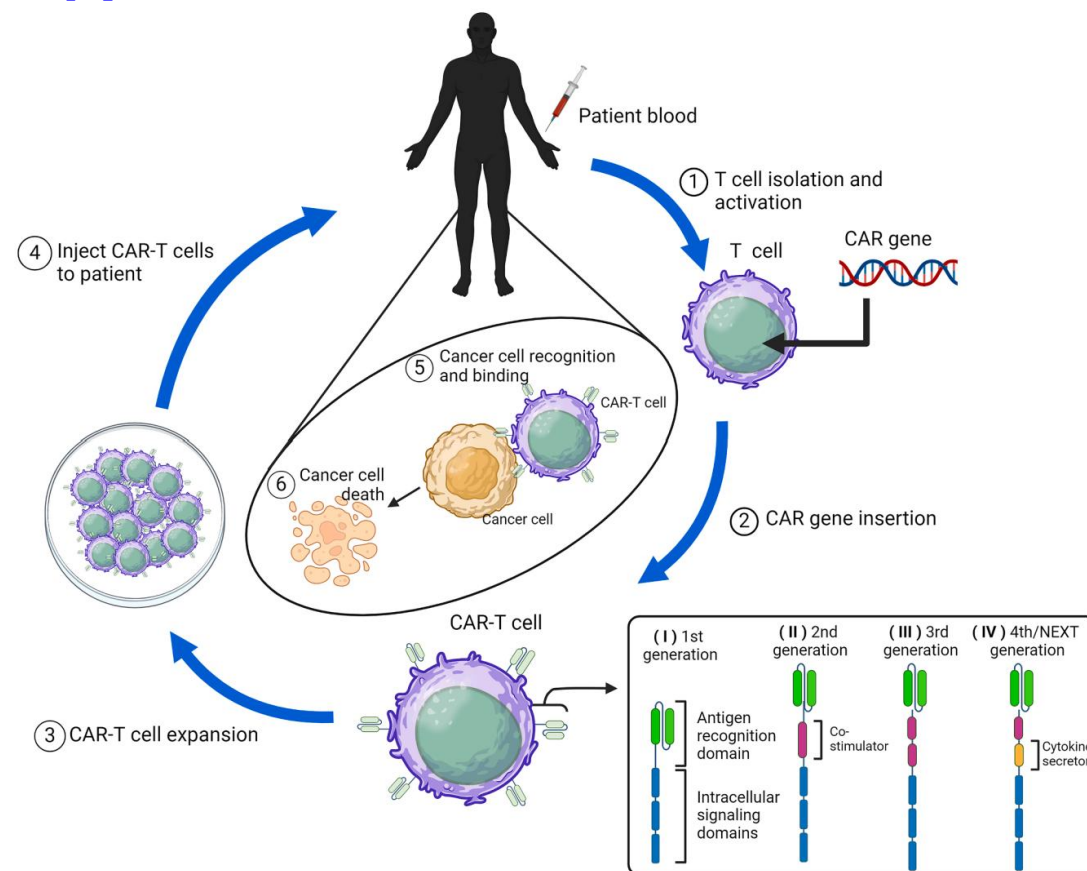


Taylor PC, et al. RMD Open. 2024;10:e004278.

Treat-to-Target

New treatment avenues: 2. CART cell therapy

- A few studies have shown potential for RA with different approaches
- Further studies required to understand clinical efficacy, safety, long-term effects, sustainability of disease remission, optimal design, dosing delivery, technical demand, expenses...
- Potential of autoantibodies for patient selection and monitoring



Schett, G., Müller, F., Taubmann, J. et al. *Nat Rev Rheumatol* 2024;**20**:531–544.

Blagov AV, et al. *Cell Mol Biol*. 2025;**71**:80-88.

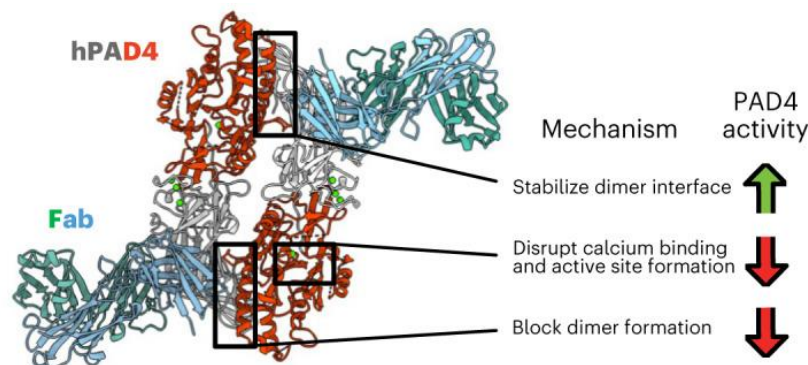
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Treat-to-Target

New treatment avenues: 3. PAD inhibition

- HCQ reduces NET formation through PAD4 inhibition
- Selective PAD inhibitors
 - Alleviation of arthritis through prevention of NETs by an orally available PAD4 inhibitor
 - Amelioration pulmonary fibrosis
 - Unlocking the potential of PAD4 as a drug target for RA requires a deeper understanding of its regulation
- Role of anti-PAD antibodies?



- Discovery of novel **PAD4 activation and inhibition mechanisms** with functional anti-PAD4 antibodies generated by Fab-phage display
- **PAD4 is present on the monocyte surface** in an enzymatically active state capable of citrullinating surface and soluble proteins, leading to the creation of known and novel RA autoantigens
- **H. pylori infection** contributes to RA progression by upregulating PAD4 and induction of cellular protein citrullination

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Take-home messages



Biomarkers such as ACPA, RF, and anti-PAD antibodies can appear years before RA onset and diagnosis, enabling **early identification** and preventive strategies that improve patient outcomes



Autoantibodies can help **predict therapeutic response** to drugs like anti-TNF, rituximab, and abatacept, supporting **Treat-to-Target** approaches



Multi-analyte testing and **autoantibody profiling** represent a cornerstone for implementing **precision medicine** in RA

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Powering Patient Care