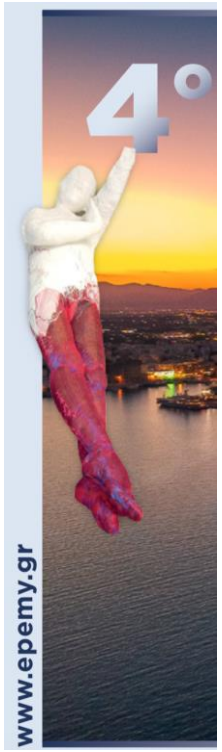
# Precision Medicine και κατευθυντήριες οδηγίες: κινούνται προς την ίδια κατεύθ

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Editor-in-Chief, Autoimmunity Reviews

Medical Degree
English Program
University of Thessaly, Greece

# Σύγκρουση Συμφερόντων Καμία

Κλινική Ρευματολογίας και Κλινικής Ανοσολογίας ΠΓΝΛάρισας

Εργαστήριο Ρευματολογίας & Κλινικής Ανοσολογίας

Medical Degree
English Program
University of Thessaly, Greece

# Ιατρική Ακριβείας και κατευθυντήριες οδηγίες: κινούνται προς την ίδια κατεύθυνση;

Όχι

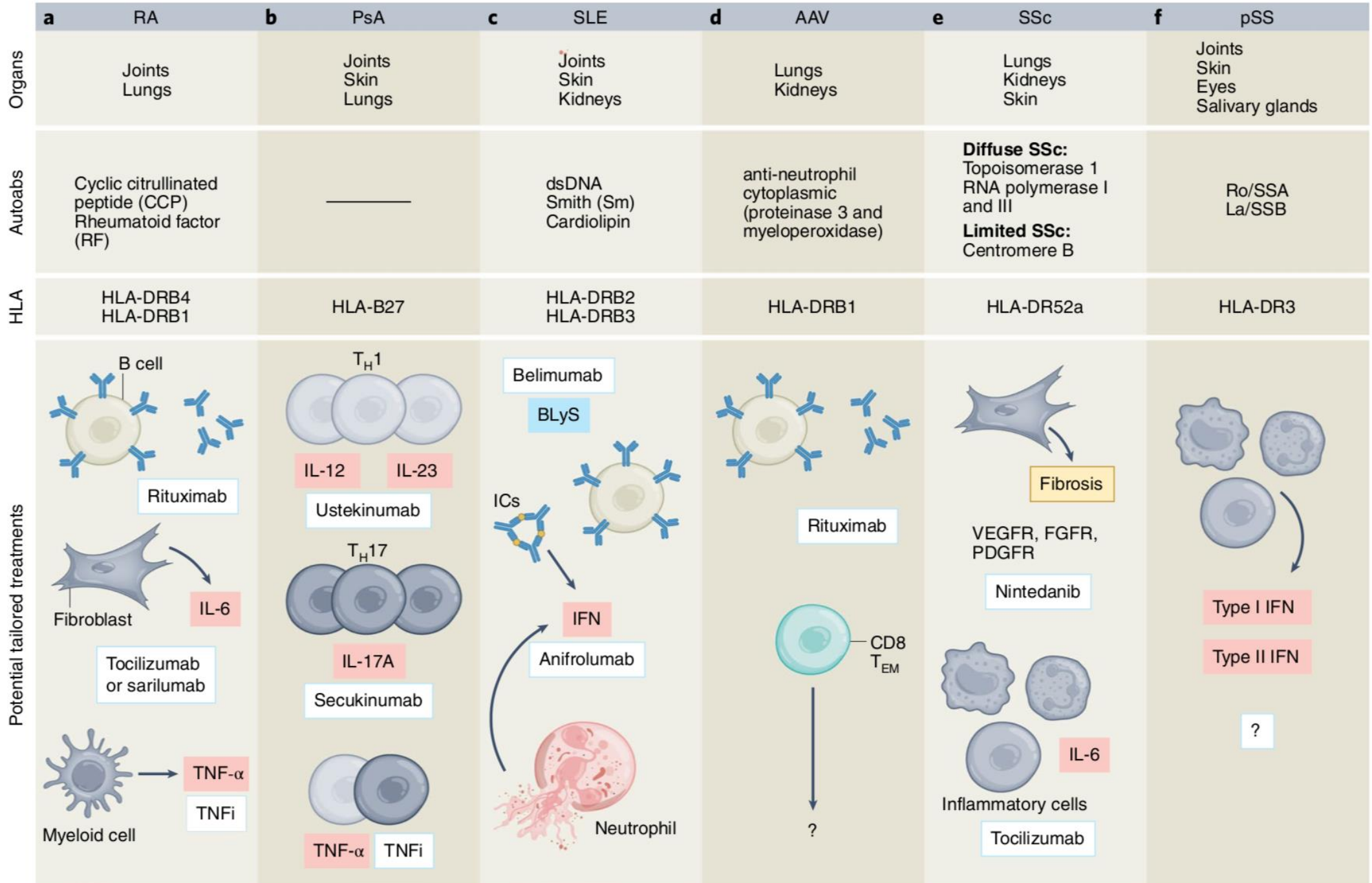
# Terminology

**Clinical practice guidelines** as "statements that include recommendations, intended to **optimize patient care**, that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options

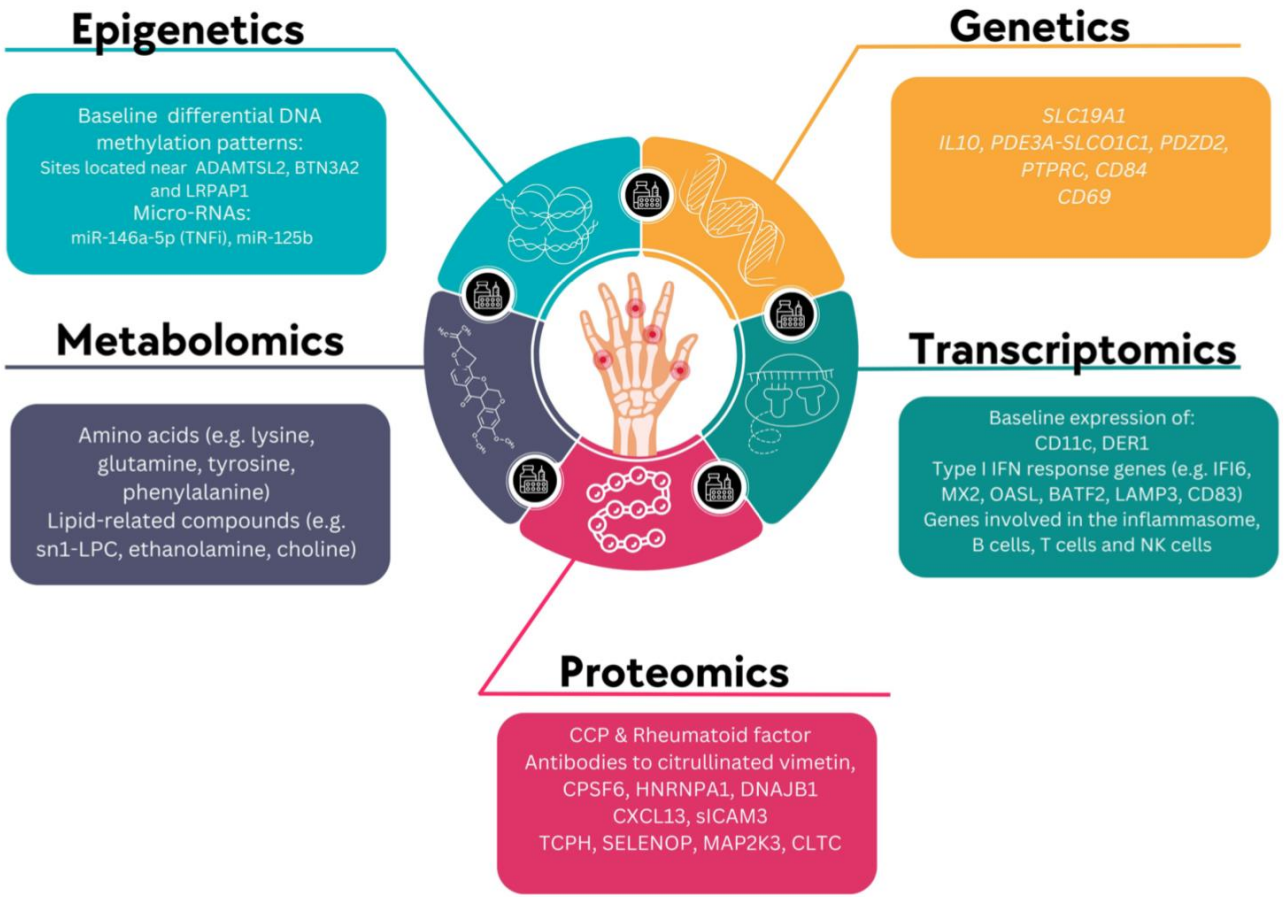
**Precision medicine**, sometimes known as "personalized medicine" is an innovative approach to tailoring disease prevention and treatment that takes into account differences in people's genes, environments, and lifestyles.

# Ιατρική Ακριβείας και κατευθυντήριες οδηγίες: Βασίζονται στα ίδια (θεραπευτικά) εργαλεία;

Ναι


a RA
b PsA
c SLE
d AAV
e SSc
f pSS
Organs
Joints
Lungs
Joints
Skin
Lungs
Joints
Skin
Kidneys
Lungs
Kidneys
Lungs
Kidneys
Skin
Joints
Skin
Eyes
Salivary glands
Autoabs
Cyclic citrullinated peptide (CCP)
Rheumatoid factor (RF)
dsDNA
Smith (Sm)
Cardiolipin
anti-neutrophil cytoplasmic (proteinase 3 and myeloperoxidase)
Diffuse SSc:
Topoisomerase 1
RNA polymerase I and III
Limited SSc:
Centromere B
Ro/SSA
La/SSB
HLA
HLA-DRB4
HLA-DRB1
HLA-B27
HLA-DRB2
HLA-DRB3
HLA-DRB1
HLA-DR52a
HLA-DR3
Potential tailored treatments
B cell
Rituximab
Fibroblast
IL-6
Tocilizumab or sarilumab
Myeloid cell
TNF-α
TNFi
TH1
IL-12
IL-23
Ustekinumab
TH17
IL-17A
Secukinumab
TNF-α
TNFi
Belimumab
BLyS
ICs
IFN
Anifrolumab
Neutrophil
Rituximab
CD8
TEM
?
Fibrosis
VEGFR, FGFR, PDGFR
Nintedanib
IL-6
Inflammatory cells
Tocilizumab
Type I IFN
Type II IFN
?

# Precision Medicine




**Μας ενδιαφέρουν τα «δακτυλικά αποτυπώματα» του ασθενούς**

**Box 1 | Current and emerging approaches for molecular characterization of patients with systemic autoimmune rheumatic disease**

**Current**

- Autoantibodies
- Clinical imaging
- Clinical lab testing: complement levels and split products
- Soluble mediators: cytokines, chemokines, and soluble receptors
- Transcriptomics: molecular signatures
- Genetics: disease-associated variants
- Immunophenotyping: flow cytometry
- Tissue histology

**Emerging**

- Genetics: genetic load, polygenic risk scores, extended HLA haplotypes
- Transcriptomics: cell-specific expression/signatures (scRNA-seq)
- Immunophenotyping: single-cell proteomics (CyTOF), proteogenomics (CITE-seq), repertoire immunomics
- Perturbomics (multi-omic evaluation after stimulation or other perturbation conditions)
- Spatial tissue analytics: multiplex tissue imaging (CODEX, serial IHC)
- Imaging mass cytometry (Hyperion, IonPath)
- Epigenomics (sorted cell and single cell): DNA methylation, histone modification, chromatin conformation (ATAC-seq), protein–DNA interactions (CUT&RUN)
- Mass spectroscopy (biofluid) and imaging mass spectrometry (tissue): proteomics, metabolomics, lipidomics, and glycomics
- Environmental factors: microbiomics, exposomics

# Precision medicine vs guidelines

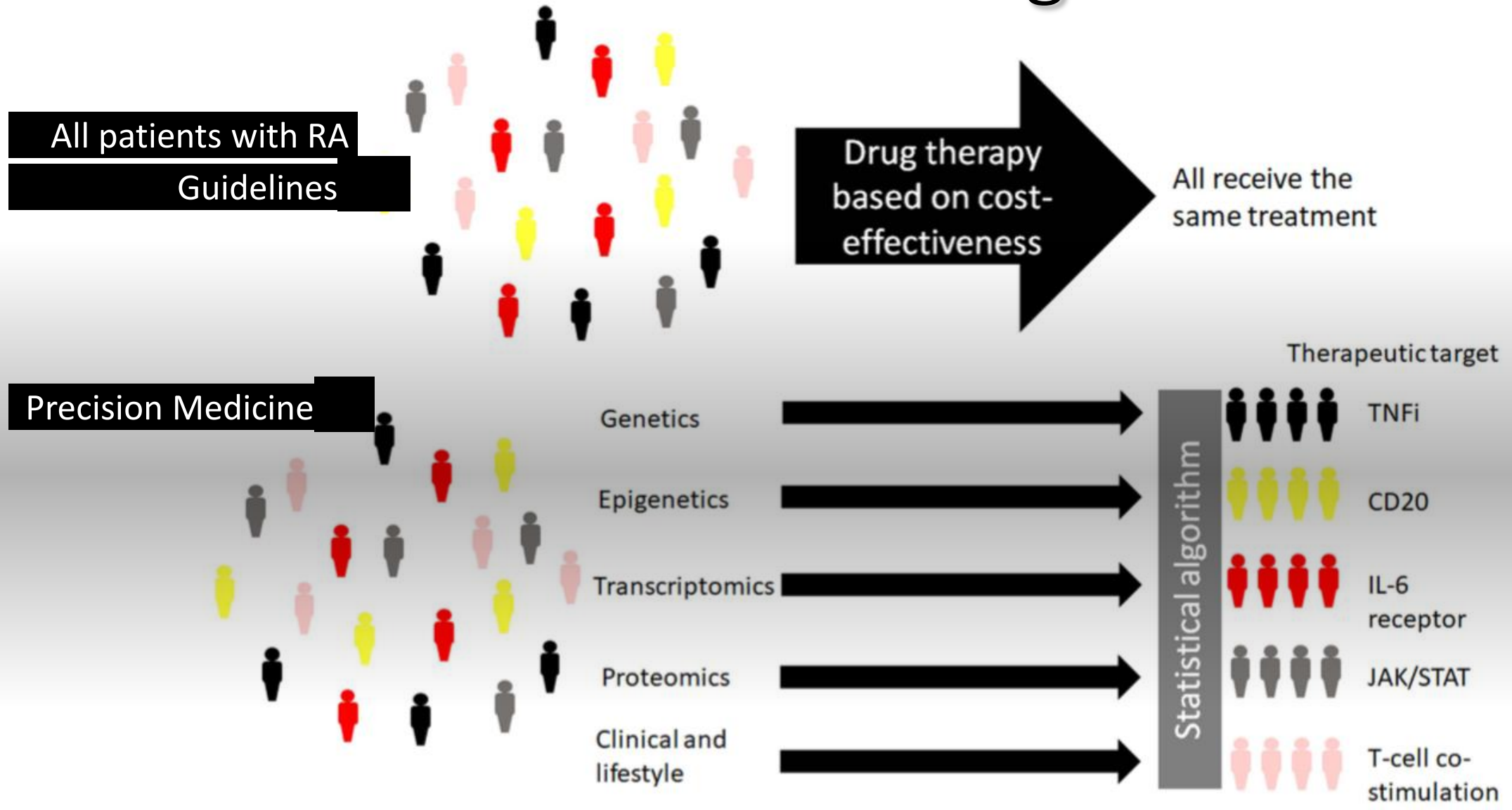



**Figure 1** Illustration of how personalized medicine approaches using biomarkers and clinical predictors of treatment outcome can be applied to select a therapeutic target with an increased likelihood of response for the individual patient.

**Box 1 | Current and emerging approaches for molecular characterization of patients with systemic autoimmune rheumatic disease**

**Current**

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**Emerging**

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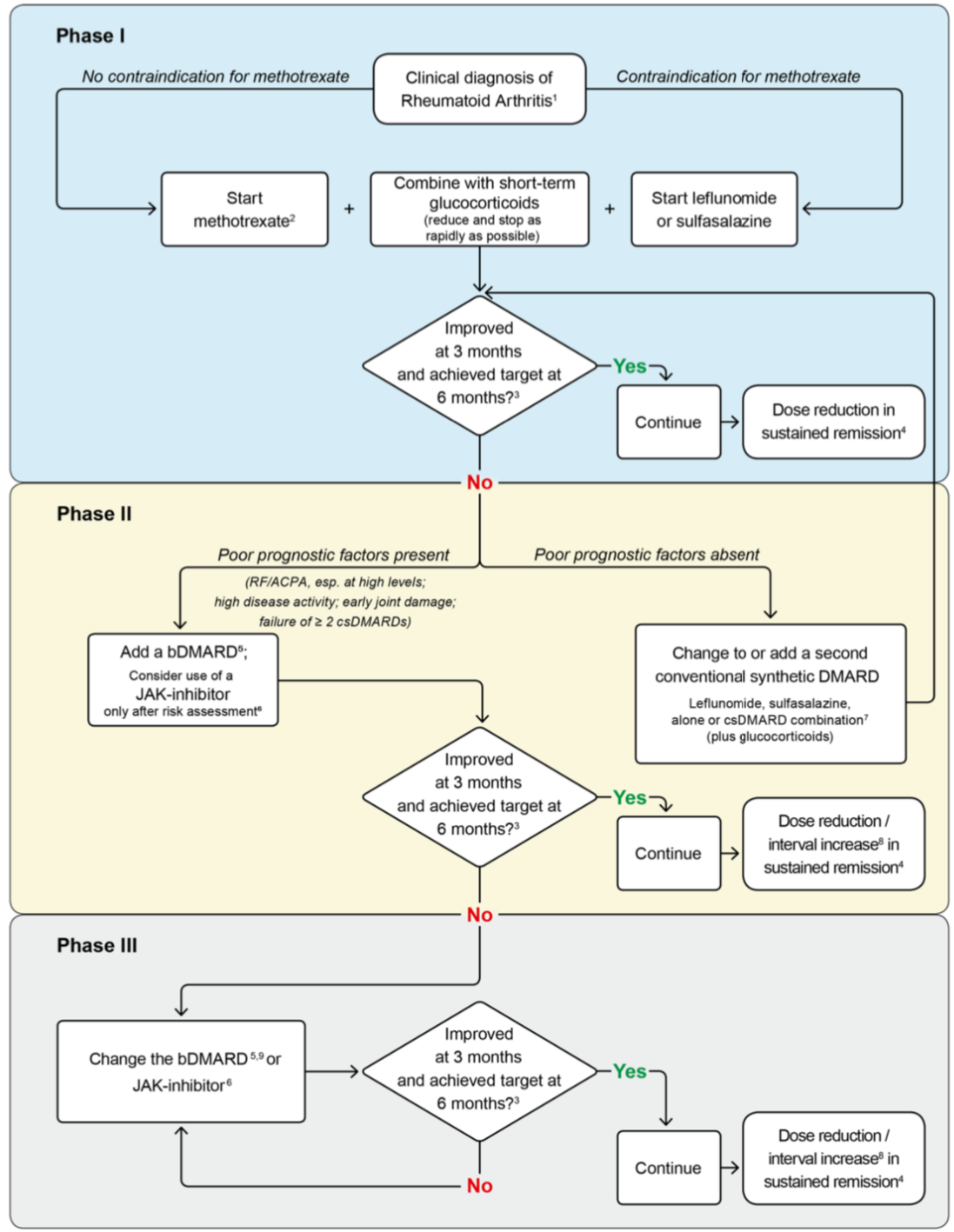
Recommendation

# EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update


Phase I
Clinical diagnosis of Rheumatoid Arthritis[1]
No contraindication for methotrexate
Contraindication for methotrexate
Start methotrexate[2]
+
Combine with short-term glucocorticoids (reduce and stop as rapidly as possible)
+
Start leflunomide or sulfasalazine
Improved at 3 months and achieved target at 6 months?[3]
Yes
Continue
Dose reduction in sustained remission[4]
No
Phase II
Poor prognostic factors present
(RF/ACPA, esp. at high levels; high disease activity; early joint damage; failure of ≥ 2 csDMARDs)
Poor prognostic factors absent
Add a bDMARD[5]; Consider use of a JAK-inhibitor only after risk assessment[6]
Change to or add a second conventional synthetic DMARD
Leflunomide, sulfasalazine, alone or csDMARD combination[7] (plus glucocorticoids)
Improved at 3 months and achieved target at 6 months?[3]
Yes
Continue
Dose reduction / interval increase[8] in sustained remission[4]
No
Phase III
Change the bDMARD[5,9] or JAK-inhibitor[6]
Improved at 3 months and achieved target at 6 months?[3]
Yes
Continue
Dose reduction / interval increase[8] in sustained remission[4]
No

Ιατρική Ακριβείας με βάση τον ιστό (ανοσοφαινότυπο) και όχι τα guidelines

# Rituximab versus tocilizumab in anti-TNF inadequate responder patients with rheumatoid arthritis (R4RA): 16-week outcomes of a stratified, biopsy-driven, multicentre, open-label, phase 4 randomised controlled trial

*Frances Humby, Patrick Durez, Maya H Buch, Myles J Lewis, Hasan Rizvi, Felice Rivellese, Alessandra Nerviani, Giovanni Giorli, Arti Mahto, Carlomaurizio Montecucco, Bernard Lauwerys, Nora Ng, Pauline Ho, Michele Bombardieri, Vasco C Romão, Patrick Verschueren, Stephen Kelly, Pier Paolo Sainaghi, Nagui Gendi, Bhaskar Dasgupta, Alberto Cauli, Piero Reynolds, Juan D Cañete, Robert Moots, Peter C Taylor, Christopher J Edwards, John Isaacs, Peter Sasieni, Ernest Choy, Costantino Pitzalis, on behalf of the R4RA collaborative group*

Lancet 2021

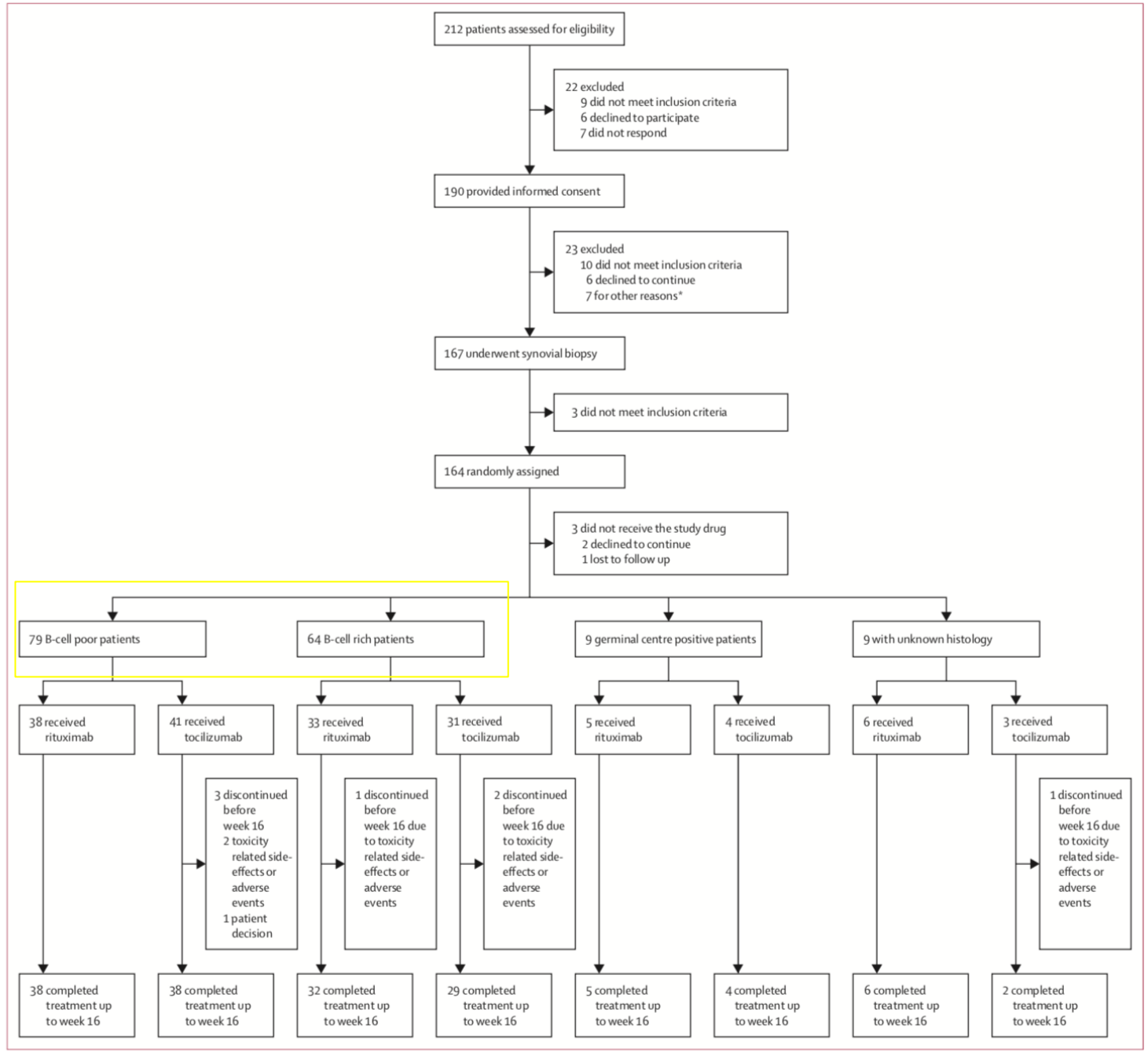



***Figure:*** **Trial profile**

*Six patients did not have suitable joints at biopsy and one for clinical reasons unrelated to rheumatoid arthritis.

# Η R4RA κλινική δοκιμή

- Συνολικά 164 ασθενείς με ρευματοειδή αρθρίτιδα υποβλήθηκαν σε βιοψία αρθρικού αρθρικού υγρού πριν από τη θεραπεία και ταξινομήθηκαν ιστολογικά είτε ως φτωχοί σε Β-κύτταρα είτε ως πλούσιοι σε Β-κύτταρα
- Στη συνέχεια, κατανεμήθηκαν τυχαία στην ομάδα tocilizumab ή στην ομάδα rituximab), με ιστολογική ταξινόμηση ως παράγοντα στρωματοποίησης
- Μετά την ταξινόμηση με αλληλουχία RNA, το ποσοστό απόκρισης CDAI50% ήταν σημαντικά υψηλότερο στην ομάδα του tocilizumab σε σύγκριση με την ομάδα του rituximab

# Συνέπειες

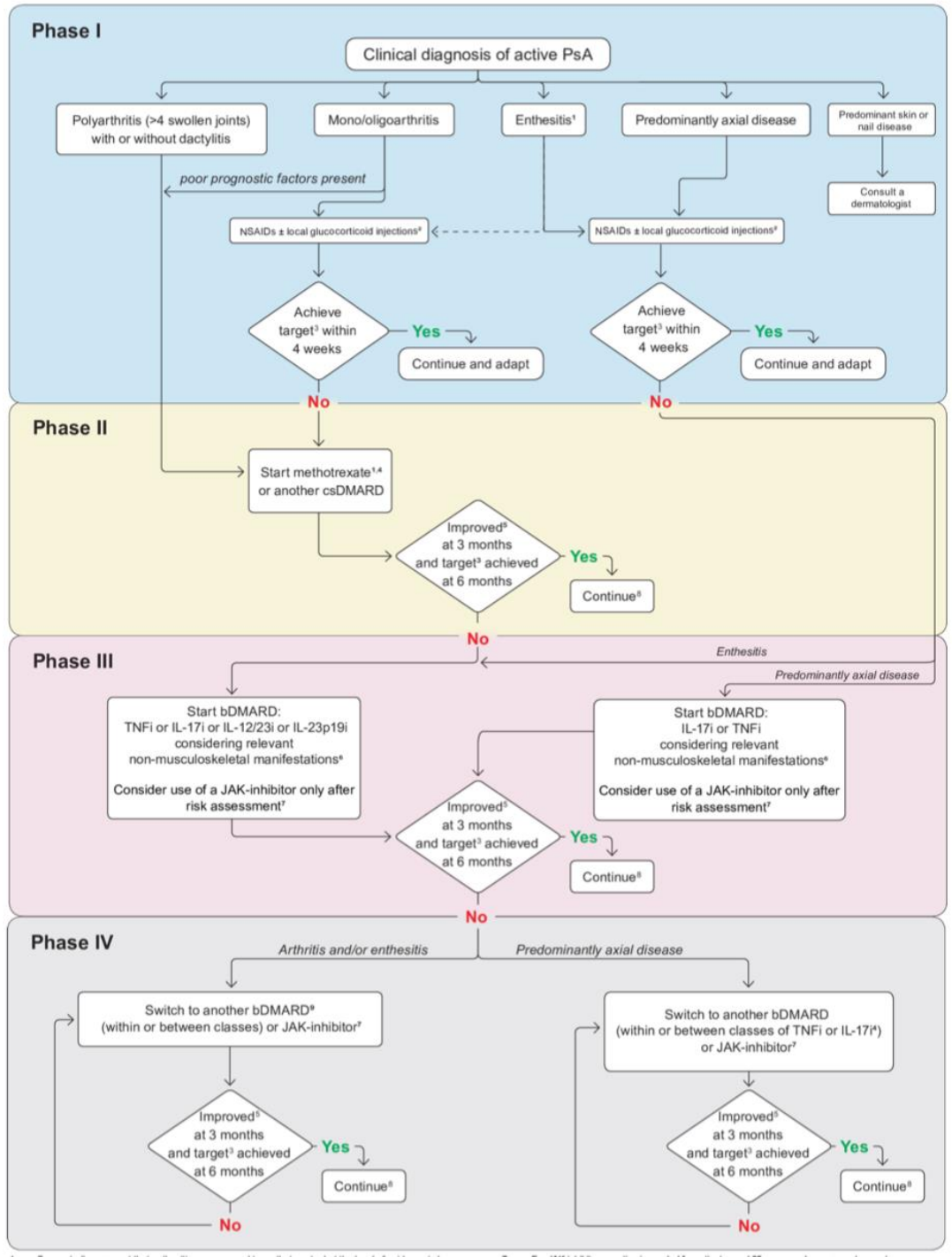
- Η κλινική δοκιμή R4RA αντιπροσωπεύει ένα ορόσημο στη μηχανιστική διερεύνηση σε επίπεδο ιστού ασθένειας της σχέσης μεταξύ του τρόπου δράσης του φαρμάκου και της κλινικής απόκρισης
- Σε σύγκριση με την τρέχουσα κλινική προσέγγιση, το R4RA δείχνει ότι σε ασθενείς με χαμηλή ή απουσία υπογραφής έκφρασης Β-λεμφοκυττάρων στον αρθρικό ιστό με αλληλούχιση RNA, η θεραπεία με αναστολή του υποδοχέα IL-6 δηλαδή με τοσιλιζουμάμπη— είναι ανώτερη από τη στόχευση Β-λεμφοκυττάρων με rituximab

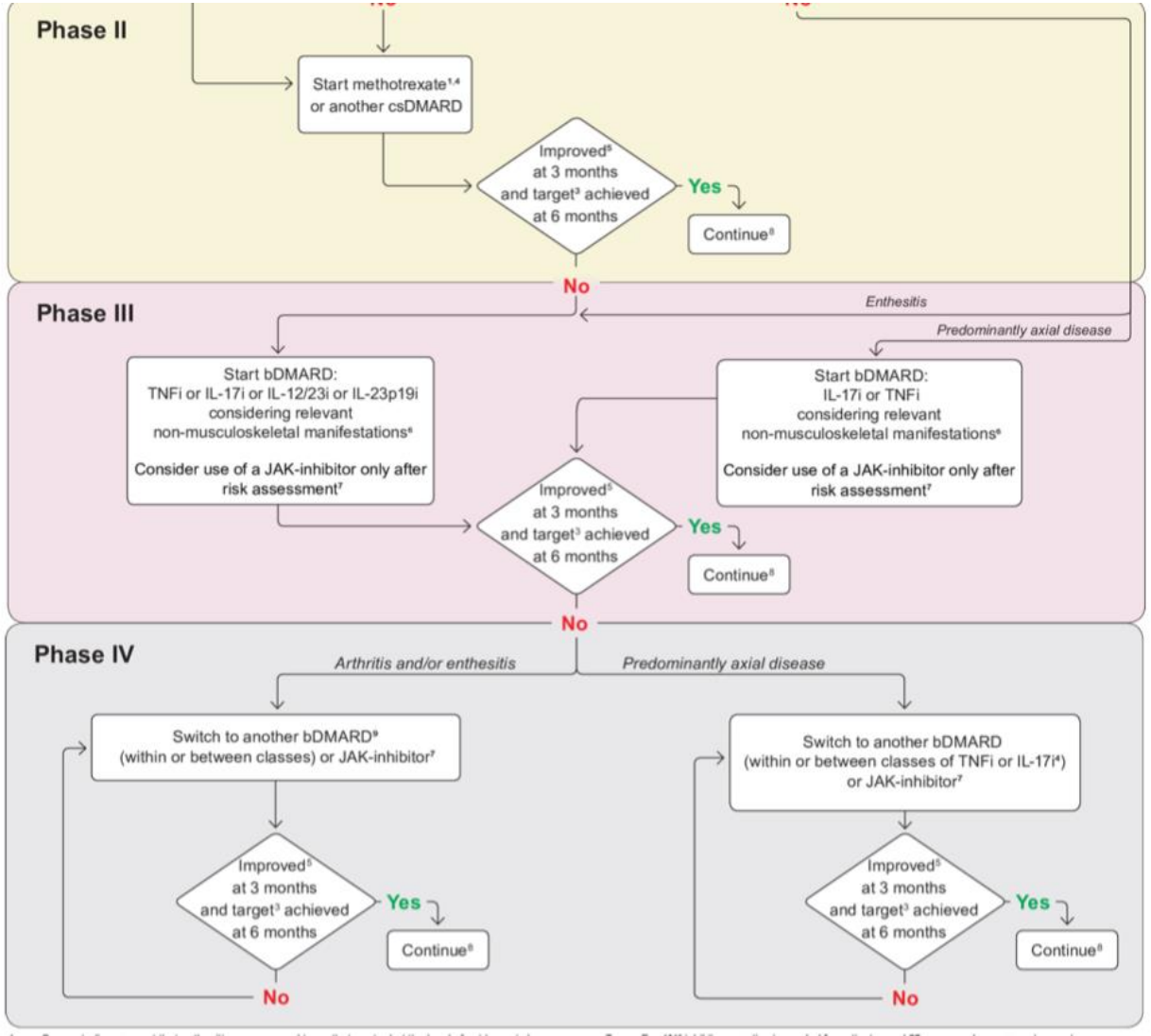
Recommendation

OPEN ACCESS

# EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2023 update

Laure Gossec ,[1,2] Andreas Kerschbaumer ,[3] Ricardo J O Ferreira ,[4,5] Daniel Aletaha ,[3] Xenofon Baraliakos ,[6] Heidi Bertheussen,[7] Wolf-Henning Boehncke,[8] Bente Appel Esbensen ,[9,10] Iain B McInnes,[11] Dennis McGonagle,[12,13] Kevin L Winthrop ,[14] Andra Balanescu,[15] Peter V Balint,[16] Gerd R Burmester ,[17] Juan D Cañete ,[18,19] Pascal Claudepierre,[20,21] Lihi Eder ,[22] Merete Lund Hetland ,[23,24] Annamaria Iagnocco ,[25] Lars Erik Kristensen,[26,27] Rik Lories,[28,29] Rubén Queiro ,[30,31] Daniele Mauro ,[32] Helena Marzo-Ortega ,[12,13] Philip J Mease ,[33,34] Peter Nash ,[35] Wendy Wagenaar,[36,37] Laura Savage,[38] Georg Schett ,[39] Stephanie J W Shoop-Worrall ,[40] Yoshiya Tanaka ,[41] Filip E Van den Bosch ,[42] Annette van der Helm-van Mil,[43] Alen Zabotti ,[44] Désirée van der Heijde ,[43] Josef S Smolen[3]


Phase I
Clinical diagnosis of active PsA
Polyarthritis (>4 swollen joints) with or without dactylitis
Mono/oligoarthritis
Enthesitis[1]
Predominantly axial disease
Predominant skin or nail disease
Consult a dermatologist
poor prognostic factors present
NSAIDs ± local glucocorticoid injections[2]
NSAIDs ± local glucocorticoid injections[2]
Achieve target[3] within 4 weeks
Yes
Continue and adapt
Achieve target[3] within 4 weeks
Yes
Continue and adapt
No
No
Phase II
Start methotrexate[1,4] or another csDMARD
Improved[5] at 3 months and target[3] achieved at 6 months
Yes
Continue[6]
No
Phase III
Enthesitis
Predominantly axial disease
Start bDMARD: TNFi or IL-17i or IL-12/23i or IL-23p19i considering relevant non-musculoskeletal manifestations[8]
Consider use of a JAK-inhibitor only after risk assessment[7]
Start bDMARD: IL-17i or TNFi considering relevant non-musculoskeletal manifestations[8]
Consider use of a JAK-inhibitor only after risk assessment[7]
Improved[5] at 3 months and target[3] achieved at 6 months
Yes
Continue[6]
No
Phase IV
Arthritis and/or enthesitis
Predominantly axial disease
Switch to another bDMARD[9] (within or between classes) or JAK-inhibitor[7]
Switch to another bDMARD (within or between classes of TNFi or IL-17i[4]) or JAK-inhibitor[7]
Improved[5] at 3 months and target[3] achieved at 6 months
Yes
Continue[6]
Improved[5] at 3 months and target[3] achieved at 6 months
Yes
Continue[6]
No
No


Phase II
Start methotrexate[1,4] or another csDMARD
Improved[5] at 3 months and target[3] achieved at 6 months
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Continue[6]
No
Phase III
Enthesitis
Predominantly axial disease
Start bDMARD: TNFi or IL-17i or IL-12/23i or IL-23p19i considering relevant non-musculoskeletal manifestations[8]
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Start bDMARD: IL-17i or TNFi considering relevant non-musculoskeletal manifestations[8]
Consider use of a JAK-inhibitor only after risk assessment[7]
Improved[5] at 3 months and target[3] achieved at 6 months
Yes
Continue[6]
No
Phase IV
Arthritis and/or enthesitis
Predominantly axial disease
Switch to another bDMARD[9] (within or between classes) or JAK-inhibitor[7]
Improved[5] at 3 months and target[3] achieved at 6 months
Yes
Continue[6]
No
Switch to another bDMARD (within or between classes of TNFi or IL-17i[4]) or JAK-inhibitor[7]
Improved[5] at 3 months and target[3] achieved at 6 months
Yes
Continue[6]
No

RHEUMATOLOGY

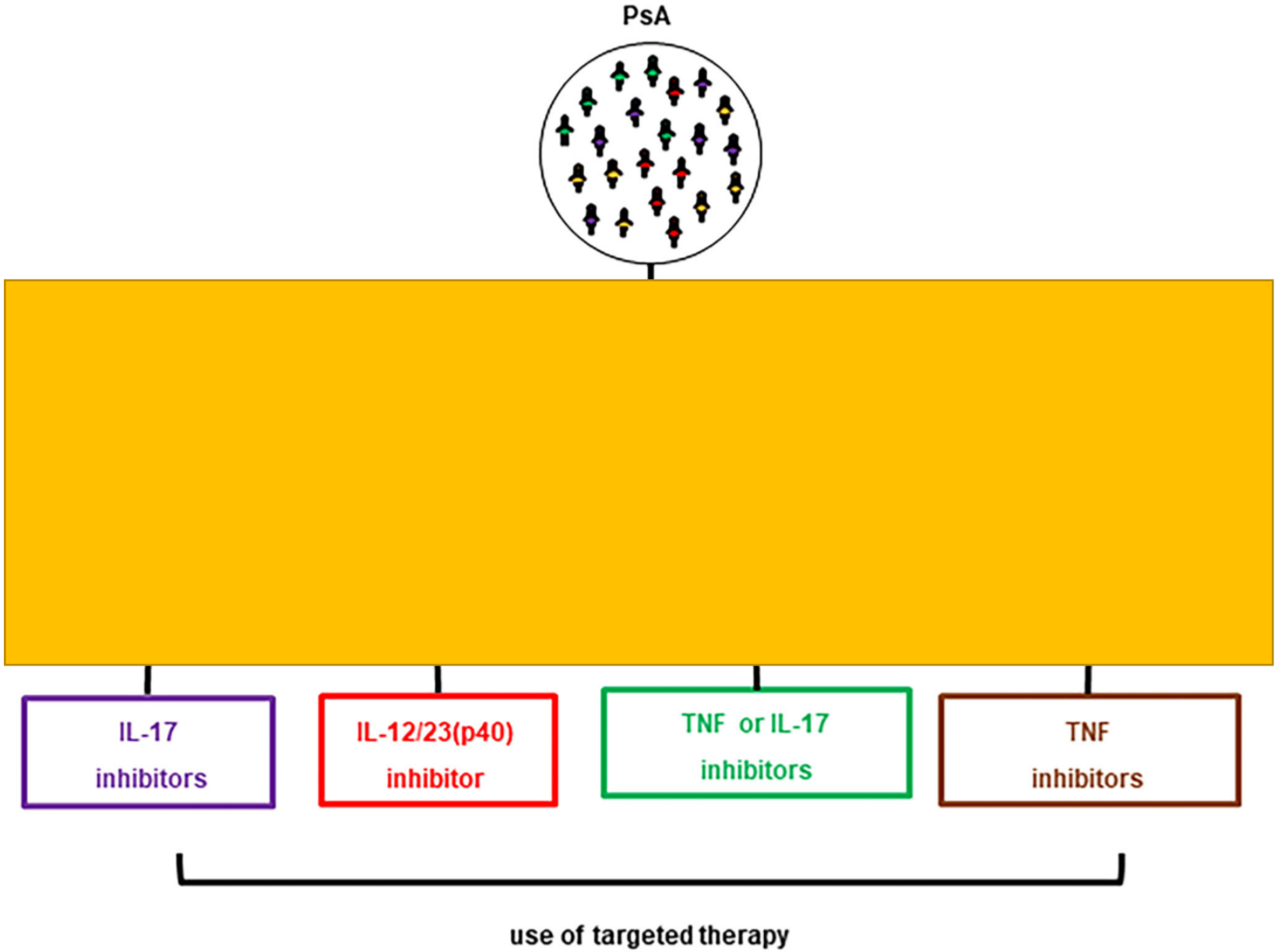
Original article

doi:10.1093/rheumatology/key069

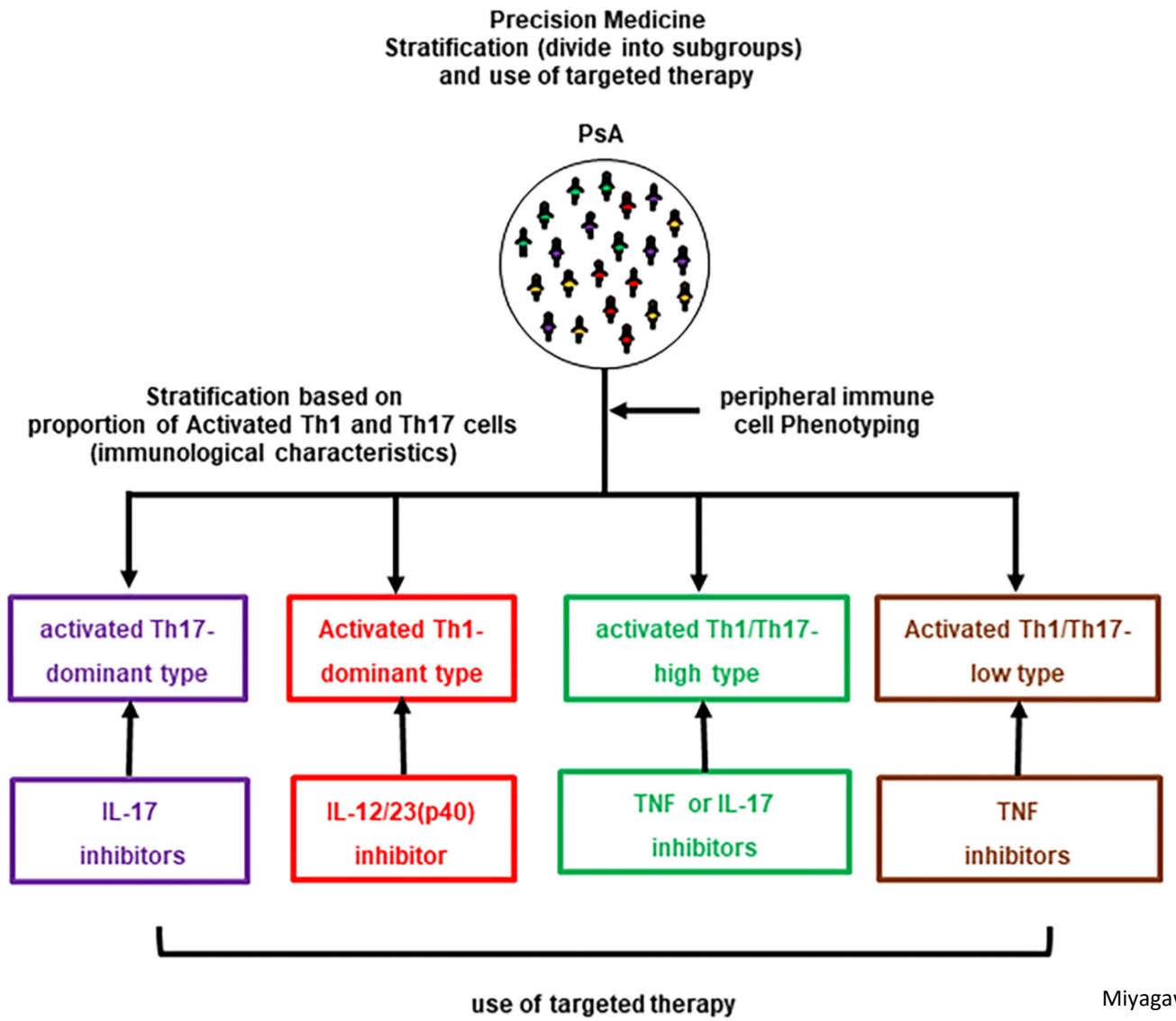
# Precision medicine using different biological DMARDs based on characteristic phenotypes of peripheral T helper cells in psoriatic arthritis

Ippei Miyagawa[1], Shingo Nakayamada[1], Kazuhisa Nakano[1], Satoshi Kubo[1], Shigeru Iwata[1], Yusuke Miyazaki[1], Maiko Yoshikawa[1], Hiroko Yoshinari[1] and Yoshiya Tanaka[1]

**Precision Medicine**
**Stratification (divide into subgroups) and use of targeted therapy**

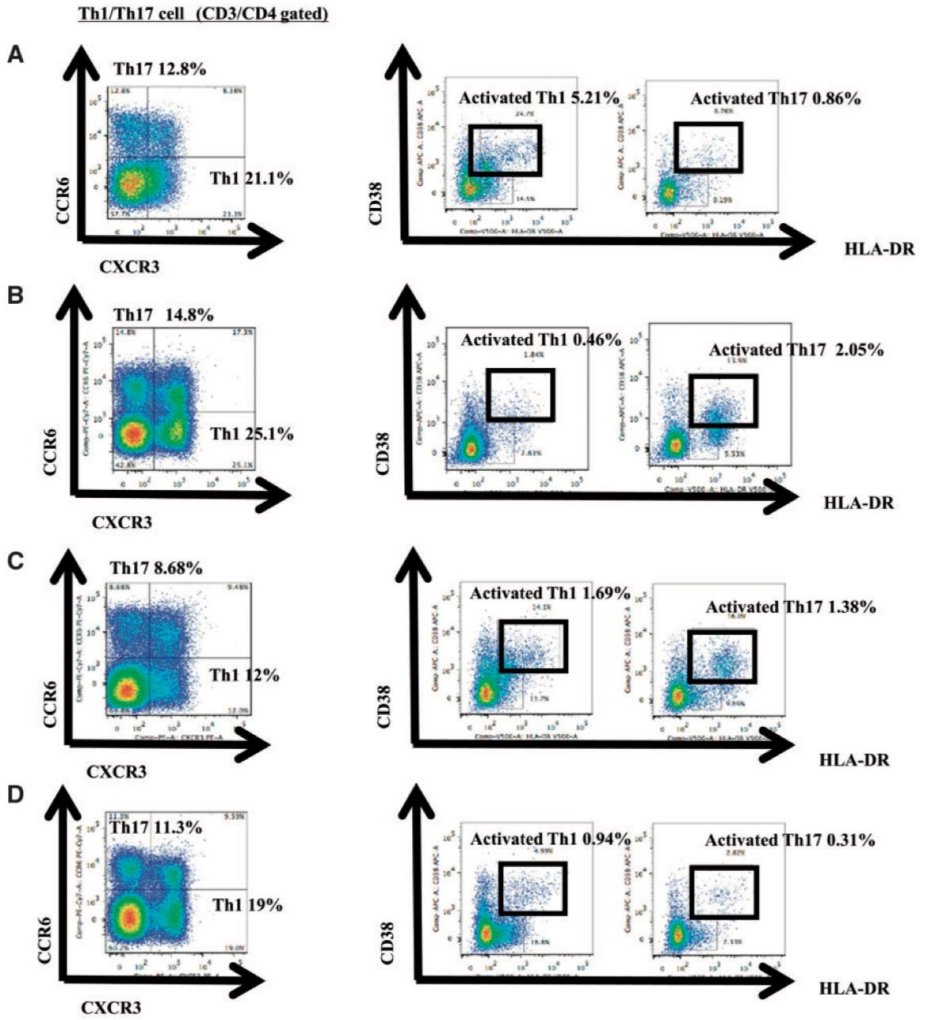


# **Standard** biologics therapy (Guidelines) vs **Strategic** Biologics Therapy




Miyagawa et al Rheumatol 2018

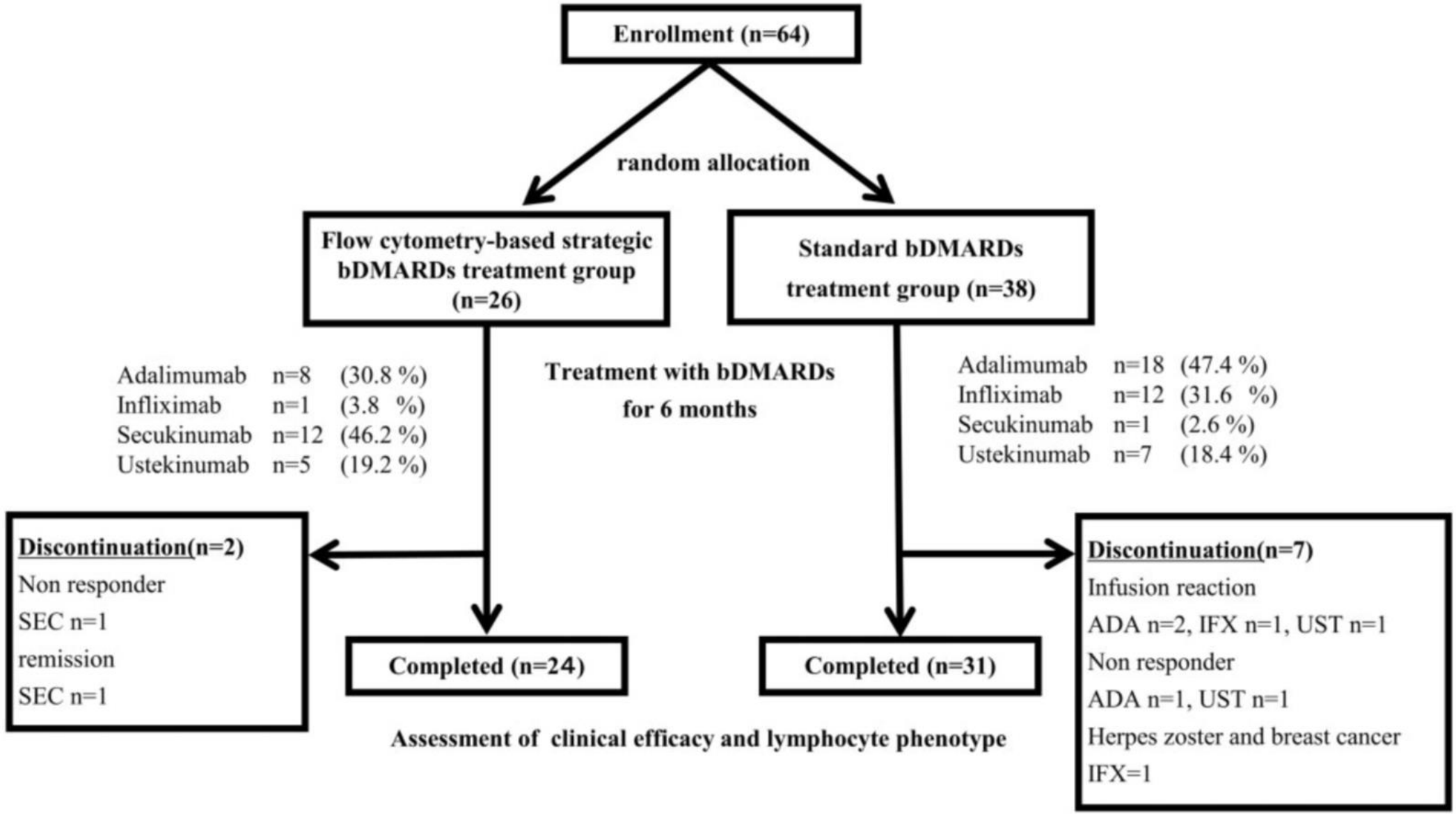
# PsA was classified into four types by peripheral blood lymphocyte analysis




Twenty-six patients with PsA were classified into the following four types according to the phenotype of $CD4^+$T cells in peripheral blood: (**A**) activated Th1-dominant (6 cases); (**B**) activated Th17-dominant (10 cases); (**C**) activated Th1/Th17-high (4 cases); and (**D**) activated Th1/Th17-low (6 cases). Results are representative of each group.

Miyagawa et al Rheumatol 2018

**FIG. 1** Study design

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# Results

- The therapeutic efficacy of strategic biologics therapy was compared with that of standard biologics therapy.

- The therapeutic efficacy was higher in the strategic bDMARDs treatment group than in the standard bDMARDs treatment group, indicating the value of precision medicine in the selection of specific bDMARDs in the treatment of PsA.

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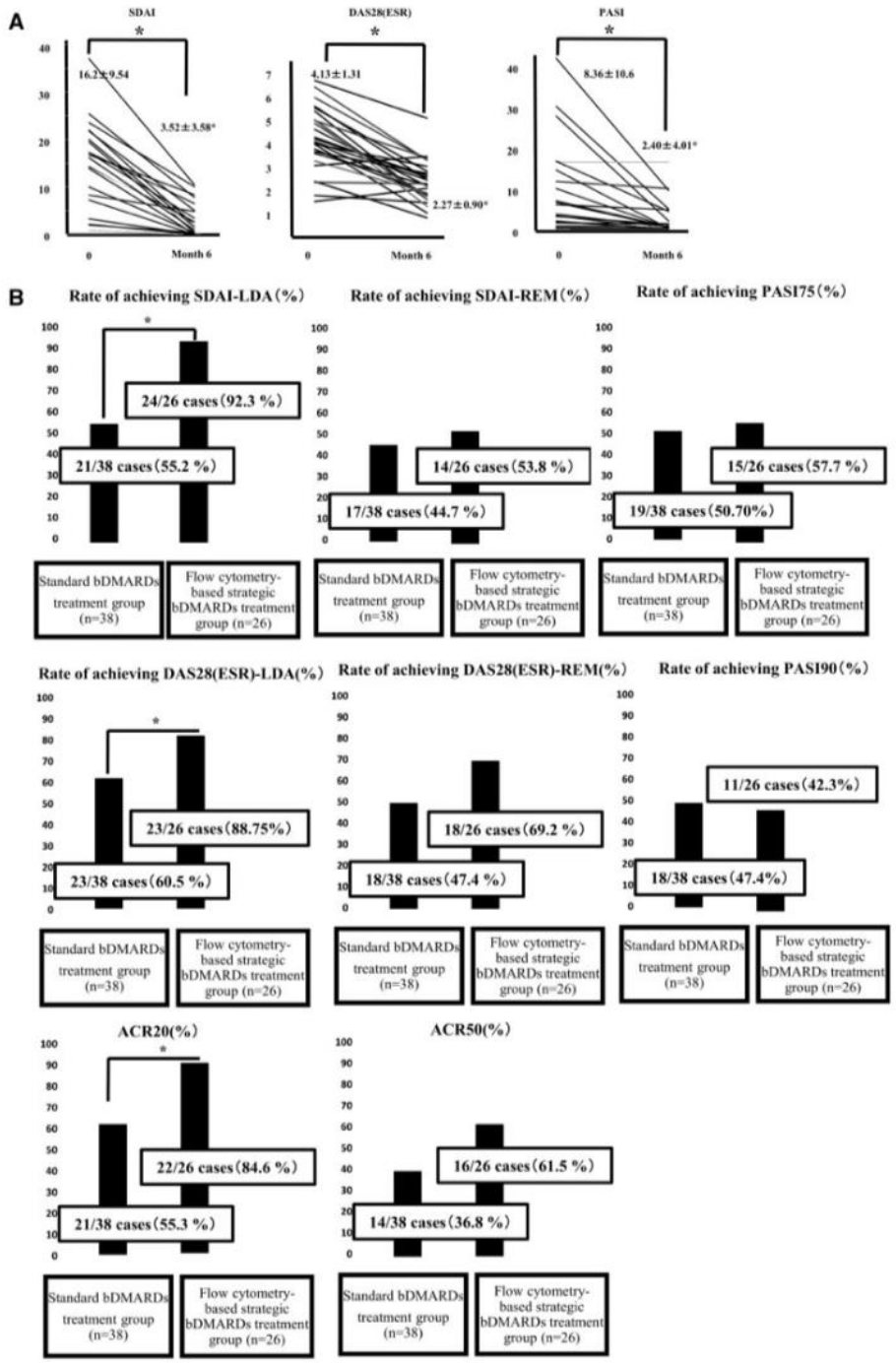
# Strategic choice of biologic products based on lymphocyte phenotype and their efficacy




Miyagawa et al Rheumatol 2018

# What is Autoprediction?

# AutoPrediction©

A disease-specific, parameter-dependent algorithm, which predicts customized response

to individualized treatment

- Flexible (not all parameters needed to predict
- Semi-quantitative
- Includes demographic, clinical, laboratory and/or histological parameters
- Immunological (autoantibody, serum cytokines, chemokines, cell subsets (Th1, Th17, Tregs, Bregs etc, surface cell subsets i.e CD24, CD27, CD39)

**Systemic Sclerosis**

**87** patients with Systemic Sclerosis, who responded to treament

**92** patients with Systemic Sclerosis, who did not respond to treatment

**Serum/plasma**
**Blood**
**DNA/RNA**
**PBMC**
Saliva
Urine
Stool Sample

**534** analytes

(17 autoab specificities,
45 cytokines,
19 angiogenic factors,
17 fibrogenic factors
27 cell-surface markers,
19 chemokines, …)

**Systemic Sclerosis**

**87** patients with Systemic Sclerosis, who responded to treament

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**Type of Treatment**

IVIG
MMF
CYC
Cyclosporin
MTX
AZT
Rituximab
Anti-TNF
Infliximab
….
Specific treatment for Pulmonary arterial hypertension, digital ulcers, etc

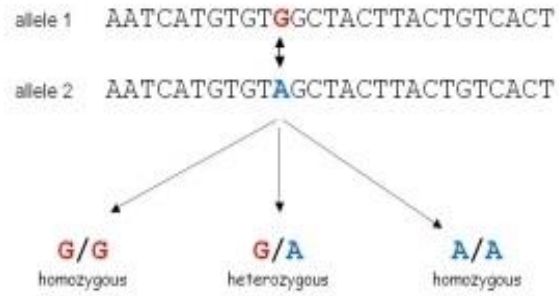
# Immunogenetic, Genetic, Pharmacogenetics,

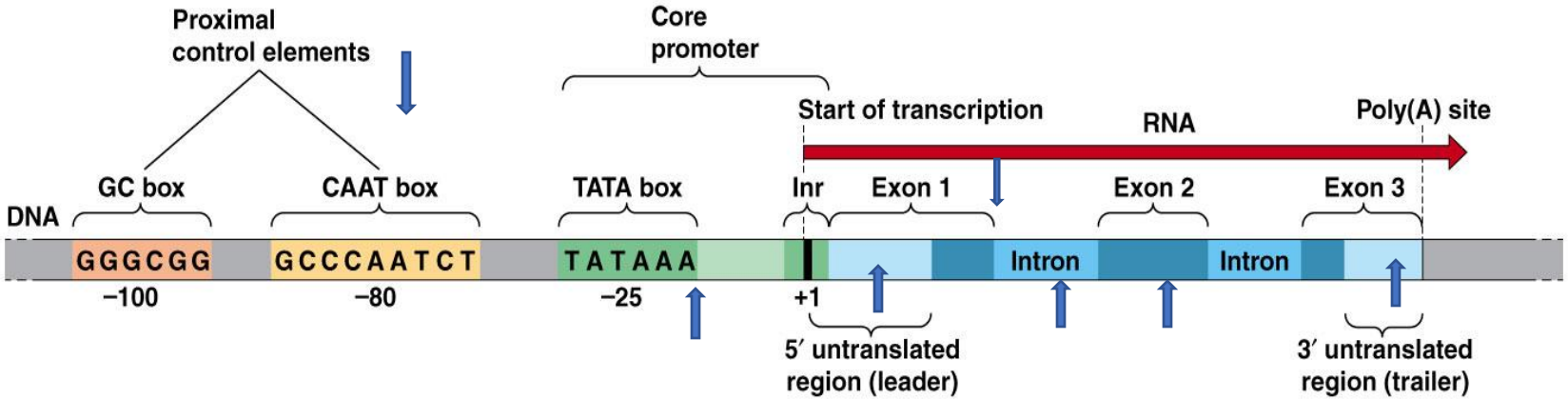
- **594,322 SNPs (single nucleotide polymorphisms)**

Infinium Global Screening Array-24 v2.0 BeadChip, Illumina

# Genetic variation- SNPs

- **Single Nucleotide Polymorphism** : the most common form of genetic variation
- Change in **one** nucleotide
- Usually one common (major) and one rare (minor) allele
- **Millions** of SNPs across the genome
- Different effects based on their location



# AutoPrediction -examples

- Prediction algorithm for response of SSc  patients to individual treatment-
- **infliximab** (27parameters 14 with positive predictive value and 13 with negative predictive value

# General Comments

- **Less than 30%** of the predictive score can be attributed to autoantibodies (mono or poly-specificity or combination
- **More than 40%** of the total predictive score is to be attributed to cell-subset phenotyping
- **Less than 20%** of the predictive score can be based on serum cytokines
- **Less than 10%** of the scoring is due to genotyping

# Example A

**Algorithm % prediction (0-92%)= ZxPre-Predict algoritm**
**(3.2autoab1)+(9.1autoab2)-(6.7autoab3)-**
**(1.2 autoab levels/cut off autoab4)+ ……..**
**(3.1cytokine1)+ (1.7cytokine2)+…….. +**
**(3.9 xCD4+CD27+) (+2.2CD4-CD39+)+ ……**
**+(9.2 B10)+ (1.3CD4C+D25+)…….**

Prediction algorithm for response of SSc to infliximab
(27 parameters 14 with positive predictive value &
13 with negative predictive value

# The roadmap to Autoprediction and Precision Medicine is not an easy task

# DO NOT PUT THE CAR BEFORE THE HORSE

**GUIDELINES και πάλι guidelines μέχρι…..**