National & Kapodistrian
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Pathophysiology Dept.
School of Medicine

Refractory RA: A different disease?

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Disclosures

- Research grants and clinical studies

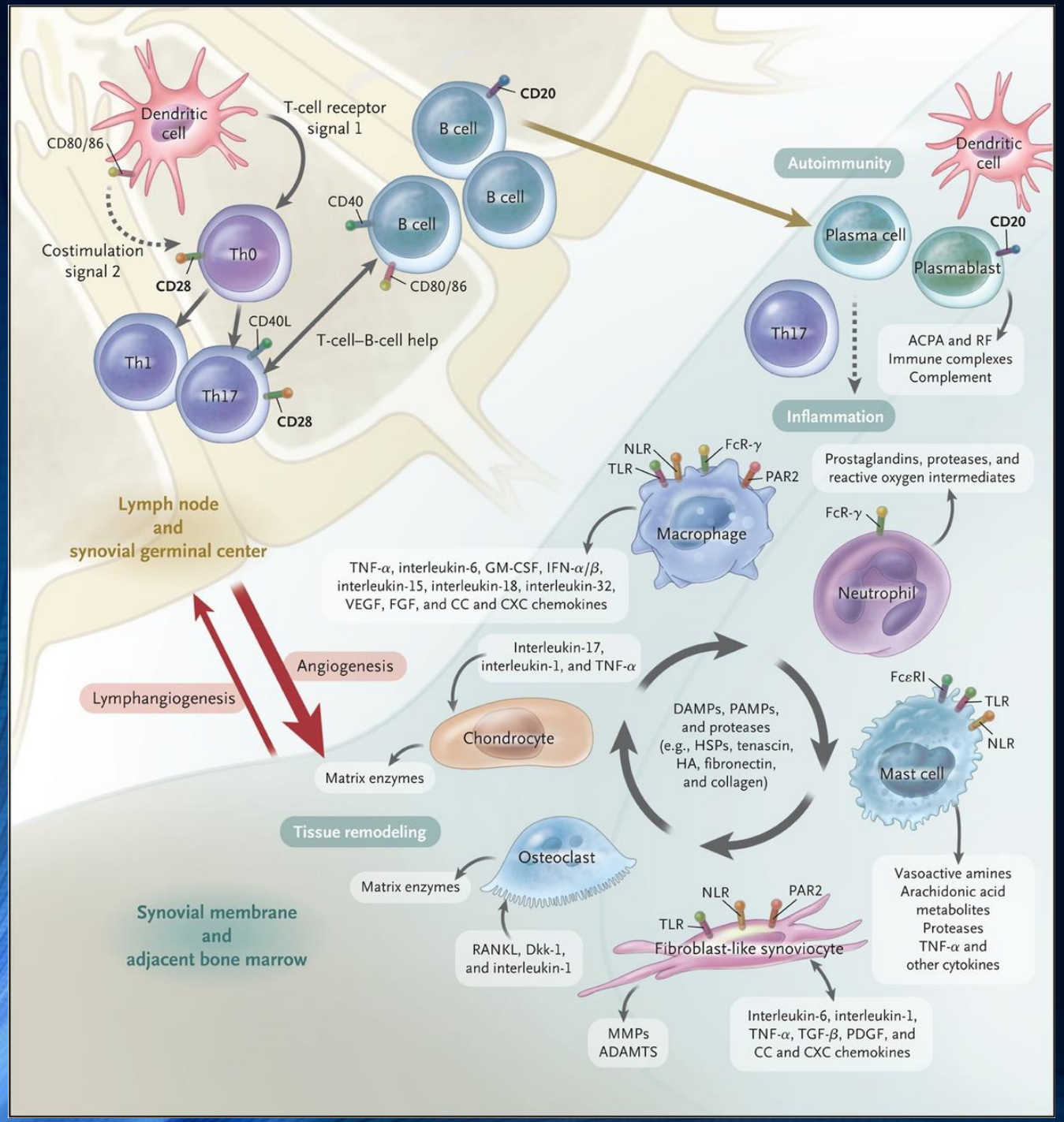
Pfizer, Abbvie, Novartis, Genesis, Eli Lilly, Jansen,

Horizon 2020

IASSYN

Outline

- Introduction
- Definitions of forms of Refractory RA
- Differences and similarities
- Mechanisms
- Readout and future perspecives



Pathophysiology of rheumatoid arthritis

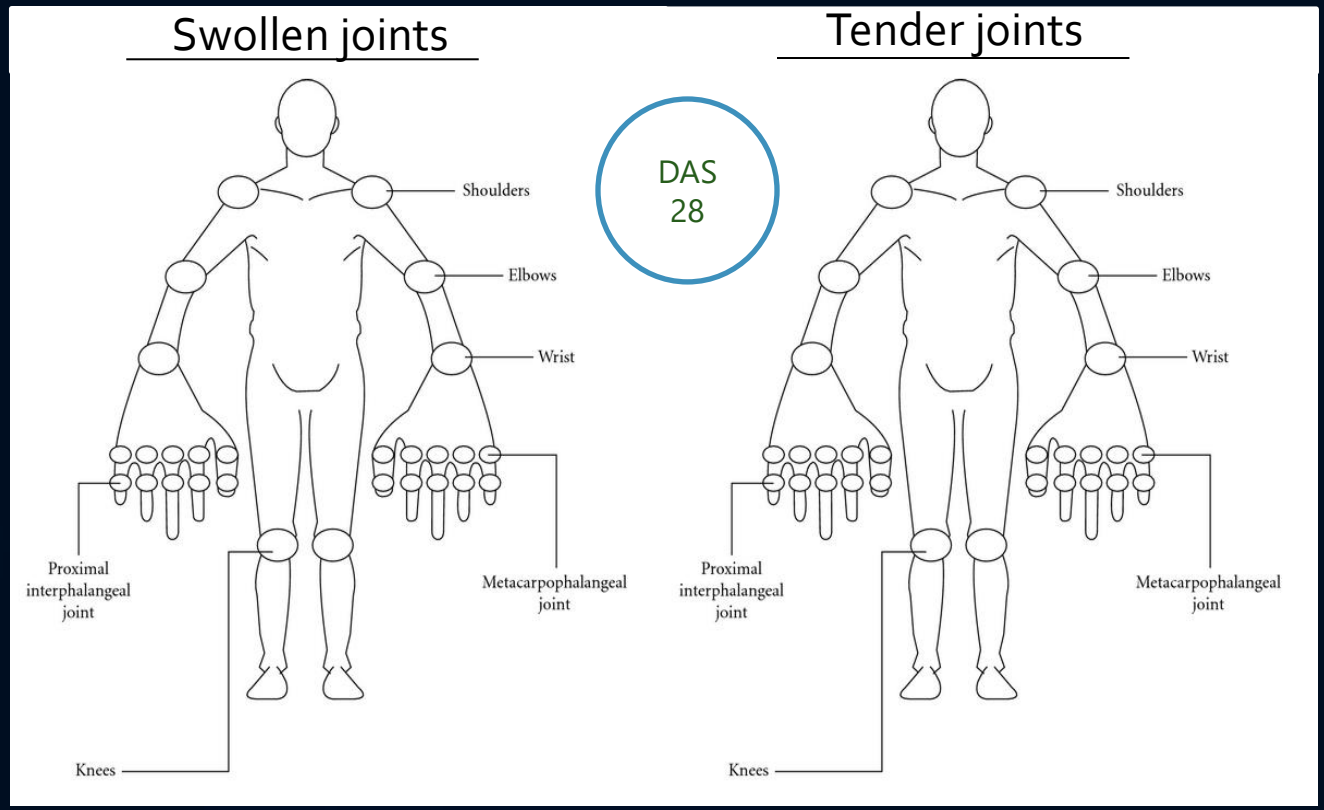
- Different tissues
- Different cell types
- Different molecules
- Different processes

- Time dependent
- Treatment dependent
- Age, gender, environment affected

Josef S. Smolen et al. Rheumatoid arthritis, NEJM, 2018

ACR composite outcome measures

- A percentage improvement of 20%, 50%, 70% in swollen and tender joints counts and at least three of the following parameters:
  - Patient global assessment of disease activity
  - Physician global assessment of disease activity
  - Patient pain scale
  - Disability/functional questionnaire (Health Assessment Questionnaire Disability Index)
  - Acute phase reactant (ESR or C-Reactive Protein)
- Dichotomous variable with a positive (=responder) or negative (=non-responder) outcome



Rheumatoid arthritis: Unmet Needs in the era of targeted therapies

- What we achieved:

Basic principles of pathogenetic mechanisms, Clinical phenotypes, Early diagnosis and treatment, metrics, cohort, multi-cohort derived information, treatment related recommendations

- Still pending…

Biomarkers related to treatment response per clinical phenotype, definition of endotypes, corresponding to clinical phenotypes, depiction of the dynamic picture for the disease, using high throughput stratification instruments, tailored therapeutic approaches, definition and therapeutic approaches of persistent refractory disease

Defining refractory RA

- Inefficacy of multiple agents
- High doses of glucocorticoids to achieve disease control in the context of the cycling of multiple therapies

- Multidrug toxicity
- Concerns around the safety profile
- Comorbidities

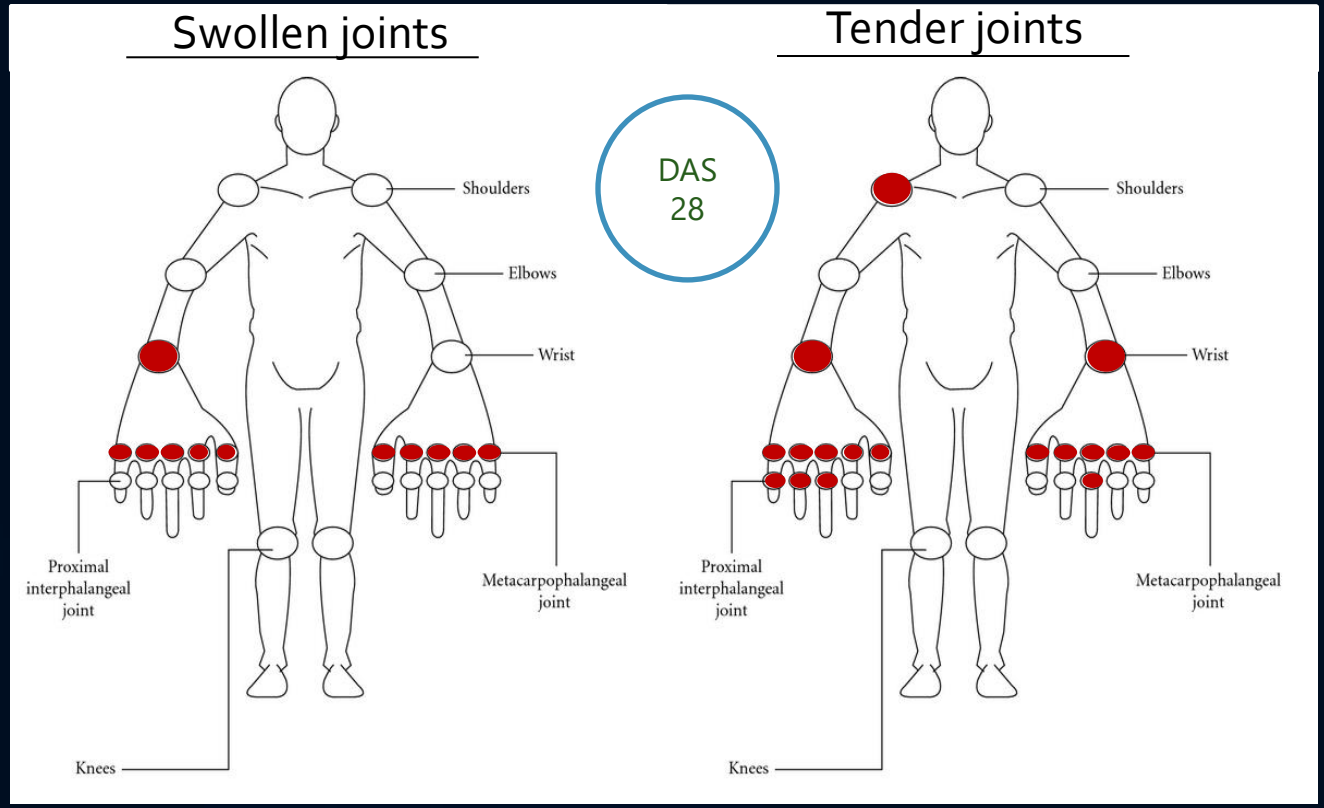
✓ Clinical case

50 years old female develops symmetric polyarthritis

⇧ CRP ⇧ ESR

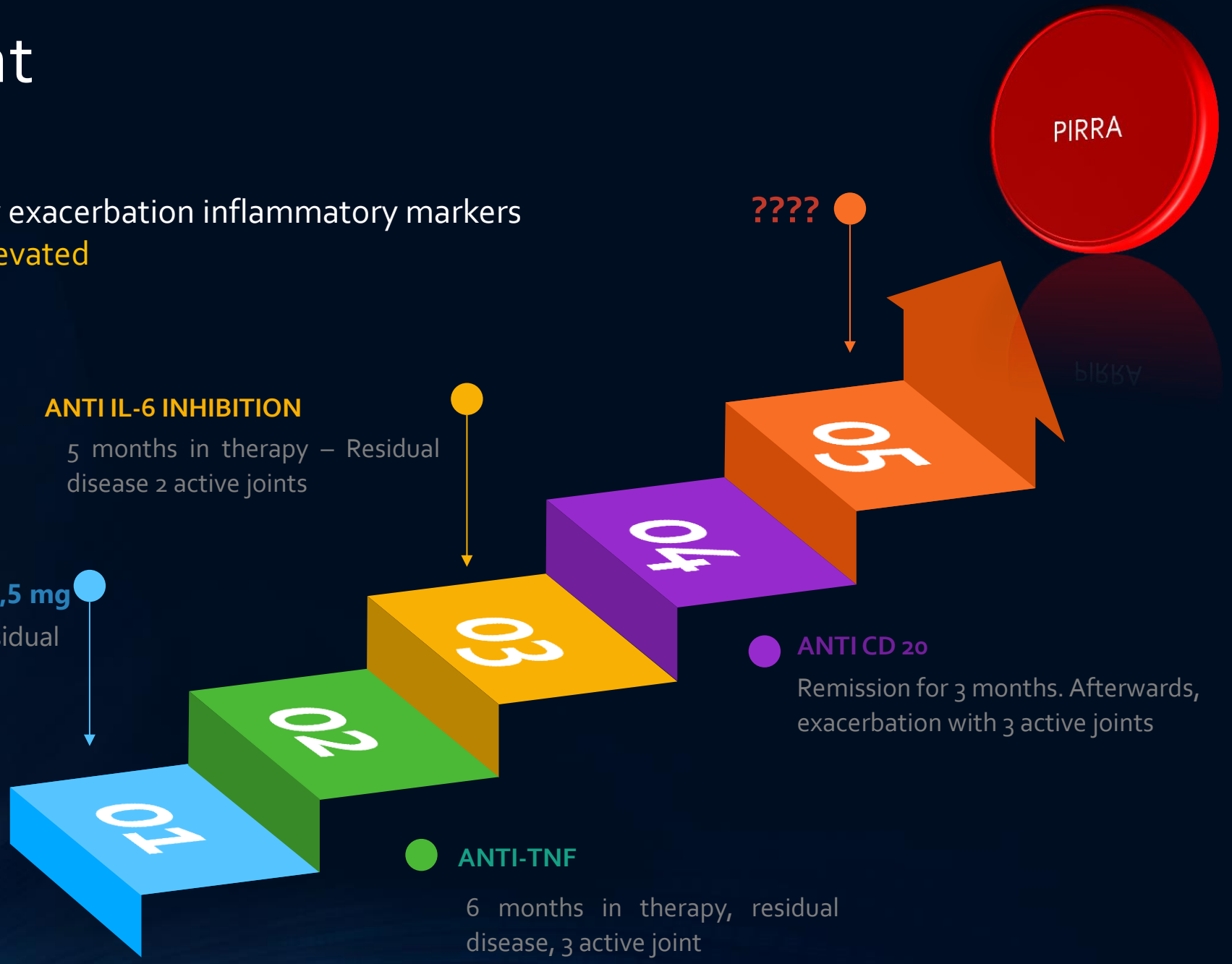
RF(+), aCCP(+)

Seropositive rheumatoid arthritis



Treatment

In every exacerbation inflammatory markers were elevated



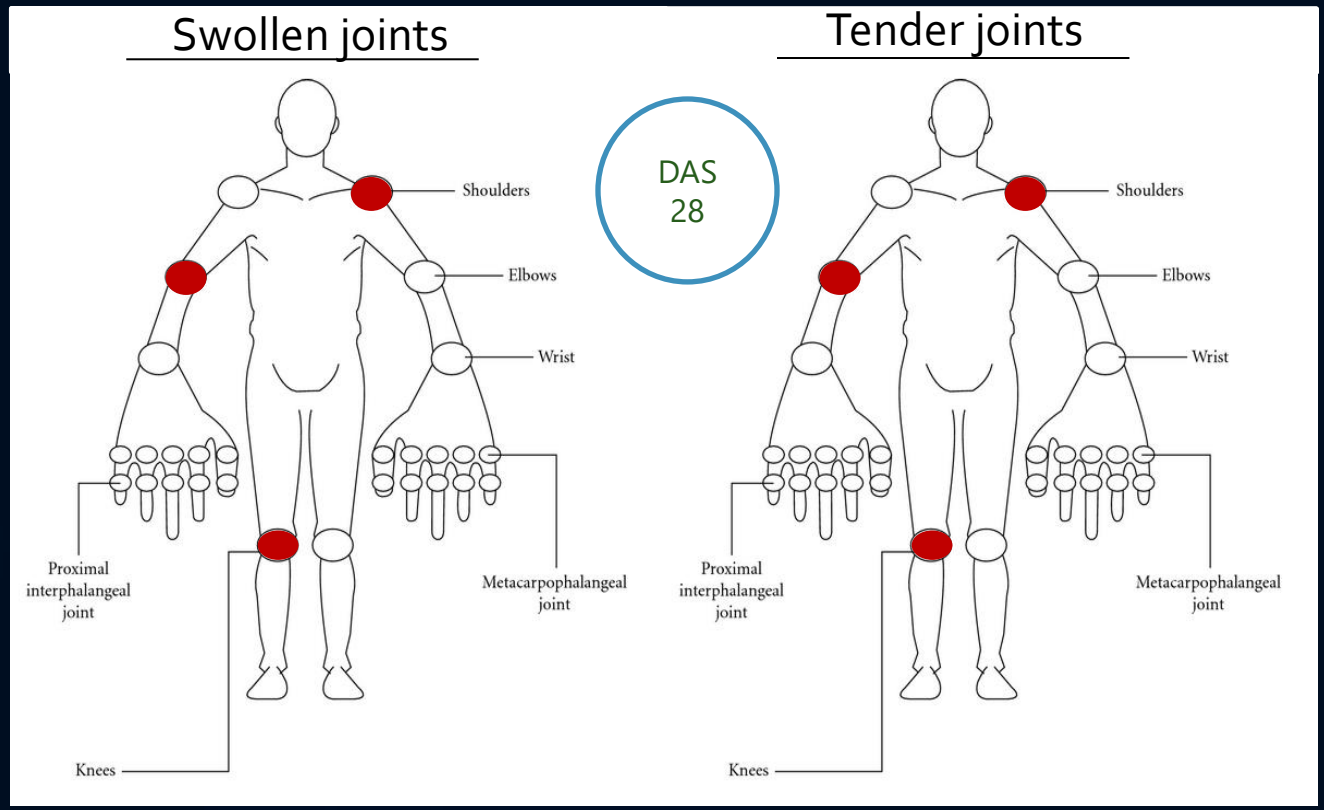
Clinical case

70 years old female develops asymmetric oligoarthritis of large joints

⇧ CRP ⇧ ESR (slight elevation)

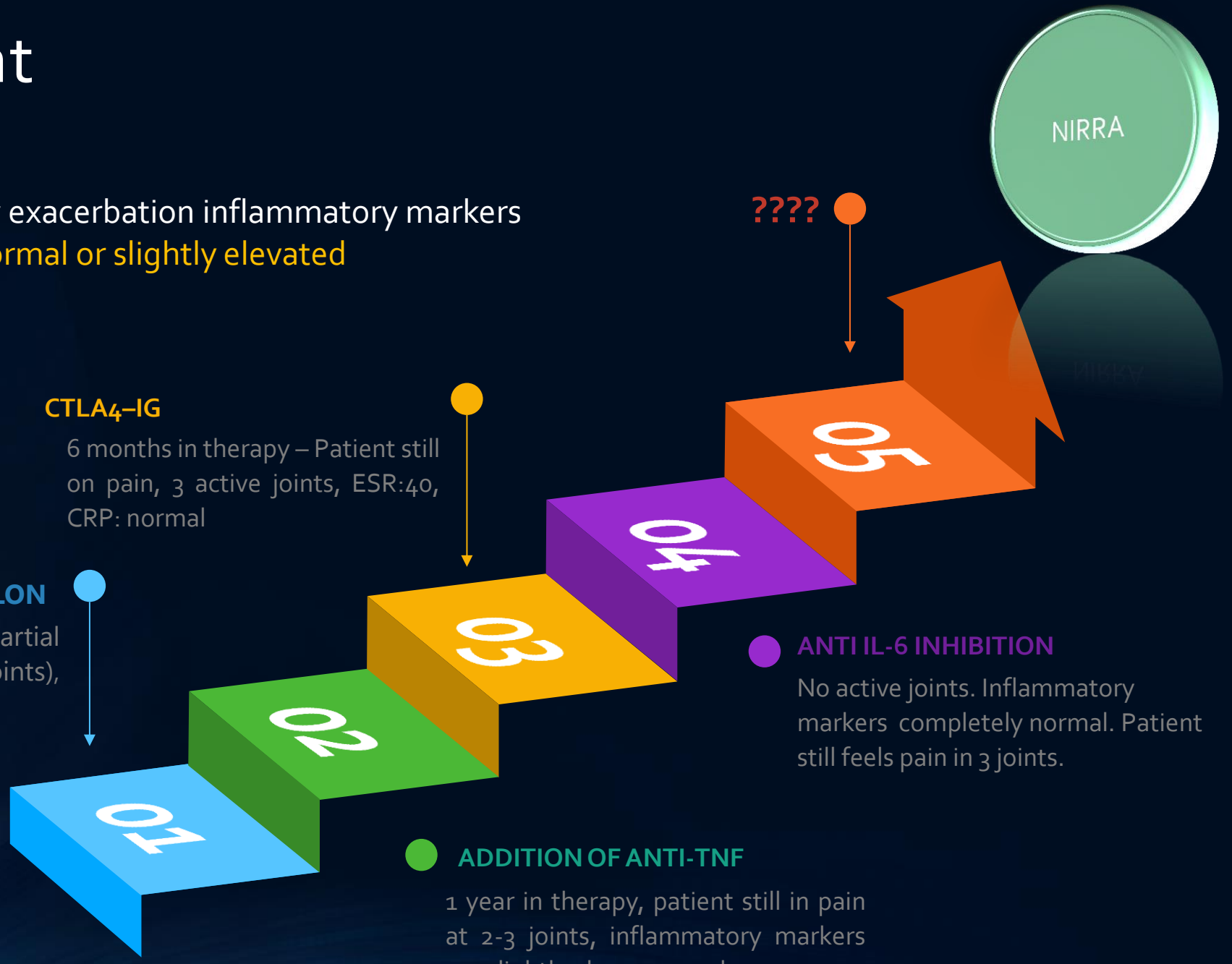
RF(-), aCCP(-)

Seronegative rheumatoid arthritis



Treatment

In every exacerbation inflammatory markers were normal or slightly elevated



LEFLUNOMIDE + PREZOLON

6 months in therapy, Partial remission (Pain in 2 joints), lowering of CRP + ESR

CTLA4–IG

6 months in therapy – Patient still on pain, 3 active joints, ESR:40, CRP: normal

ADDITION OF ANTI-TNF

1 year in therapy, patient still in pain at 2-3 joints, inflammatory markers are slightly above normal

ANTI IL-6 INHIBITION

No active joints. Inflammatory markers completely normal. Patient still feels pain in 3 joints.

Types of refractory RA

PIRRA

Persistent Inflammatory Refractory RA

⇧ Markers of inflammation

- Lack of efficacy of multiple DMARDs
- Ongoing radiographic signs of inflammation
- Present as monoarthritis, oligoarthritis or polyarthritis

NIRRA

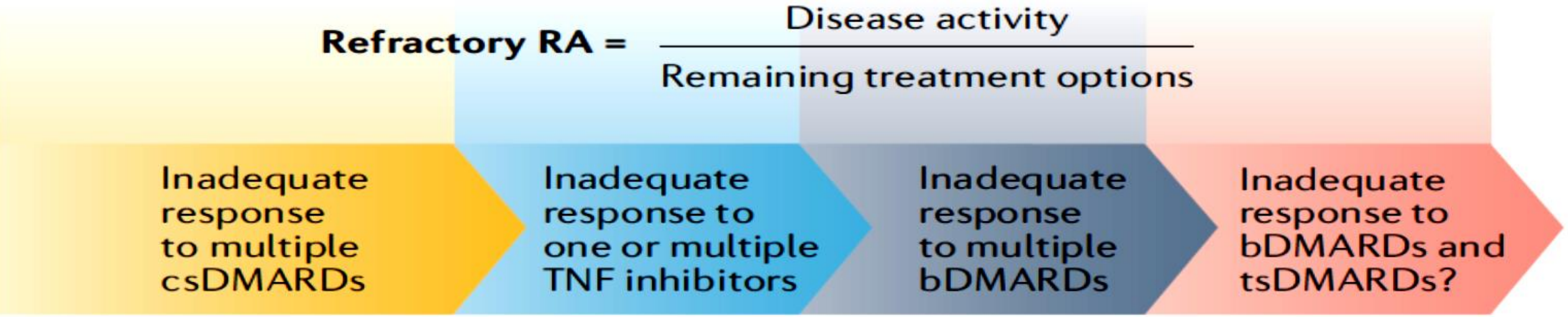
Non inflammatory refractory RA

⇩ Markers of inflammation

- Symptomatic RA with little objective inflammation:
  - **Chronic pain syndrome** and/or fibromyalgia
  - Functional decline
  - Accrued damage and/or secondary OA
  - Central sensitization

Maya H. Buch et alPersistent inflammatory and non-inflammatory mechanisms in refractory rheumatoid arthritis, Nat Rev Rheumat. 2020

Treatment and therapy cycling in refractory



- B cell- depletion tx
- T cell co-stimulation blockade
- IL-6- targeted tx

Proposed terminology

- Persistent inflammatory refractory rheumatoid arthritis (PIRRA)

  - ✓ Advantages
    - Confident of active RA pathology in the face of multiple therapies
    - Identifies a group of patients with a poor prognosis
    - Accurate basis for investigation and target validation

  - ✓ • Disadvantages
    - Status can change over time as drugs with different mechanisms of action are trialled
    - Could dismiss inflammatory or autoimmune pain mechanisms

Refractory Rheumatoid Arthritis (RA)

Proposed terminology

- Non- inflammatory refractory RA (NIRRA)
  - ✓ Advantages
    - Mitigates against unnecessary treatment changes or cycling
    - Identifies a distinct cohort for investigation of residual patient-reported outcomes and alternative pain mechanisms
  - ✓ • Disadvantages
    - Risk of missing low- level inflammation
    - Unclear basis
    - Possible overlap with entheseal pathology, osteoarthritis and pain syndromes

Prevalence of refractory RA

Only a handful of reports have described the prevalence of refractory RA, each of which used a different definition of the condition and none of which was designed to clearly identify PIRRA

British Society of Rheumatology Biologics Register for RA (2018)

Medical University of Vienna (2019)

PREDICTORS OF REFRACTORY DISEASE

13 502 RA Patients

A) Delayed initial treatment

- Failure of 2 bDMARDs
- TNFi inhibitor as first bDMARD

B) Female gender

C) High composite disease activity scores

6%

Refractory RA patients

17%

2423 RA Patients

- Failure of 3 DMARDs
- At least one bDMARD

Refractory RA patients

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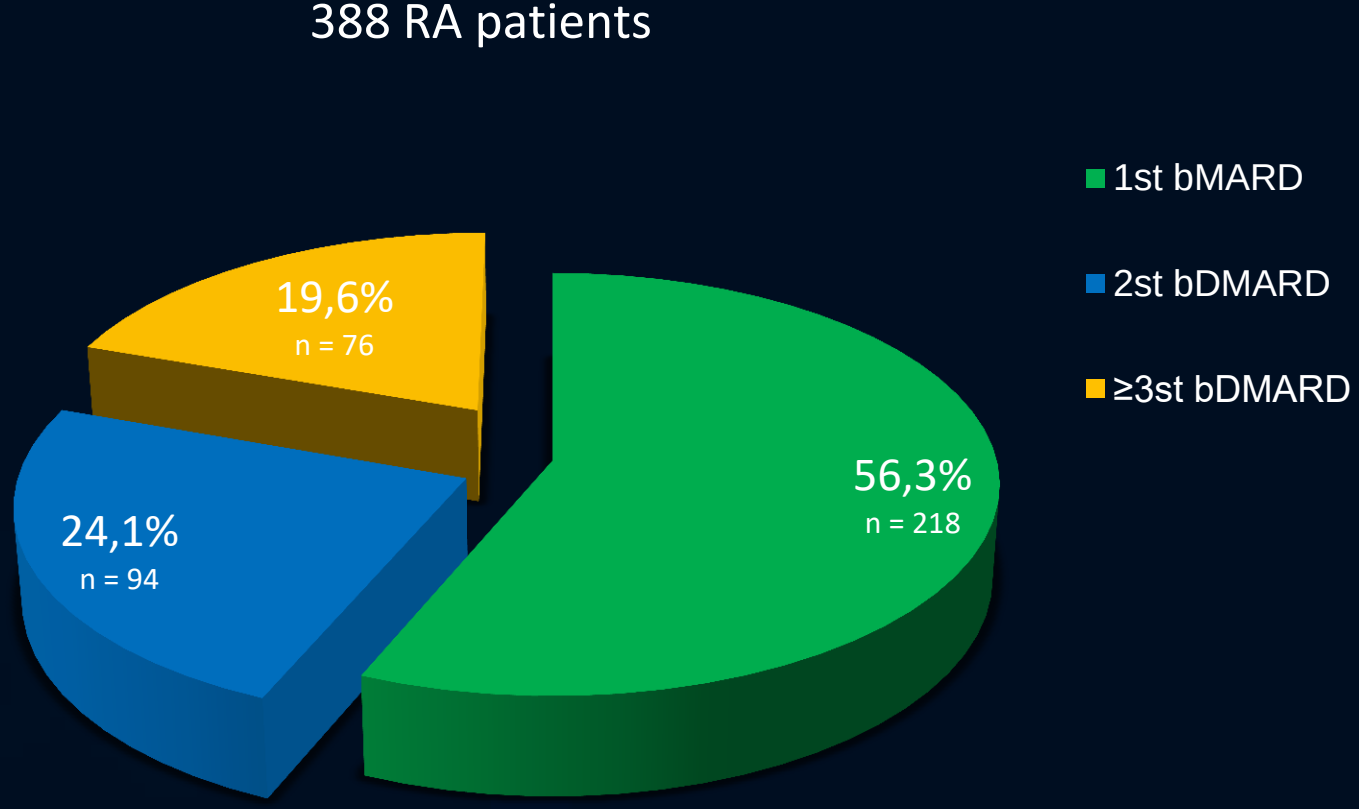
✓Refractory RA in Pathophysiology



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O. Katsouli, P. Vlachoyiannopoulos et al., Unpublished observations

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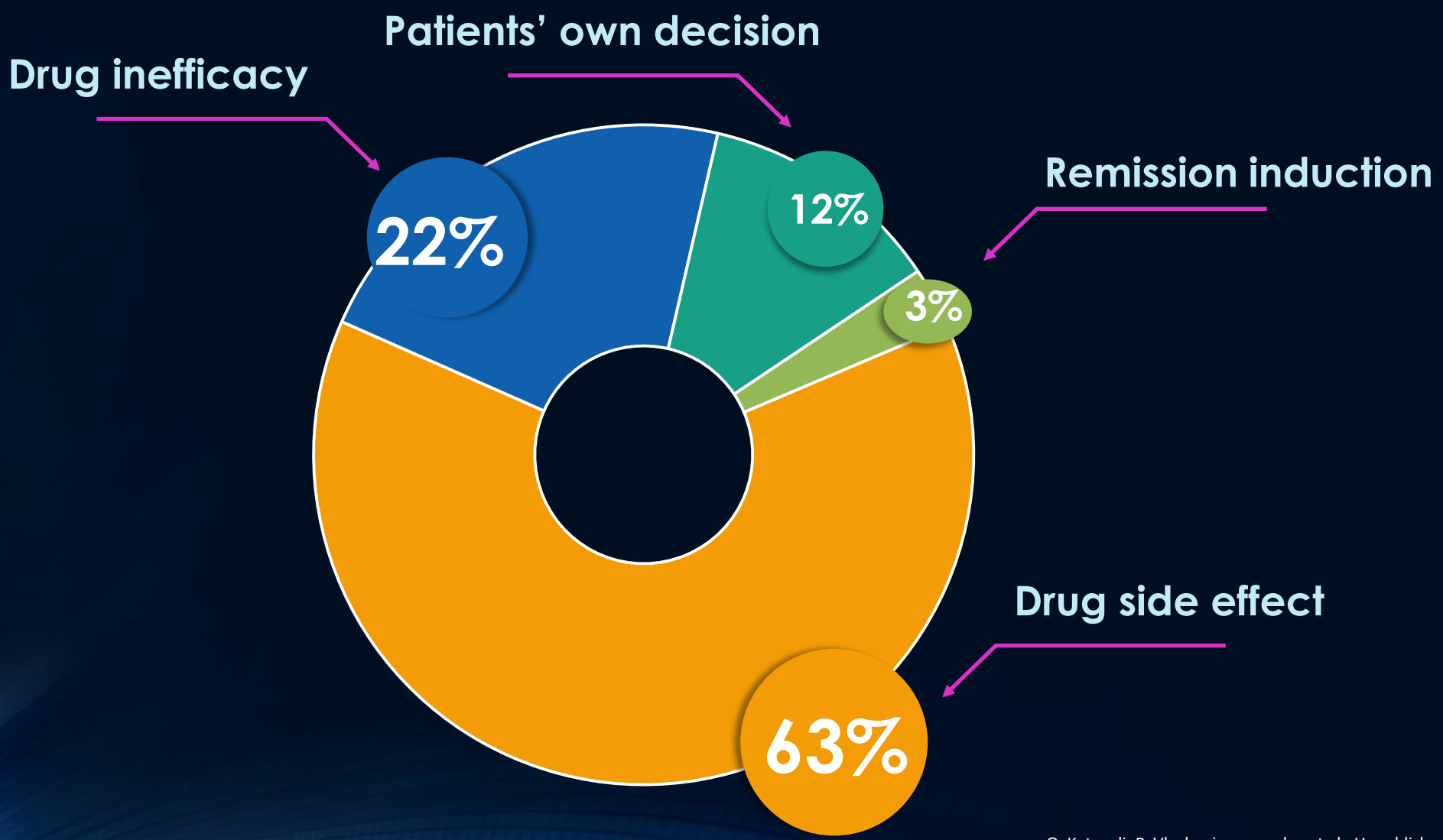
✓Reasons for stopping 1st bDMARD



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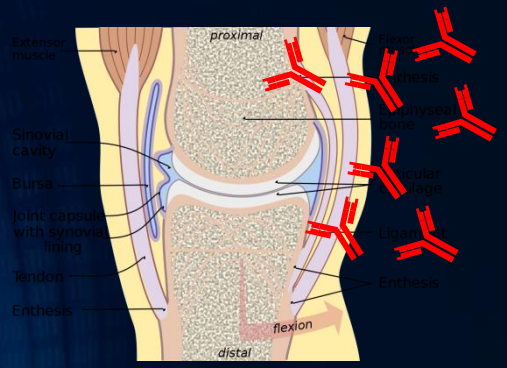


- Rheumatoid Factor
- ACPAs
- Anti-carbamylated protein

No autoantibodies present

Seronegative

Seropositive

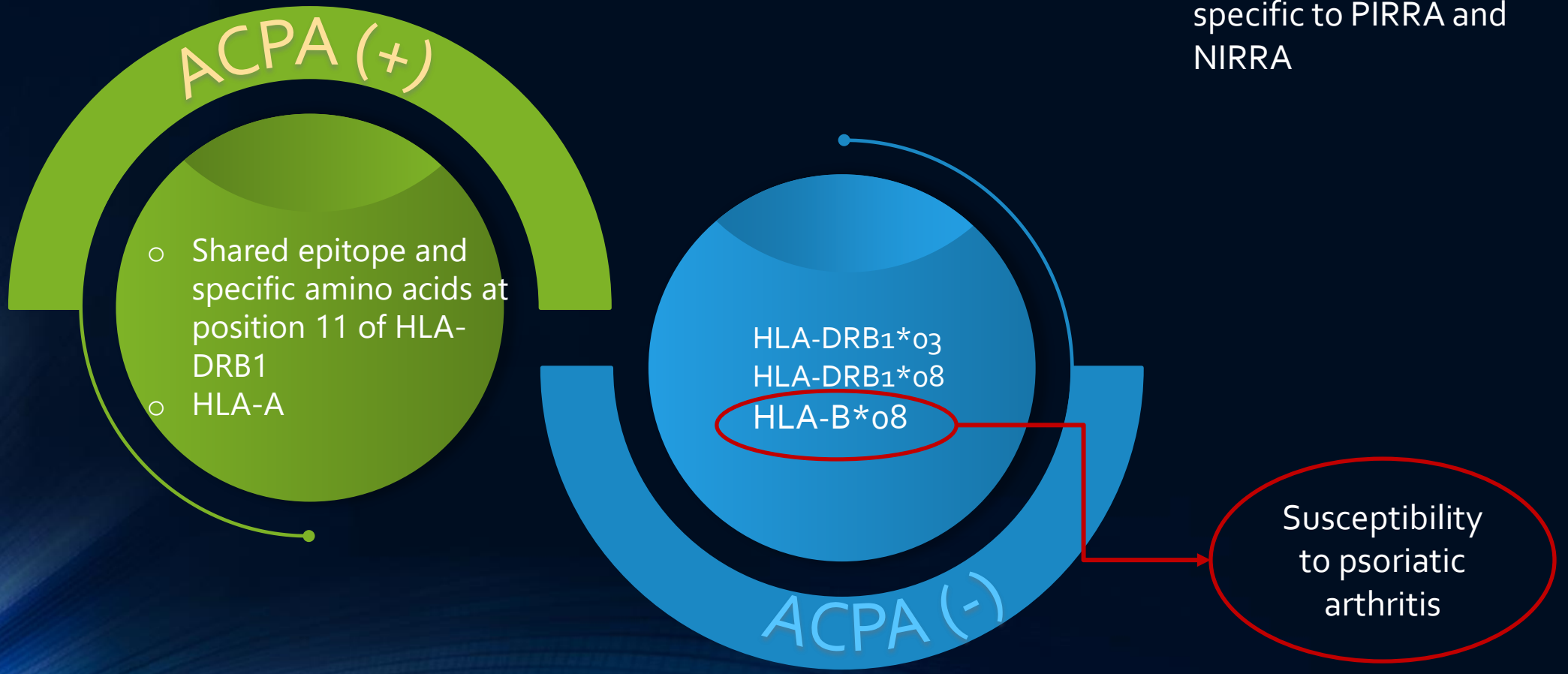
- Severe disease, poor outcomes
- Increased mortality
- Aggressive phenotype
- Good response to B and T cell oriented biologic drugs

RA

- Mild disease, better outcomes
- Decreased mortality

The role of Genetics

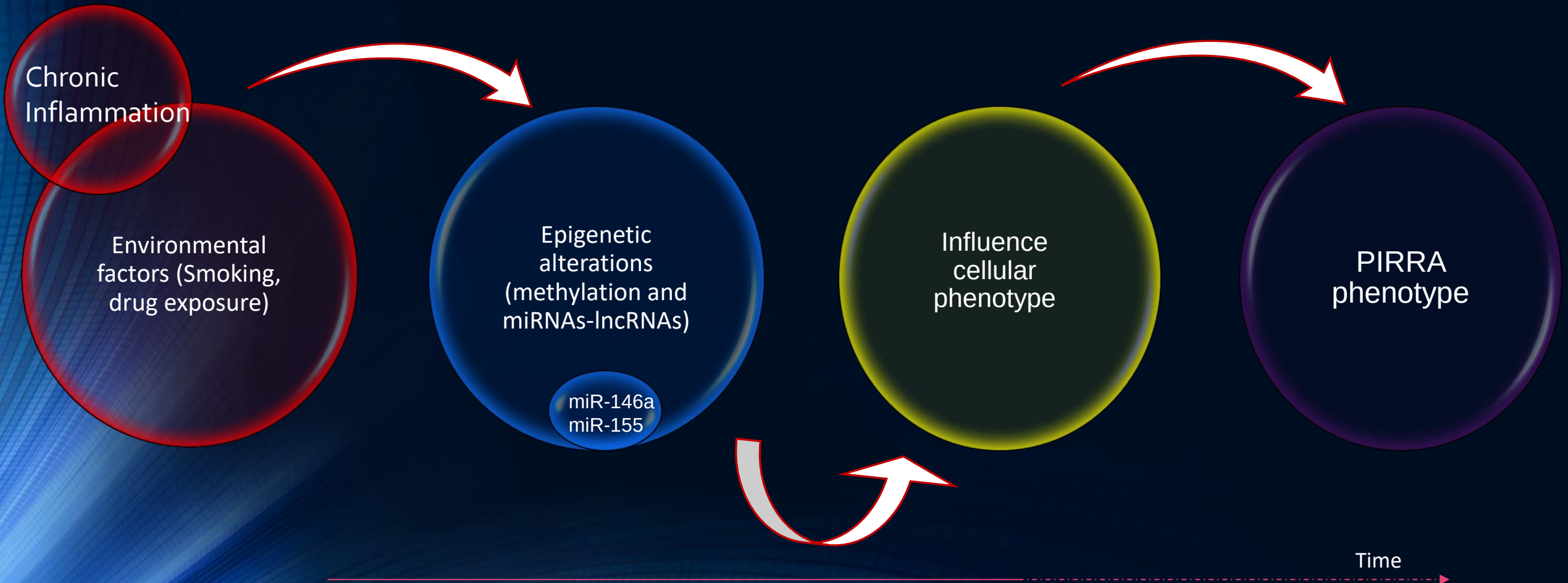
Specific genetic loci contribute to ACPA (+) and ACPA (-) RA



- No studies have reported a genetic architecture specific to PIRRA and NIRRA

The role of Epigenetics

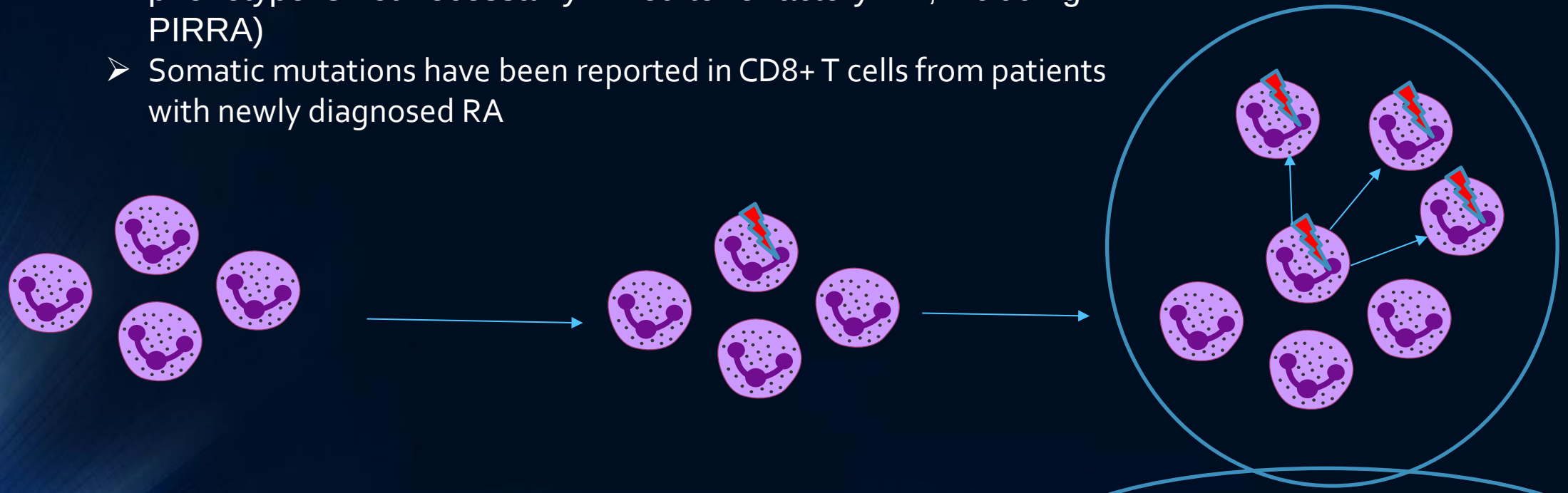
It is likely that PIRRA develops over time revealing the dynamic picture of the disease



The role of de novo mutations

Epigenetic changes might also be promoted through somatic mutations in RA and increased somatic mutation burden might be a mediator of Refractory RA

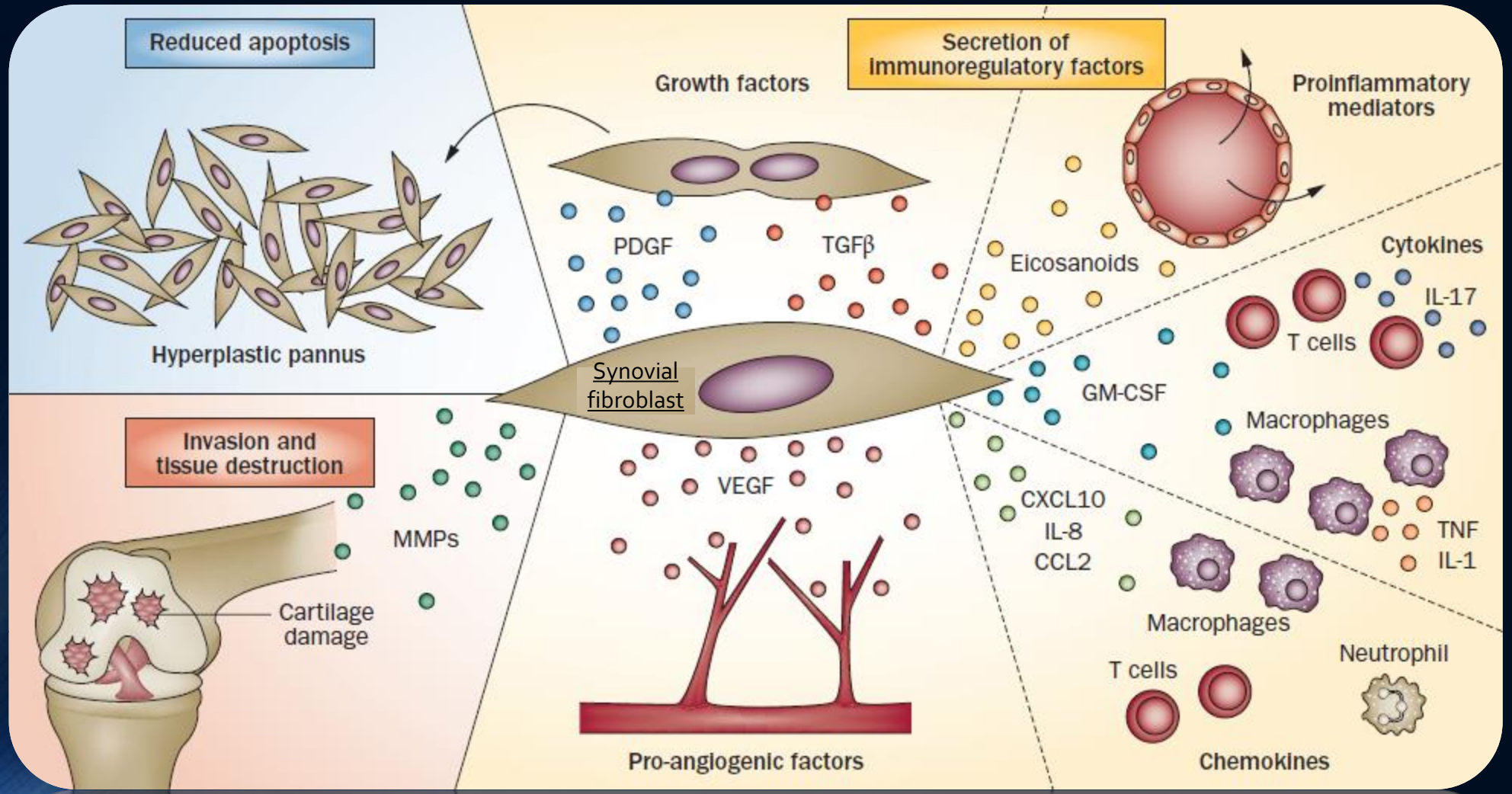
- *STAT3* mutations are associated with Felty syndrome (although this phenotype is not necessarily linked to refractory RA, including PIRRA)
- Somatic mutations have been reported in CD8+ T cells from patients with newly diagnosed RA



Seronegative arthritis sharing a polymyalgia rheumatica- like phenotype

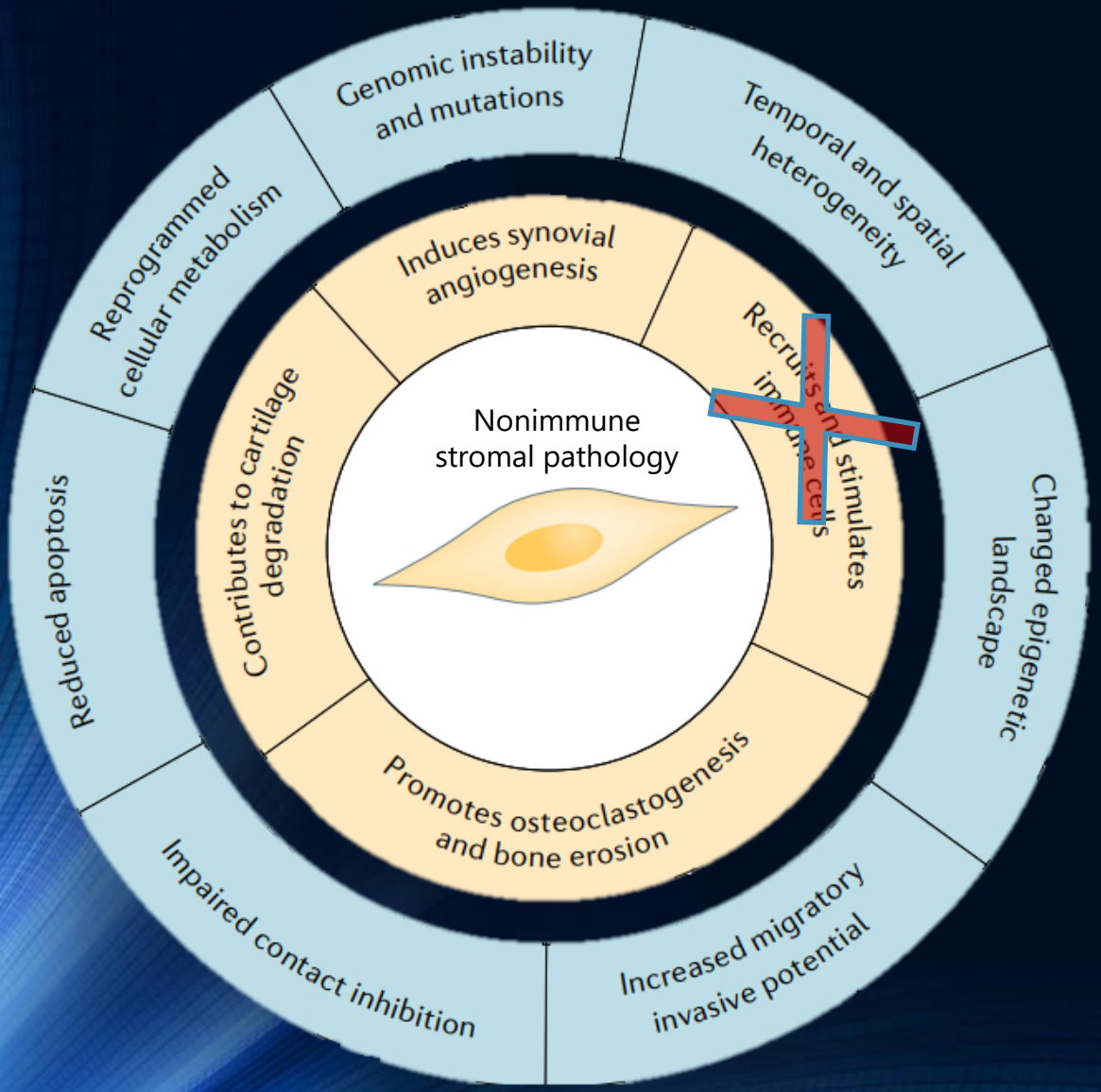
Clonal hematopoiesis of indeterminate potential (CHIP)

The role of Synovial fibroblasts in EARLY inflammatory RA



Nunzio Bottiniet al. Duality of fibroblast-like synoviocytes in RA: passive responders and imprinted aggressors, Nat Rev Rheumat. 2013

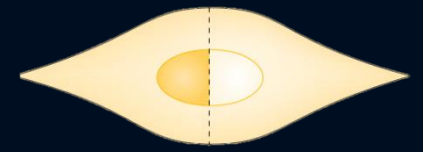
The role of Synovial fibroblasts in resistant non-inflammatory RA



NONIMMUNE STROMAL PATHOLOGY

- Resistance to anti-inflammatory DMARDs which fail to address fibroblastic disease
- Site specific disease (monoarthritis - oligoarthritis)

Novel treatments that target the tumor stroma



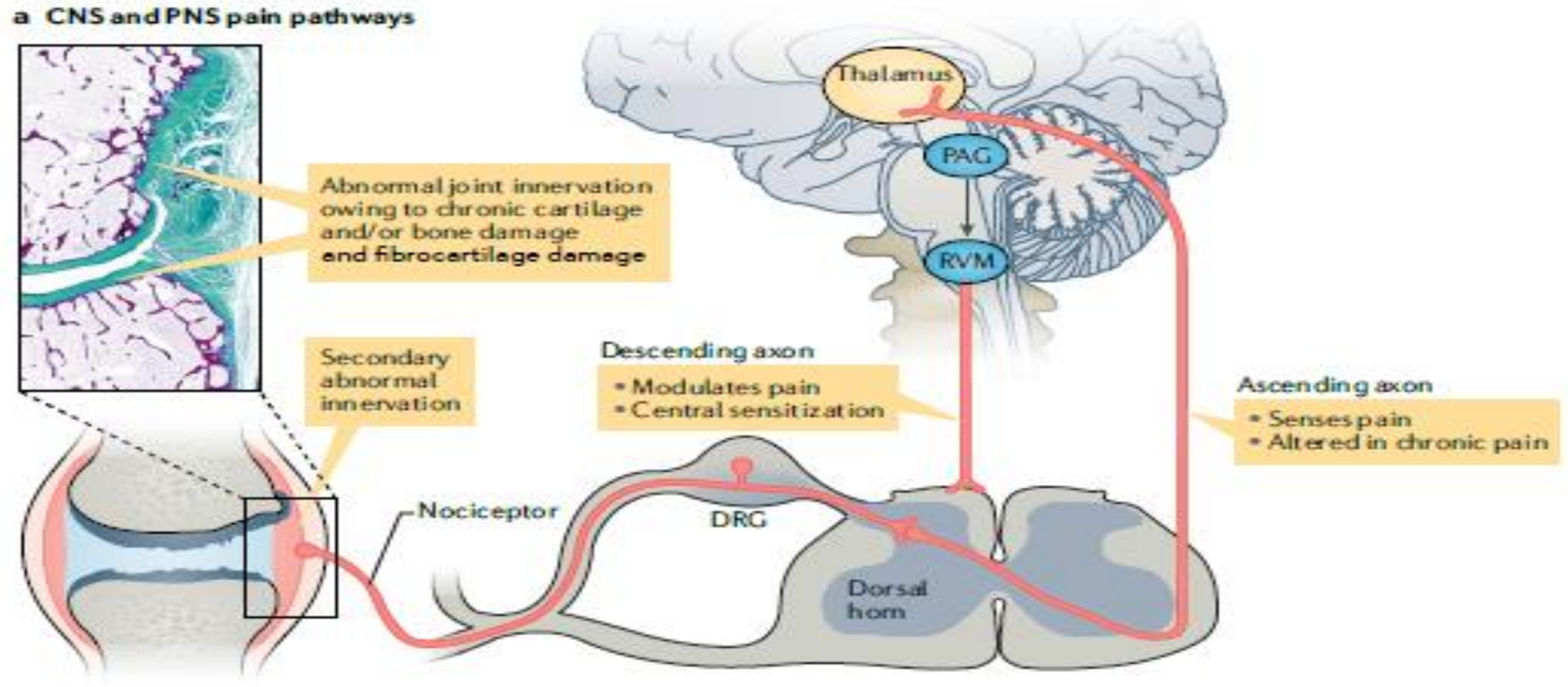
Gyrid Nygaard et al. Restoring synovial homeostasis in rheumatoid arthritis by targeting fibroblast-like synoviocytes, Nature Review Rheumatology, 2020

✓ NIRRA unaddressed question

What is behind such a clinical profile?

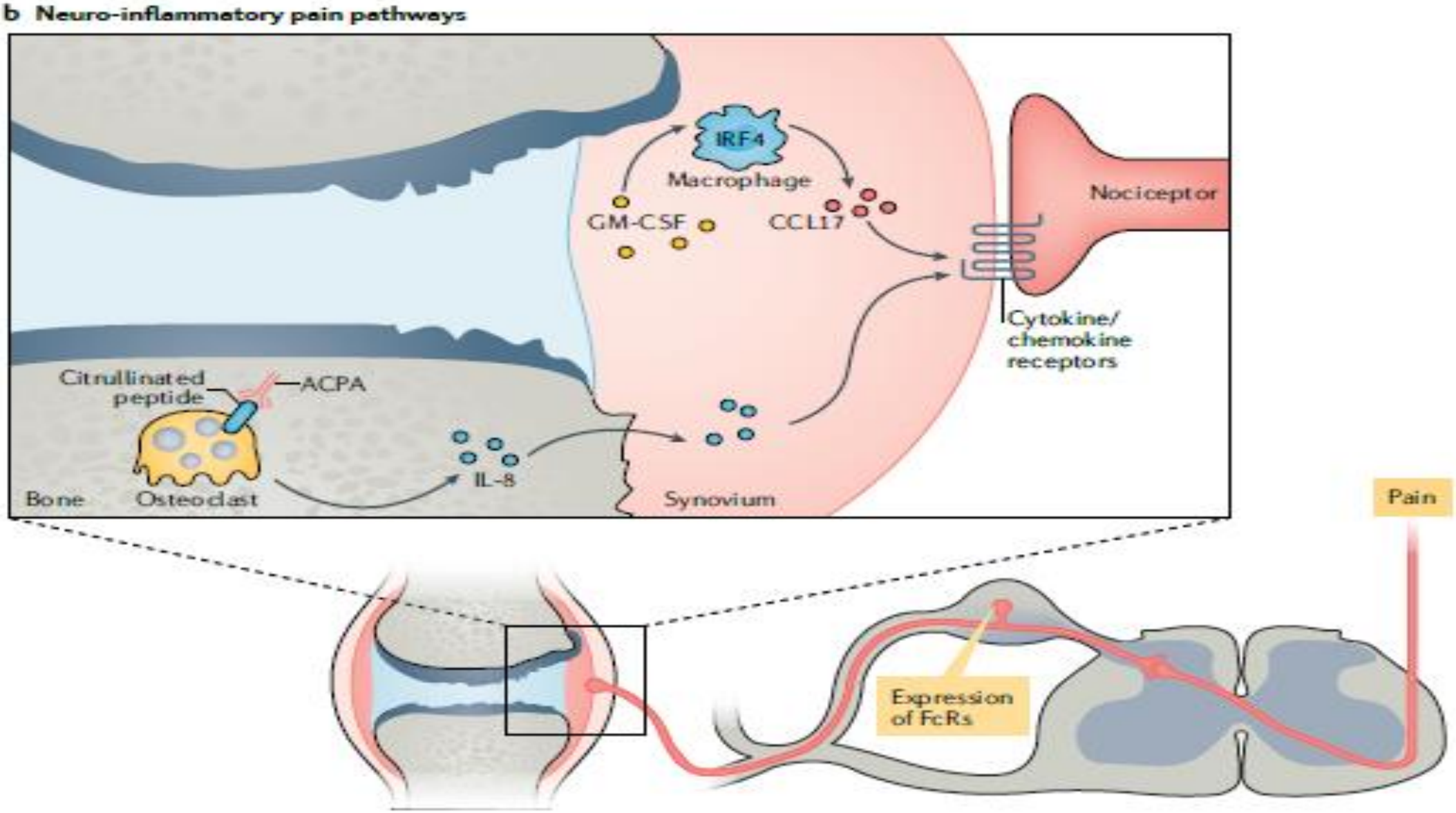
What are the long-term implications for the patient?

Candidate mechanisms of pain in non-inflammatory refractory RA

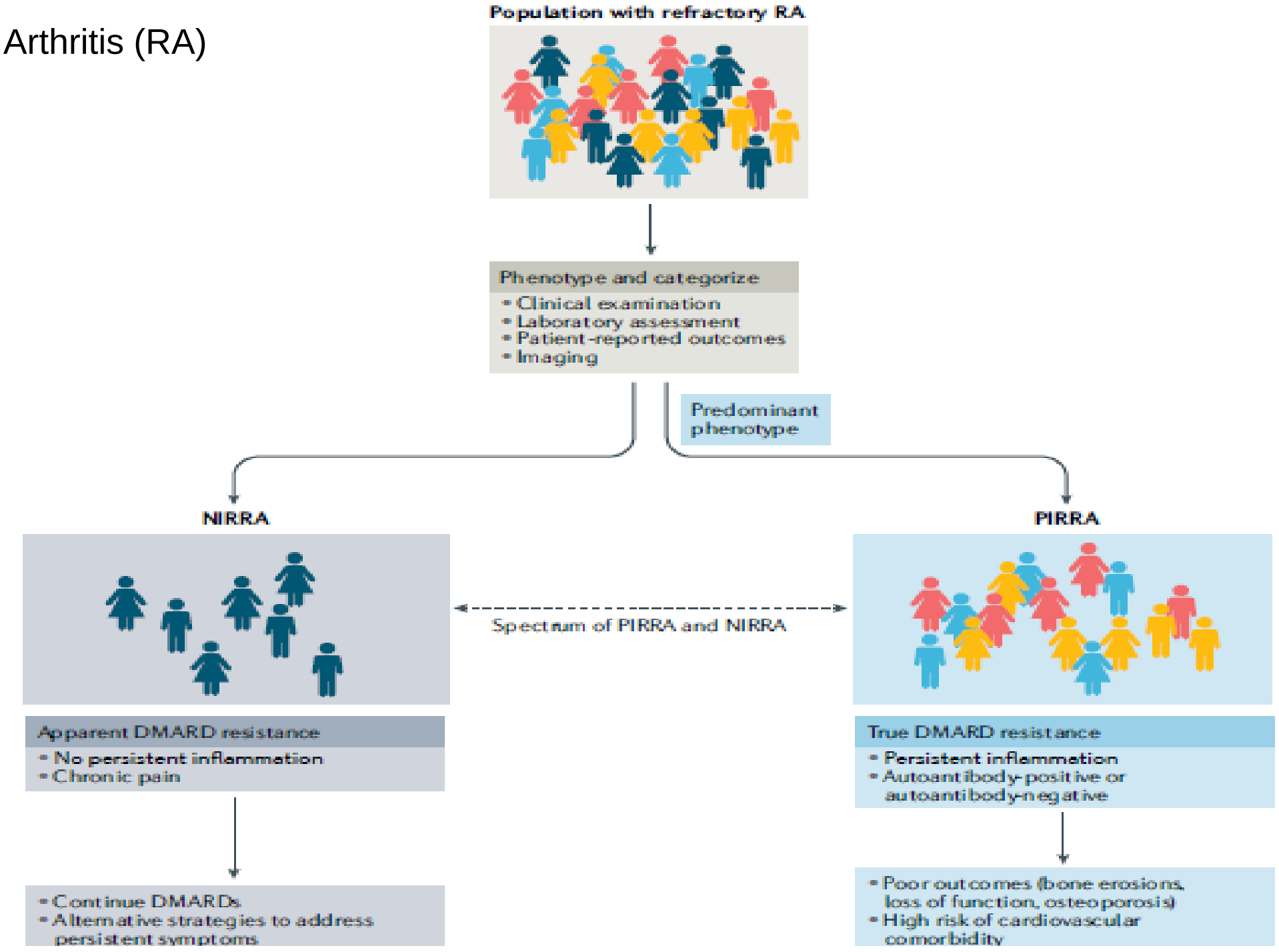


Refractory Rheumatoid Arthritis (RA)

Candidate pain mechanisms in non-inflammatory refractory RA



Stratification



Refractory RA – Next what?

- Careful total stratification (Clinical-cellular-molecular)
- Application of systems biology approaches
- Definition of new biomarkers RELATED to individual endotype.
- Combinational therapeutic approaches

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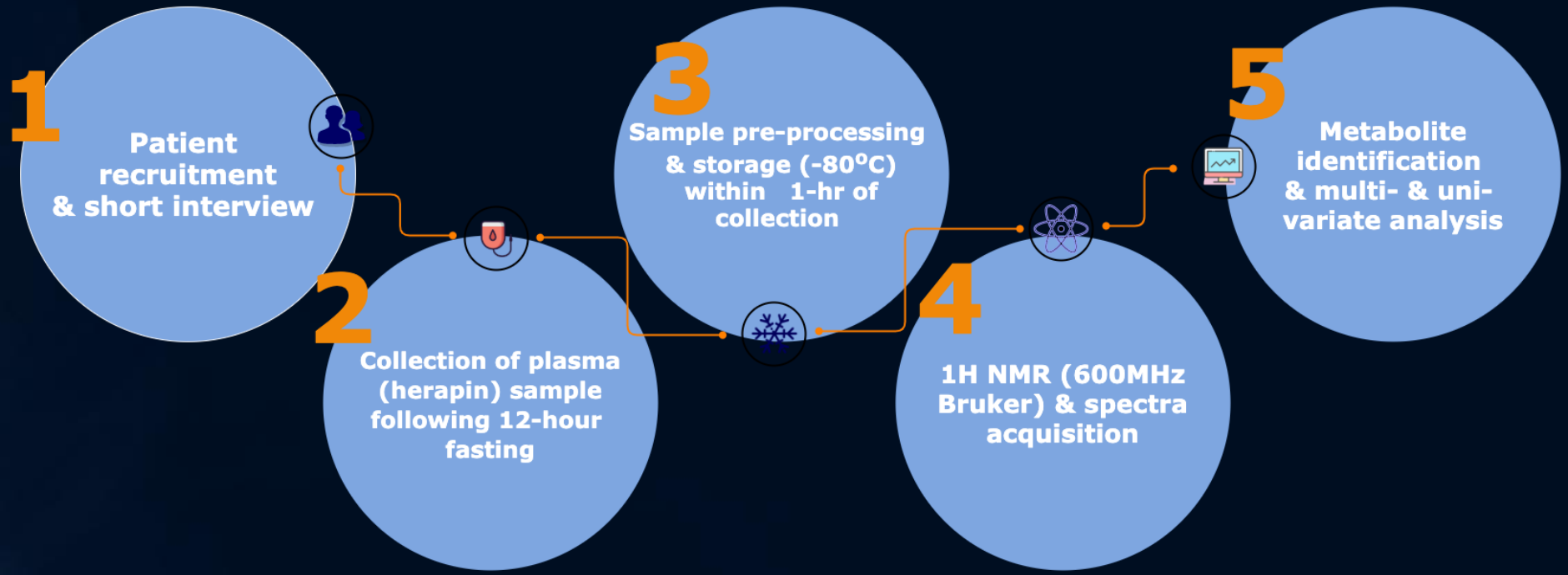
✓ Methodology



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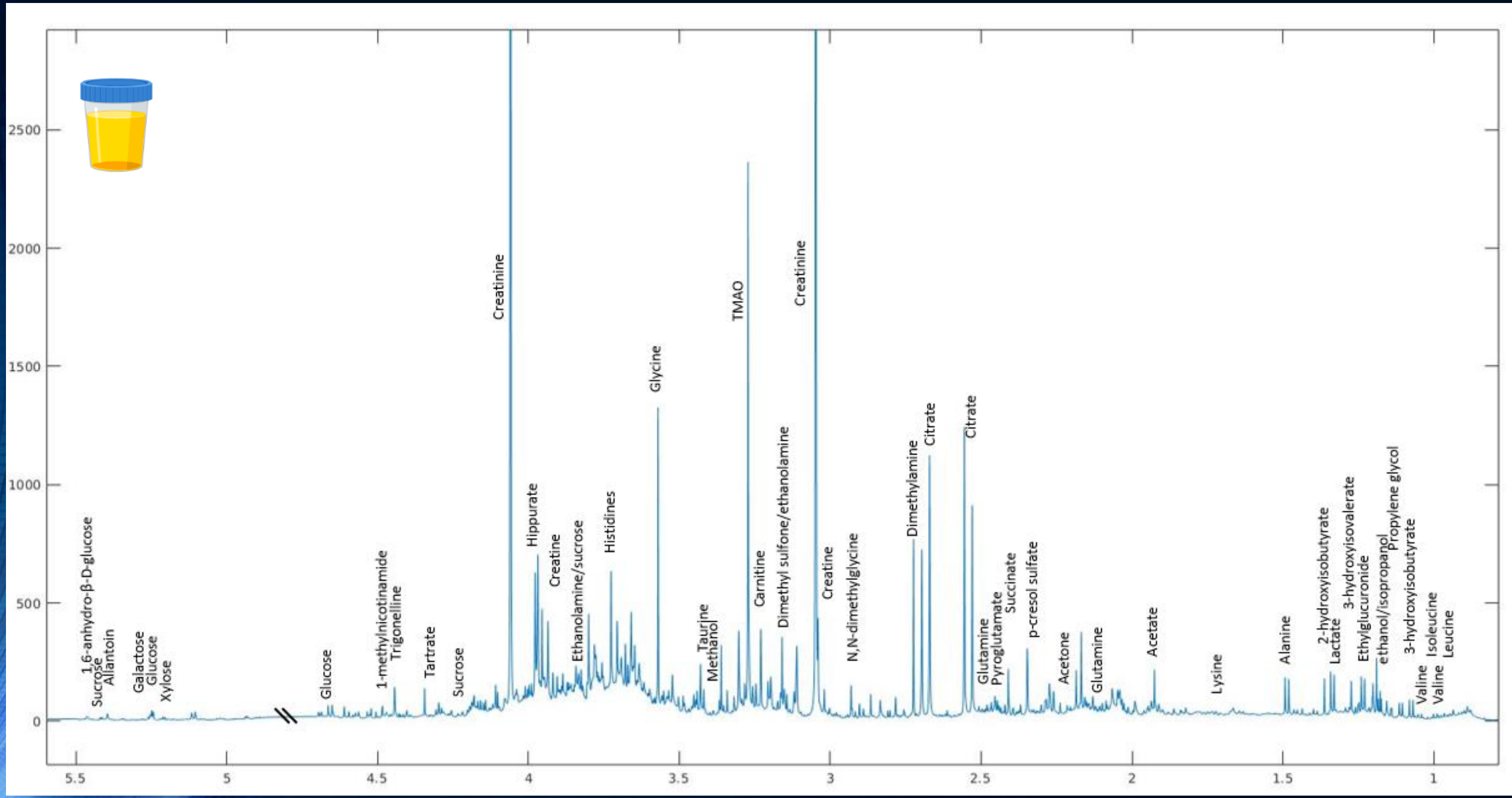
K. Tsezou , E. Mikros , P. Vlachoyiannopoulos et al., Unpublished observations



Tsezou K., Mikros E., Vlachoyiannopoulos P. et al., Unpublished observations

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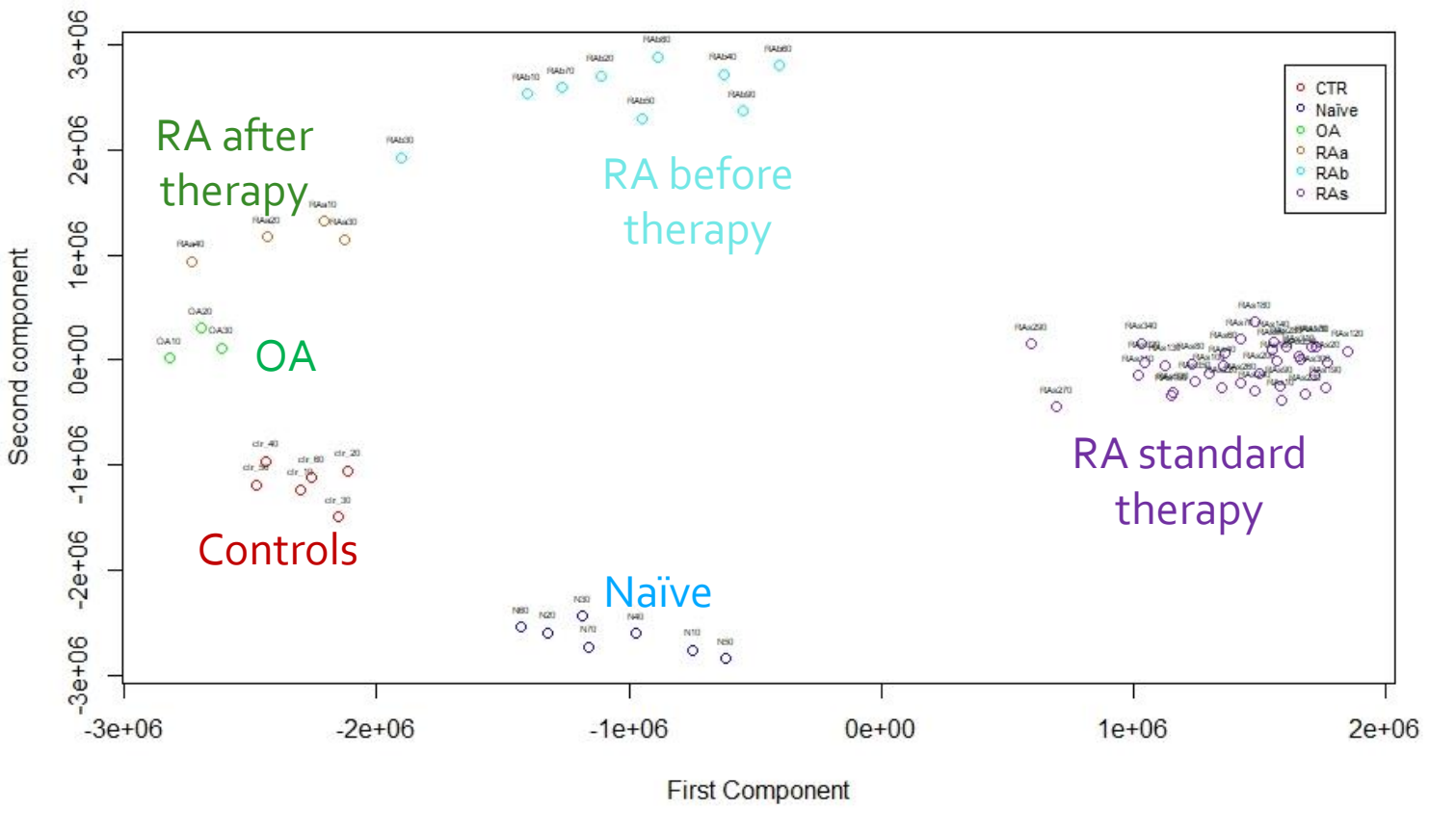
✓ Accurate Patient Stratification



Distinct metabotypes for the six experimental groups

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Tsezou K., Mikros E., Vlachoyiannopoulos P. et al., Unpublished observations

Future research needs

Refractory RA patients are genetically heterogenous with complex overlaps of innate and adaptive mechanisms

Clinical, laboratory indices, genes and proteins of interest

Definition of disease-associated markers

Seronegative disease probably involves either involves either an unrecognized humorally mediated disease, CD8+ metabolic T cell- mediated disease and predominantly innate immune cell- mediated disease

Genomics, proteomics, transcriptomics,

Definition of biomarkers

Resistant seropositive RA despite + humorally targeted approaches remain unclear

Hardware

Software

Functional interactions, time/host/environment-depended on/off signals

Definition of procedures

Precision Medicine

Refractory RA: Is it a new disease?

- Response: Who cares, all I need is to cure my patient

Acknowledgments

- All collaborators of Pathophysiology
- All physicians referring patients with RA
- All sponsors in our research work
- OUR PATIENTS