Amsterdam Rheumatology & immunology Center
Research by AMC, Reade and VUmc

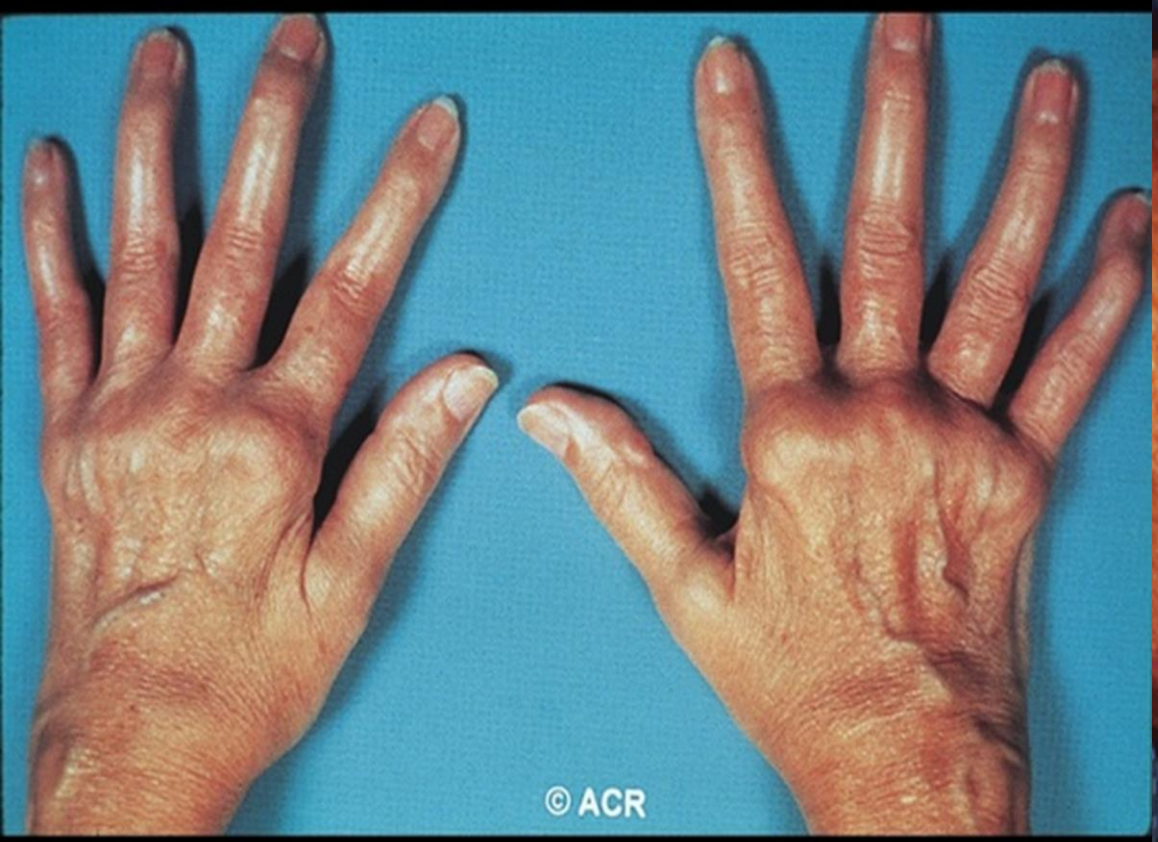
‘Personalized medicine’ bij reumatoïde artritis

Congres Goed Gebruik Geneesmiddelen
7 april 2016
Dirkjan van Schaardenburg, namens MODIRA

amc
Reade
revalidatie | reumatologie

Disclosure belangen spreker

(potentiële) belangenverstrengeling	Zie hieronder
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Bedrijfsnamen
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk …	• MODIRA consortium (ZonMw) • Geen • Geen • Geen • Geen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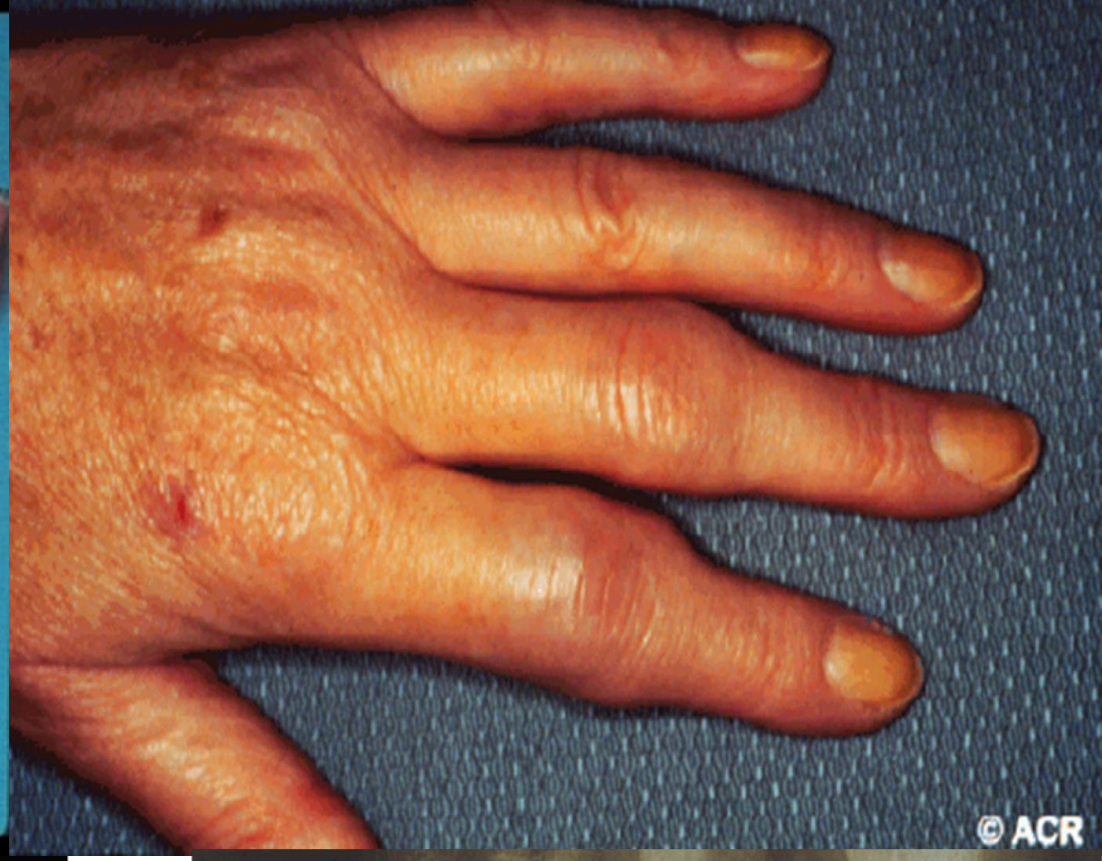
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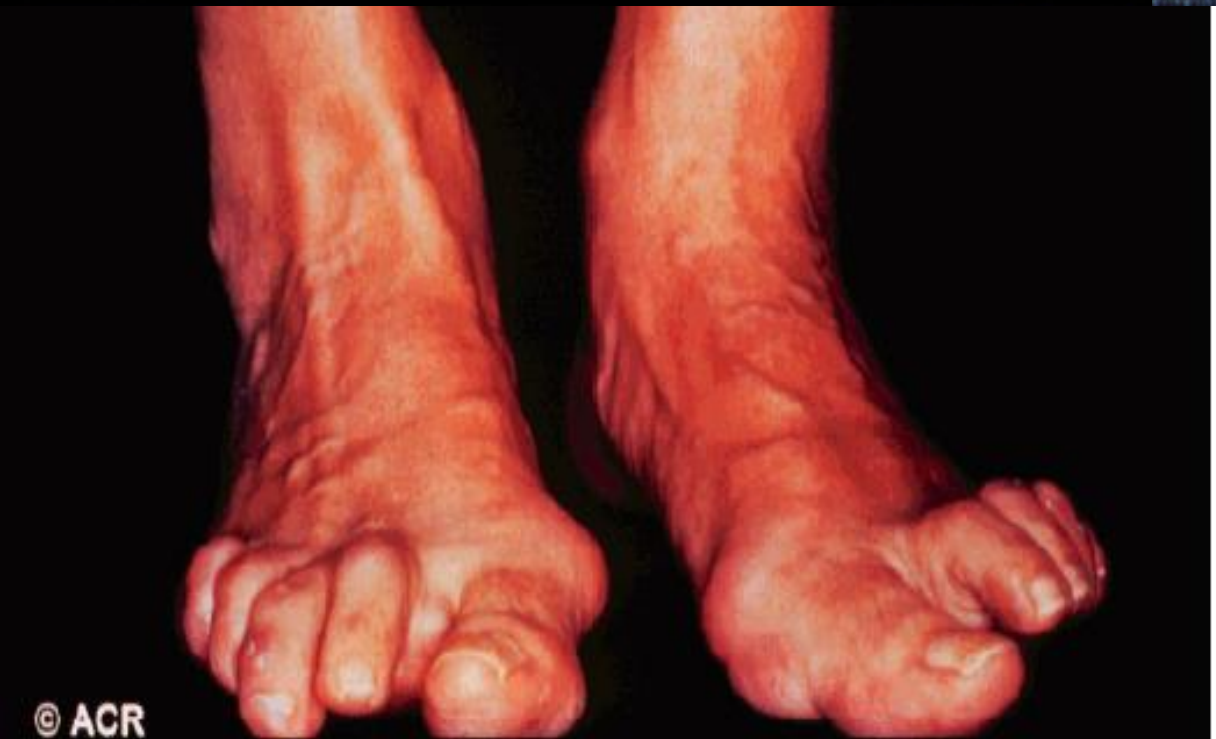
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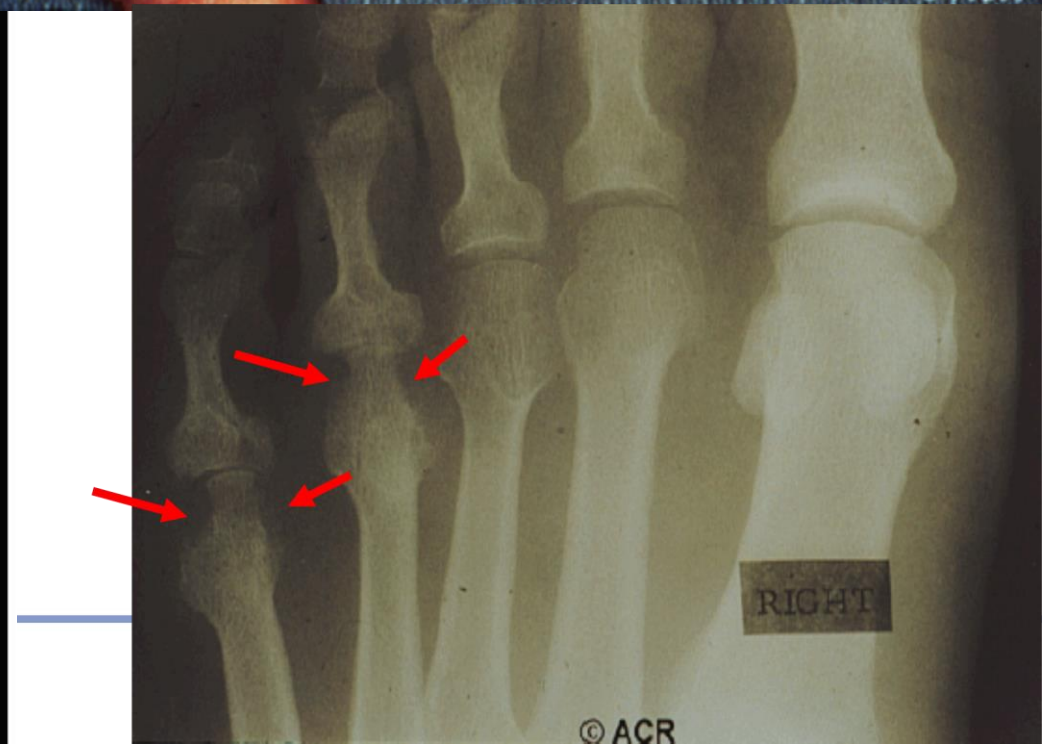
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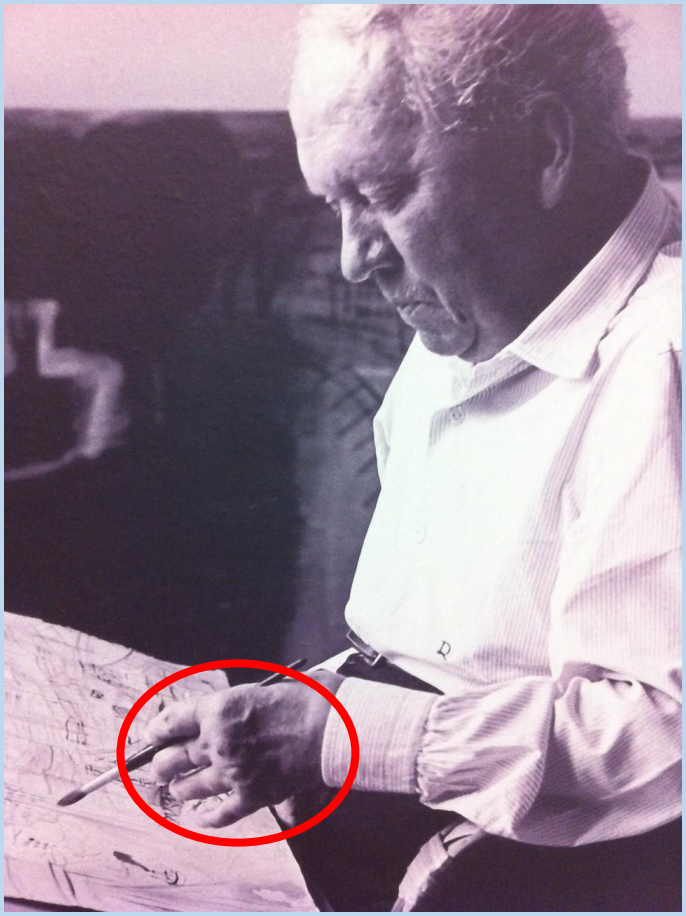
Auguste Renoir



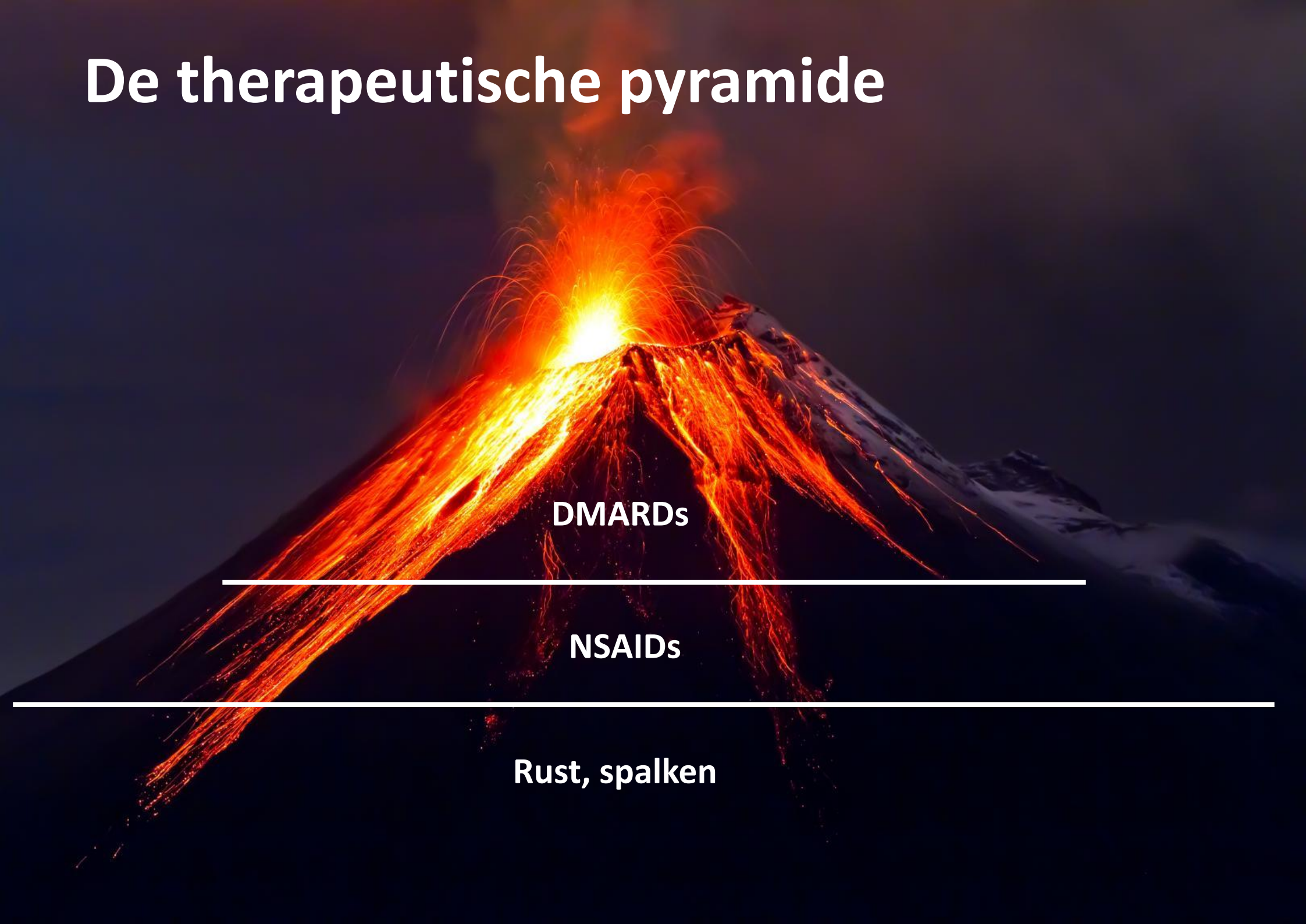
Raoul Dufy

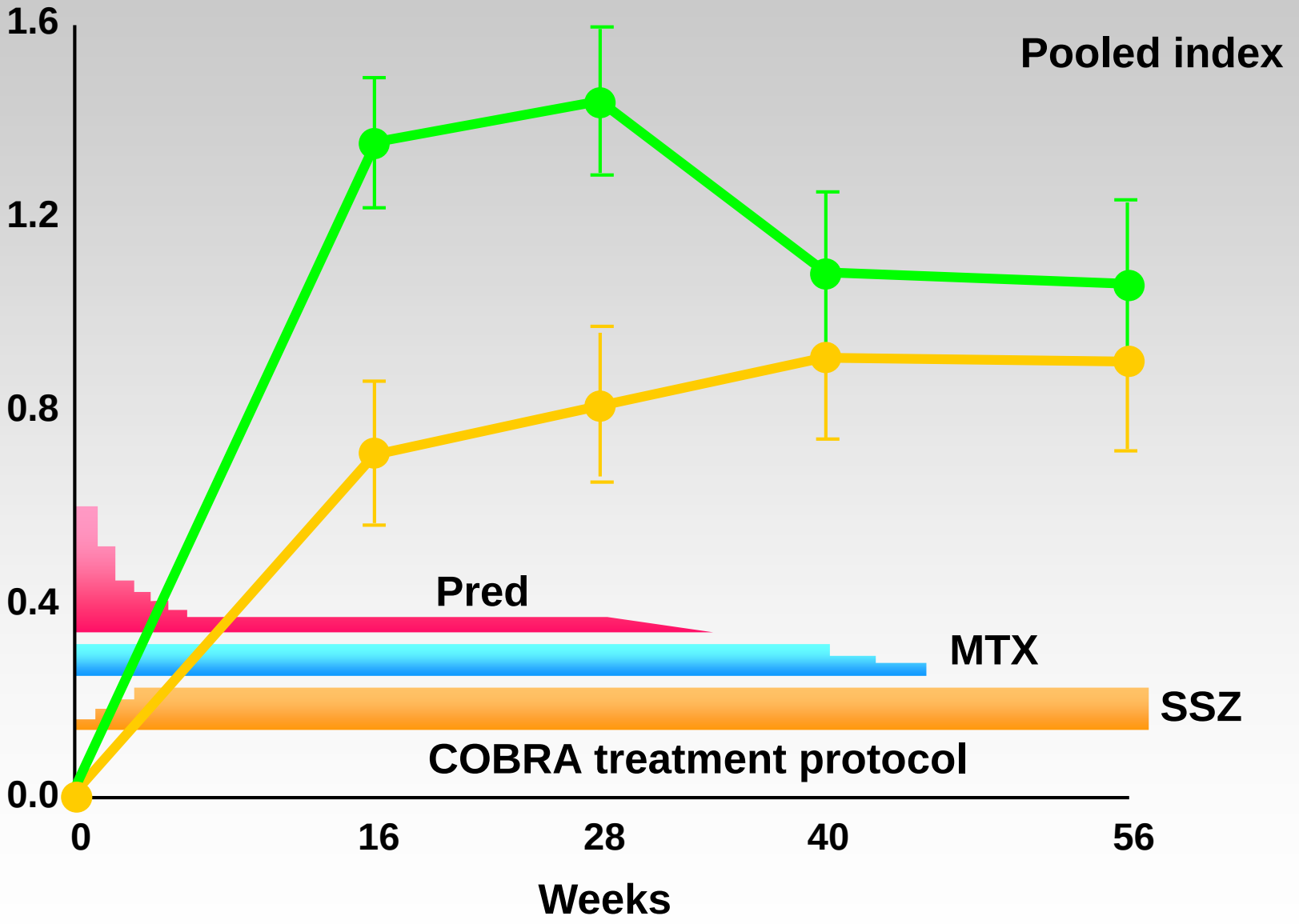
Natuurlijk beloop van RA

Ongecontroleerde, aanhoudende ontsteking →
Gewrichtsschade →
Functionele achteruitgang →
Comorbiditeit →
Broosheid, infecties, cardiovasculaire events →
Voortijdige dood

Late interventies → hoge toxiciteit

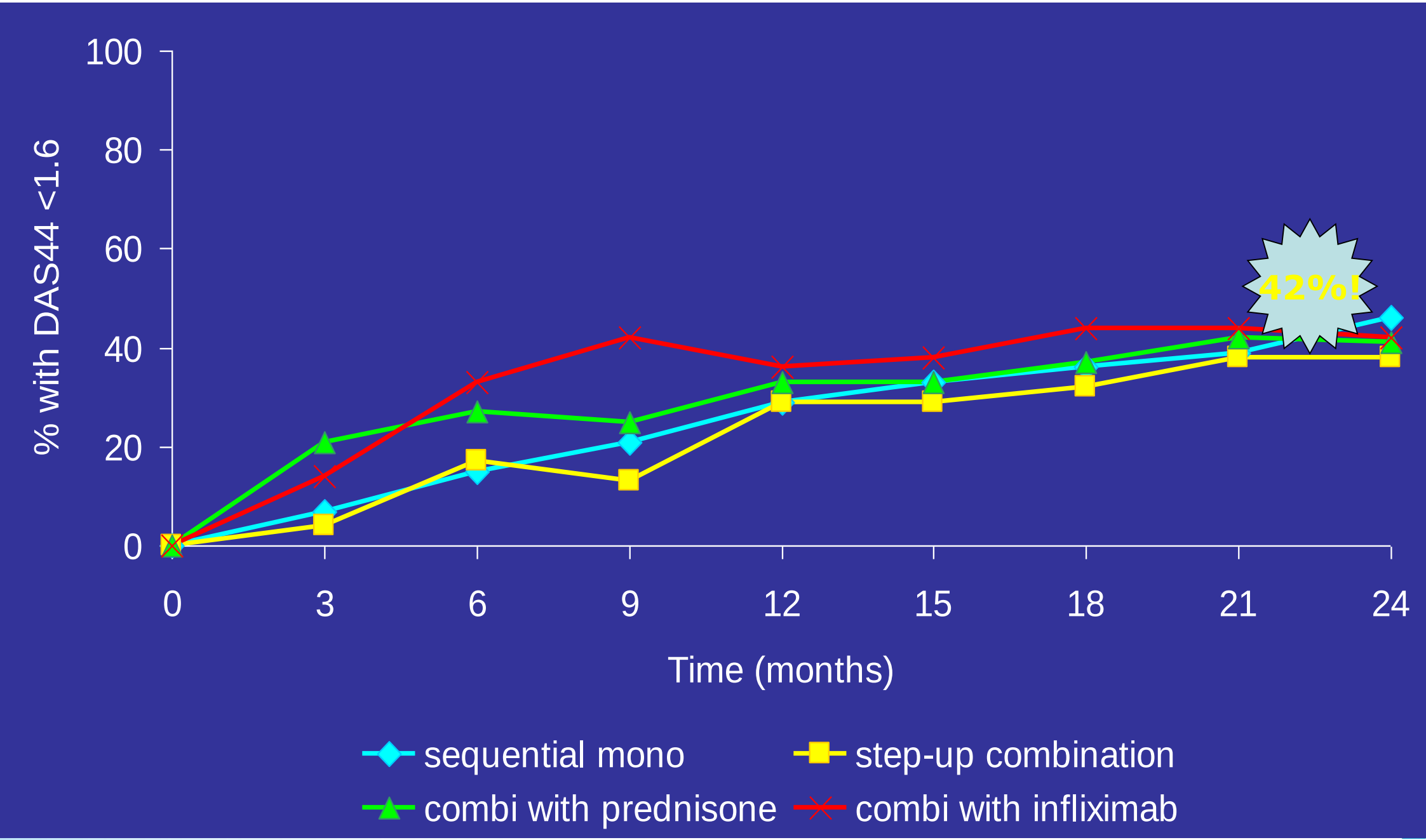
De therapeutische pyramide





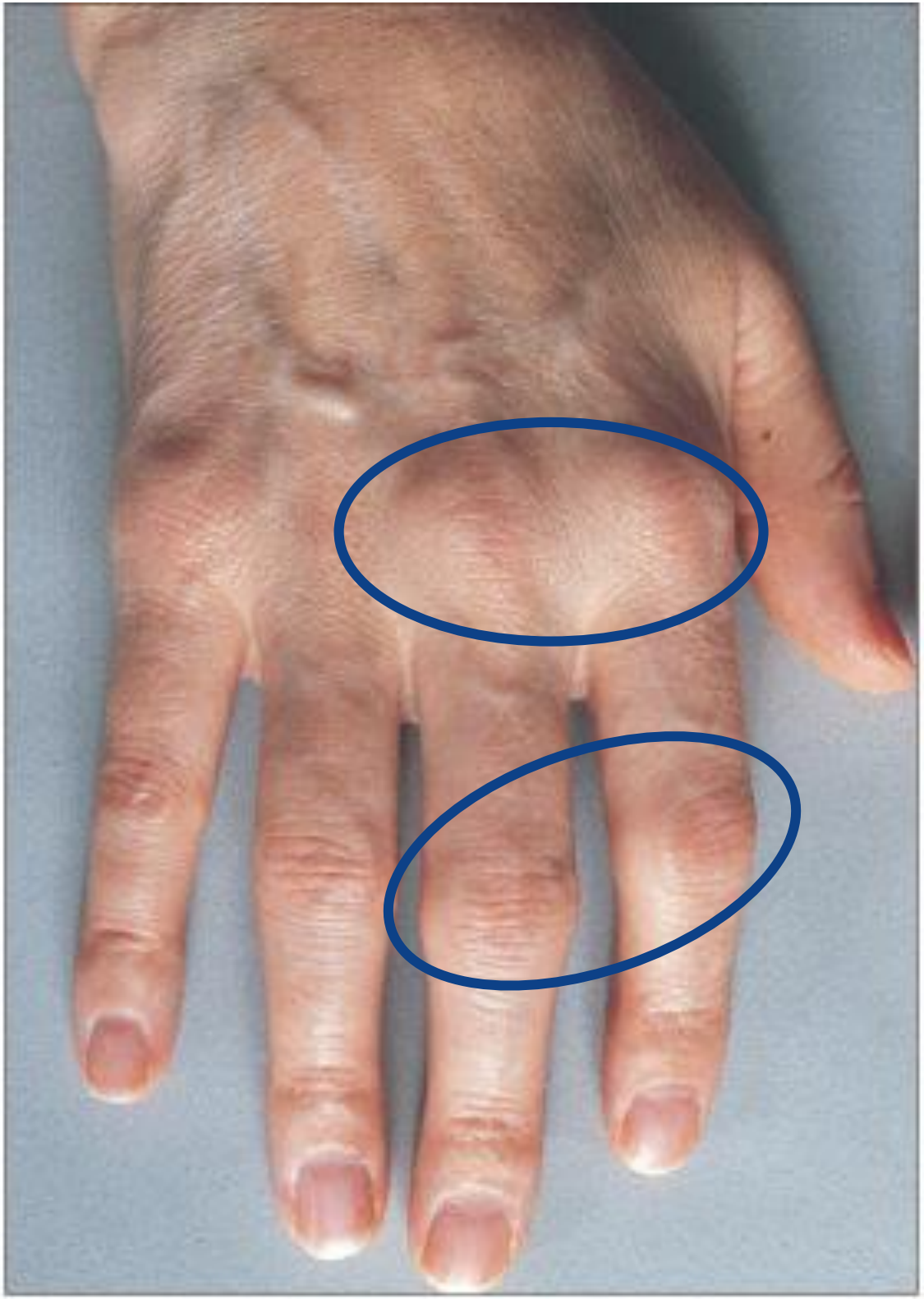
Boers Lancet 1997

BeSt: % in remissie



Conclusies RA strategie trials

- Vroege behandeling beter dan late
- ‘Treat to target’ verbetert het resultaat
- Combinaties beter dan monotherapie
- Geen toename, zelfs afname toxiciteit!



Vroege RA

Reade
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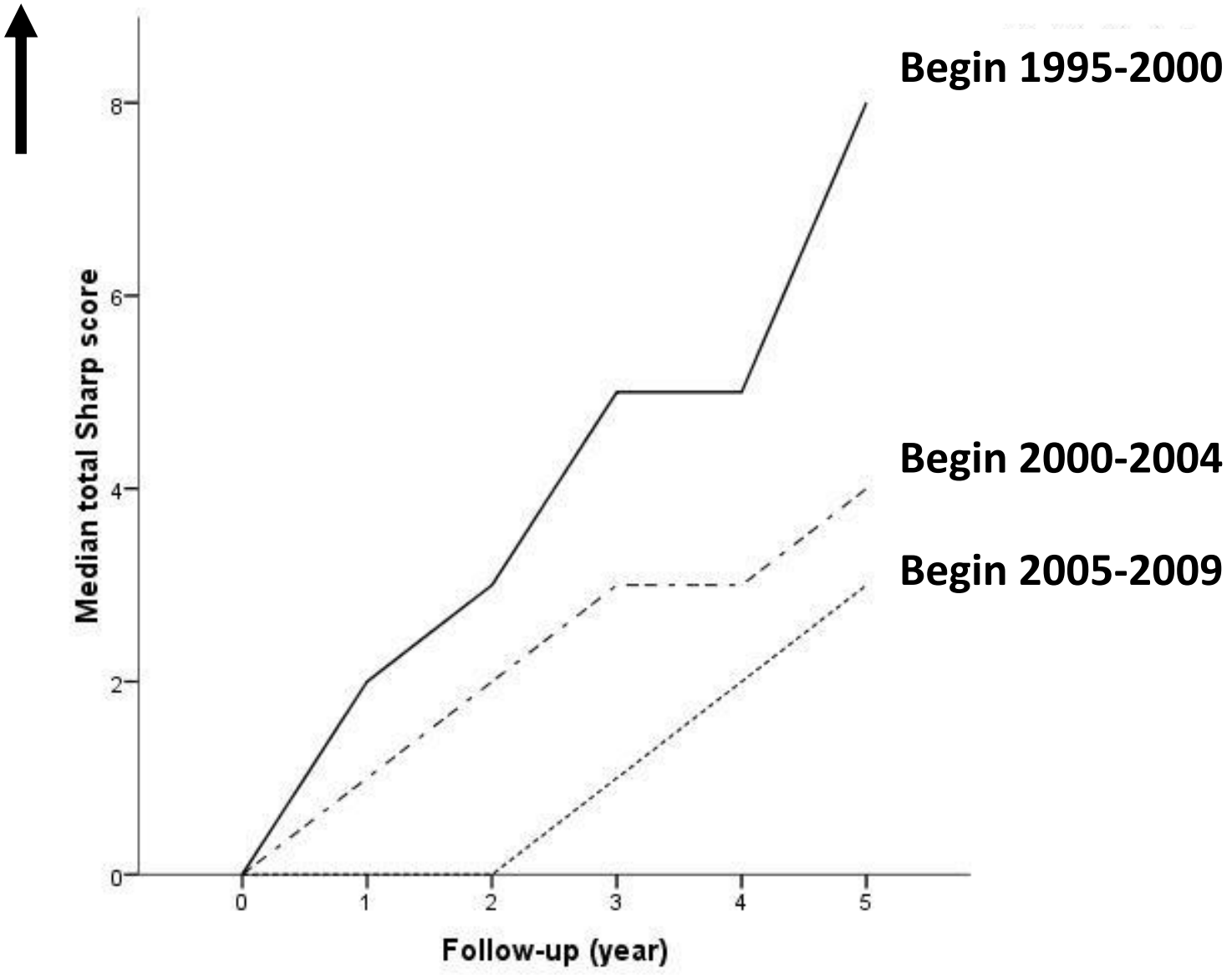
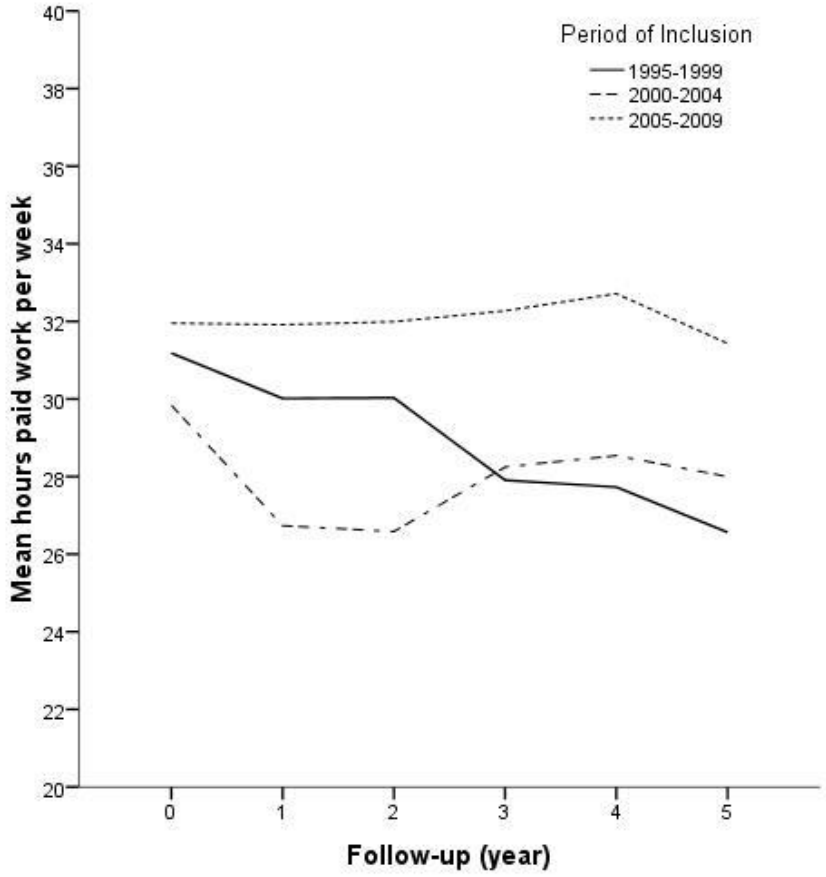
Schade op de röntgenfoto



Britsemmer, unpublished

Benefits of earlier more aggressive treatment: work retention



Prognostische factoren bij RA

- Schade bij het begin
- Reumafactor / ACPA
- HLA-SE
- Roken

Prognostische factoren bij RA bij intensieve behandeling

- ~~Schade bij het begin~~
- ~~Reumafactor / ACPA~~
- ~~HLA-SE~~
- Roken

Medicatie opties bij RA (1): NSAID

- Zo min mogelijk, zo kort mogelijk

Medicatie opties bij RA (2): DMARD

- **Prednison**
- **Methotrexaat**
- Sulfasalazine
- Leflunomide
- Hydroxychloroquine

- Azathioprine
- Cyclofosfamide

Medicatie opties bij RA (3): Biologicals

- Anti-TNF (5 soorten)
- Anti-B cel (rituximab)
- IL-6 antagonist (tocilizumab)
- Costimulatie blokker (abatacept)

Medicatie opties bij RA (4): JAK remmers

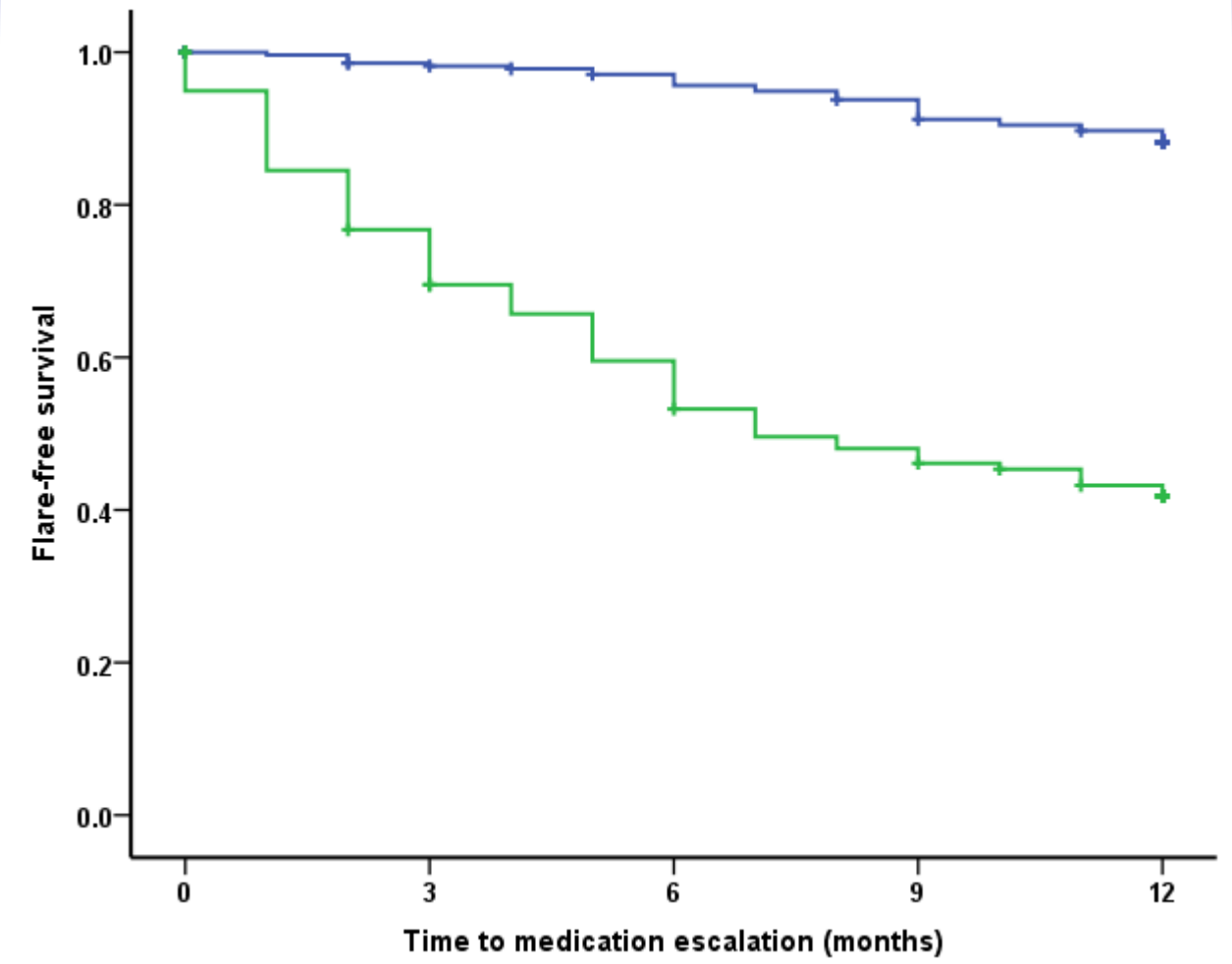
- Tofacitinib in VS, nog niet in Europa

Reade
revalidatie | reumatologie

Huidige aanpak nieuwe RA

- Methotrexaat met prednison, gericht op remissie
- Toevoegen sulfasalazine en hydroxychloroquine
- Toevoegen biological (30%)

Nederlandse stopstudie van biologicals bij remissie RA



Ghiti, Arthritis Rheumatol 2016

Openstaande kwesties bij RA

- Treat to target, hoe strak?
- Combinatie-therapie voor iedereen?
- Positie goedkope biosimilars?
- Hoe vroeg beginnen?
- ***Prognose-gestuurde behandeling***

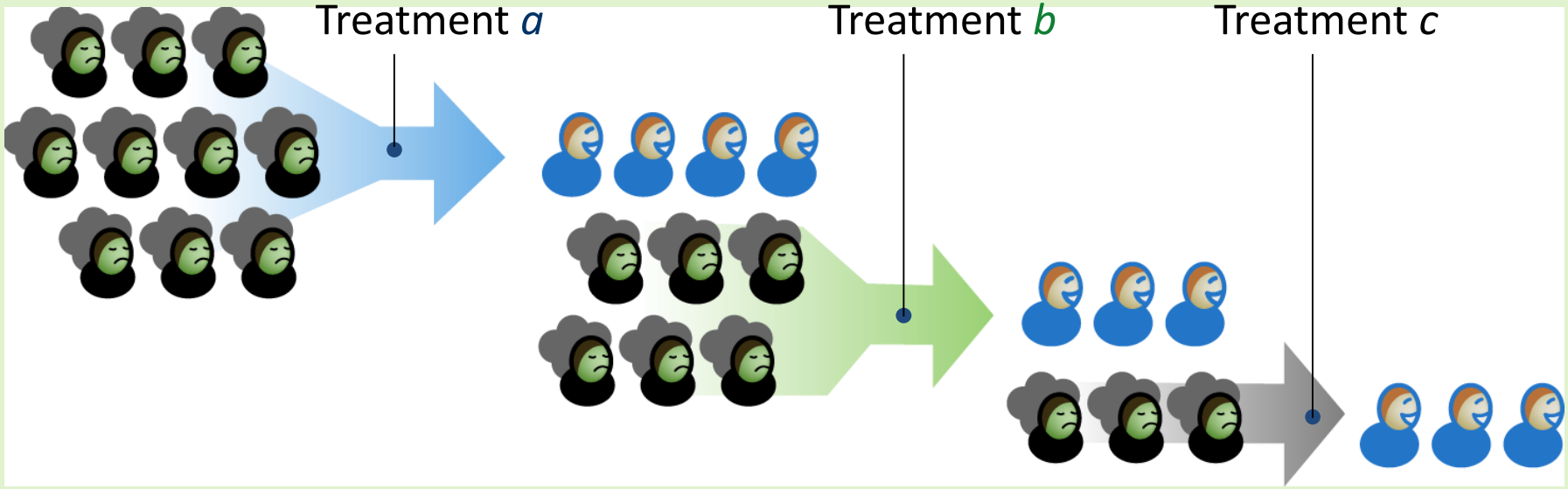
LSH-ZonMw 2Treat programma

- Response prediction to biologicals in RA
- Develop diagnostic tests to enable personalized treatment

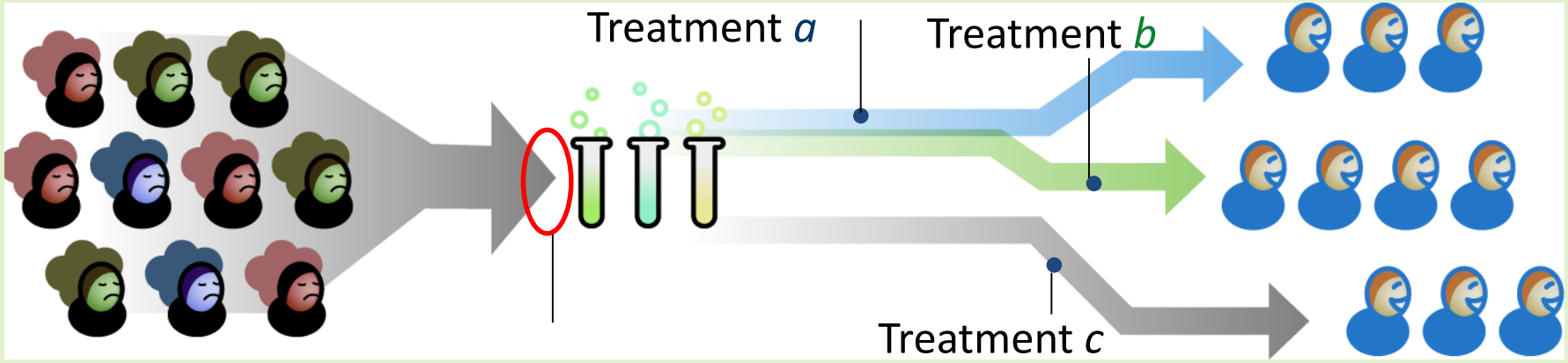
Top 10 medication costs 2011

	Million euro's	Compared to 2010
1. Adalimumab	198	+12
2. Etanercept	160	+8
8. Infliximab	69	
Certolizumab pegol	*No data*	
Golimumab	*No data*	
Total TNF blockers	>400	

Empirical Medicine

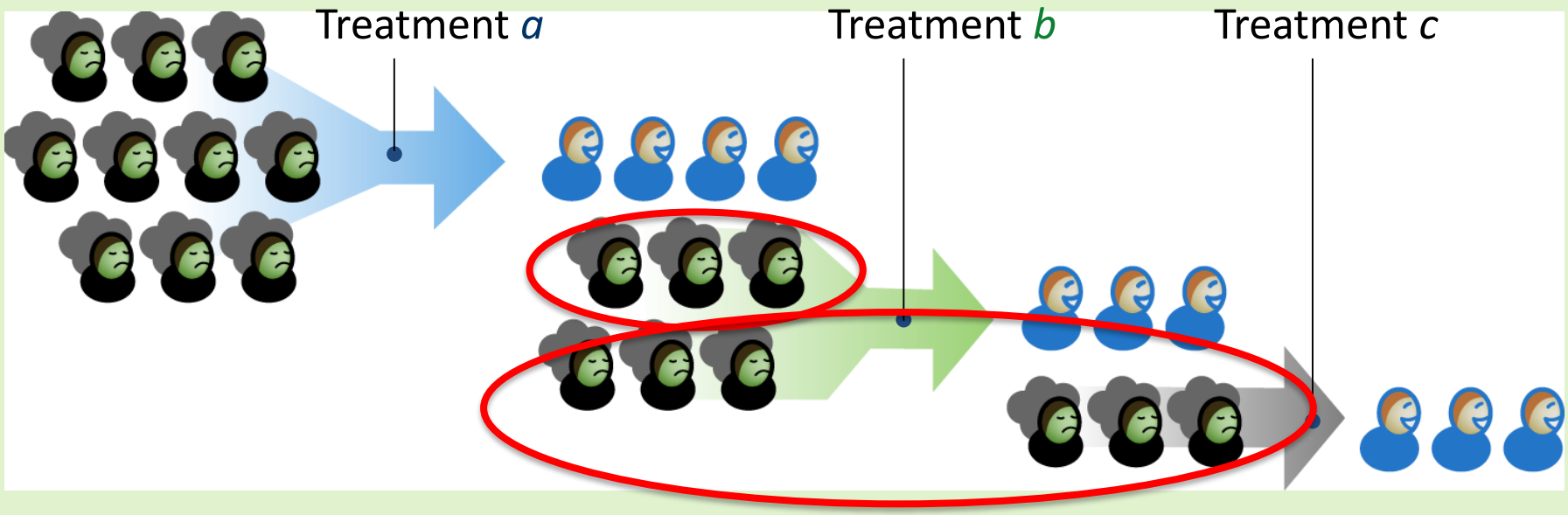


Biomarker-Guided Medicine



Prof. van der Greef, TNO

Empirical Medicine



→ Medication cost similar in both strategies

→ Pain, doctor's visits, sick leave (short term)

→ Extra joint damage, functional loss (long term)

MODIRA

MOlecular Diagnostics in Rheumatoid Arthritis

- Academia: Reade, VUmc, AMC, UMCU, LUMC
- Small-medium enterprise: Sanquin, Microbiome, Cyclotron, Hemics, Sectra
- Pharma companies: Roche, Abbvie, Pfizer, UCB, BMS
- Health funds: Dutch Arthritis Association

Few validated biomarkers

- **DMARD**
  - Thiopurine methyltransferase polymorphism (azathioprine)
- **Response to TNF blockade**
  - Smoking
  - TNF-alpha 308 polymorphism
- **Response to rituximab (anti-B cel)**
  - Rheumatoid factor (RF)
  - Anti-citrullinated antibodies (ACPA)
  - FC gamma receptor IIIA (FCγR IIIA) polymorphism

Patent position (EATRIS)

- MODIRA has a good patent position:
  - Transcript-based test for response to rituximab
  - B/T cell clonality
  - HandScan
  - Anti-CarP

- Few competing patents on prediction of response to:
  - TNF blockade
  - Rituximab
  - Tocilizumab

EATRIS
European Infrastructure for Translational Medicine

Potential biomarkers in MODIRA

- **Serology**
  - ACPA/anti-CarP/Rheumatoid factor
  - Autoreactive B-cells
  - TNF load
- **Cell-based**
  - Transcript-based tests
  - Lymfocyte fingerprinting
- **Imaging**
  - Macrophage PET(-CT)
  - HandScan
  - DXR

Work plan

- **Discovery/validation 1**
  - Technical development
  - Existing cohorts: 1750 patients

- **Midterm review**
  - Decision which markers can continue

- **Validation 2/ Implementation**
  - Prospective multicenter cohort for validation studies
  - Randomized trial of e.g. TNF load?

2.3B. Pharmacotherapy & Molecular Diagnostics

Area: Companion diagnostics in RA

MODIRA

- ✓ World-class research group
- ✓ Good patent position
- ✓ Several promising techniques
- ✓ Selection method in place
- ✓ Market development of biomarkers…

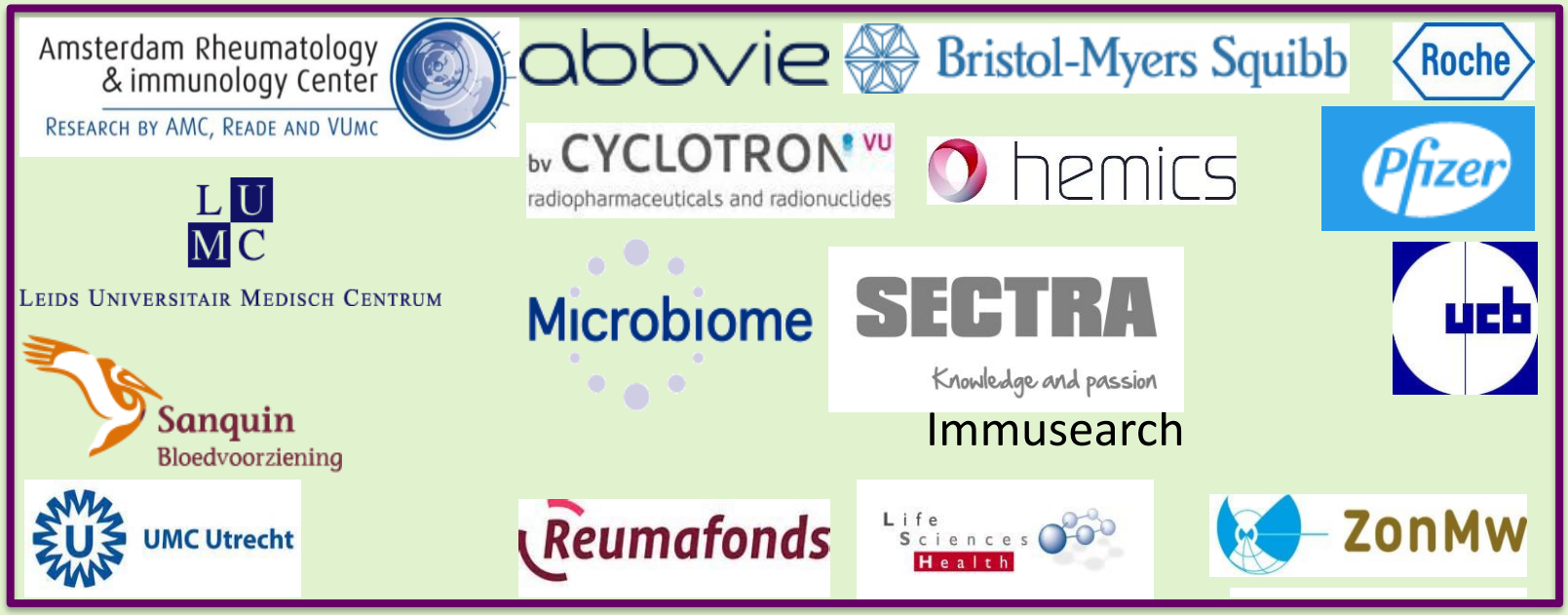
Conclusies aanpak RA

- Vroeg herkennen
- Agressief behandelen

- Rol ‘personalized medicine’ thans nog beperkt
- Leefstijl belangrijk bij preventie en therapie

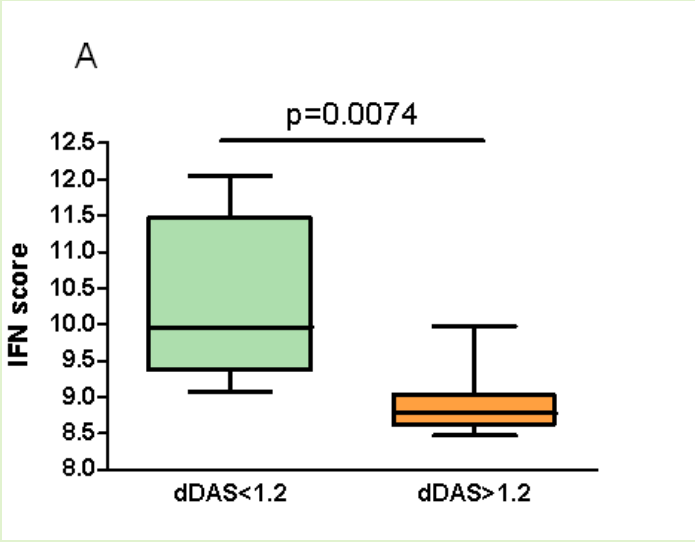
MODIRA

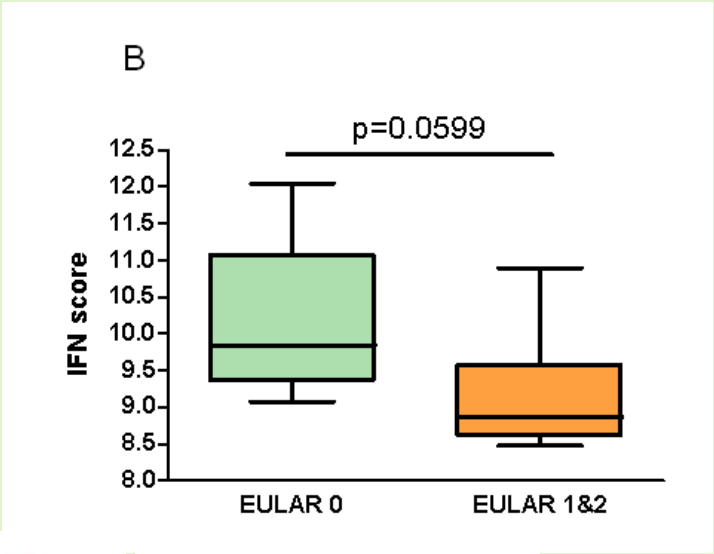
Molecular diagnostics in rheumatoid artritis



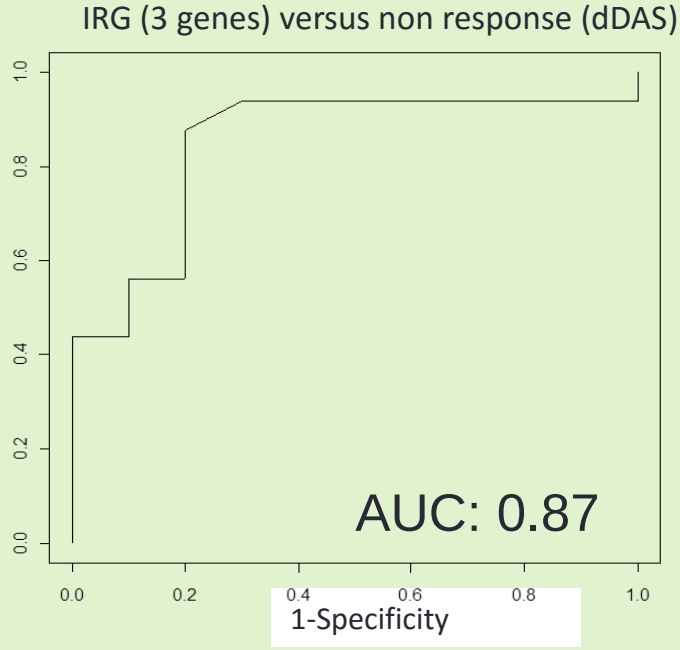
The next slides are not part of the presentation, but can be used to answer questions

IFN score as a predictive biomarker for RTX outcome





- ROC curve characteristics (n=40 RA patients)



- Improved specificity and sensitivity after inclusion of clinical characteristics in the prediction rule

Raterman Arthritis Res Ther. 2012 Apr 27;14(2):R95

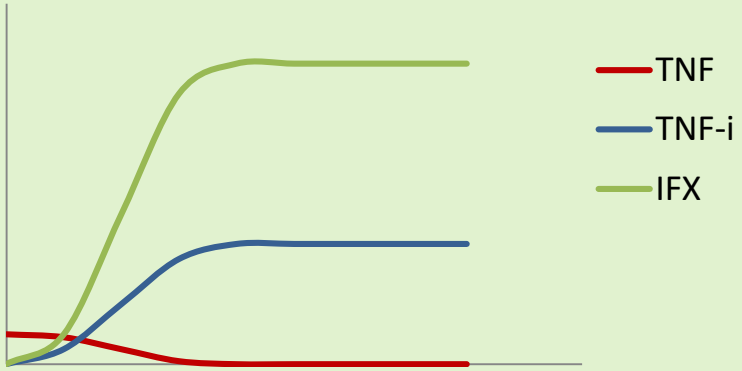
Validation, assay development and implementation

	Timeline	Part of MODIRA
• Validation in large, international multicenter studies and optimalisation of the prediction rule (ongoing)	6 months	No
• Development of a CE-marked IVD (ongoing)	8 months	No
• Cost-effectiveness study to determine economic value (first data available)		No
• Prospective study (preparations started)	18 months	YES
• Implementation		YES

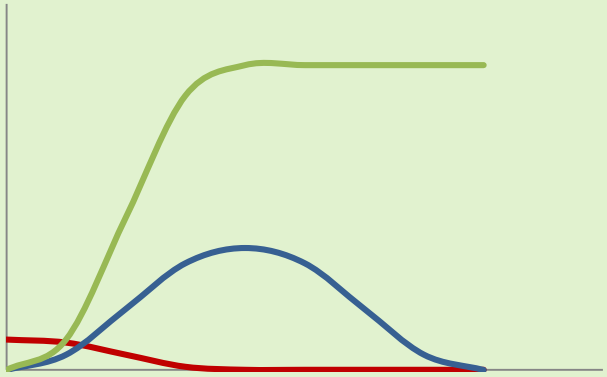
Preselect Diagnostics

ctmm

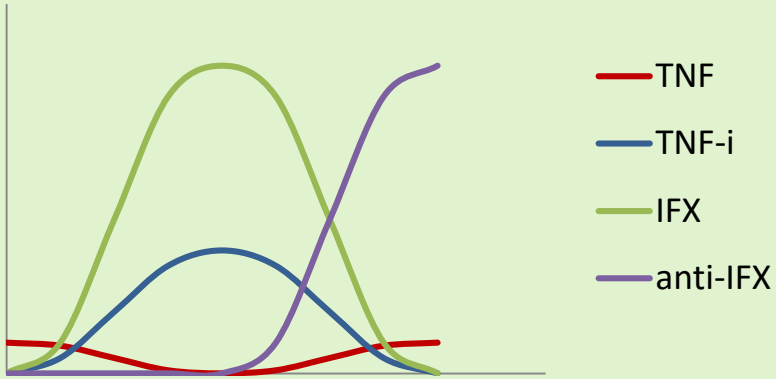
Optimizing biomonitoring of response to therapy in rheumatoid arthritis



response, TNF complexes:
continue treatment
consider tapering



response, no TNF complexes:
stop treatment



no response:
measure drug levels / ADA

Procedure biomarker development

Biomarker identification

↓

Determination of predictive value compared to/ in combination with other biomarkers

↓

Validation in multicenter, international setting

↓

Cost-effectiveness study

↓

Freeze assay

↓

CE-IVD Technical Dossier

↓

Implementation

Biomarker search for RTX treatment in RA

Unmet medical need

- 40-50% of RA patient do not benefit from RTX.
- Response is evaluated 6-9 months after start.
- Non-responders suffer from adverse effects of ineffective treatment, disease continuous without effective treatment → high socioeconomic costs

Biomarkers to predict treatment outcome are warrented

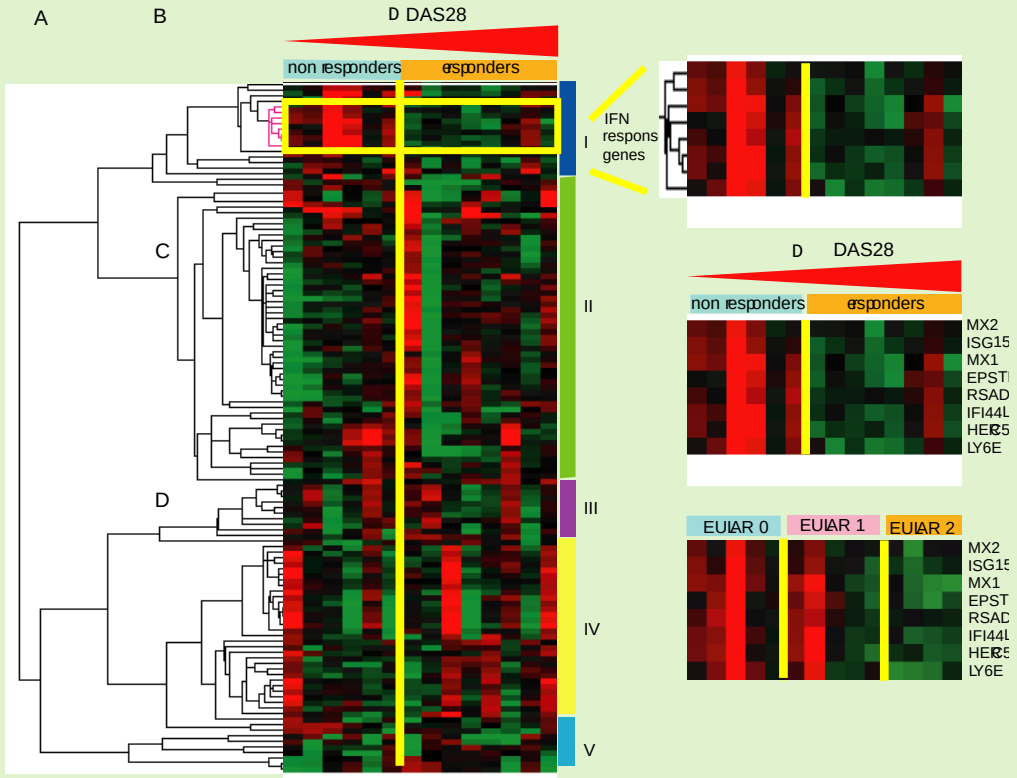
Biomarker selection: procedure

- Test cohort: 14 RA patients starting on RTX treatment
- Blood collection at baseline (PAXgene system)
- Whole genome expression profiling (Illumina bead arrays Human HT12)
- (Statistical) data analysis

Selection of DEGs

- At least 2-fold differences in expression in at least 3 patients
- One way supervized clustering on baseline expression levels

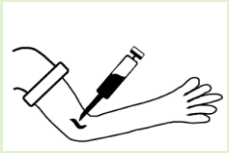
Results

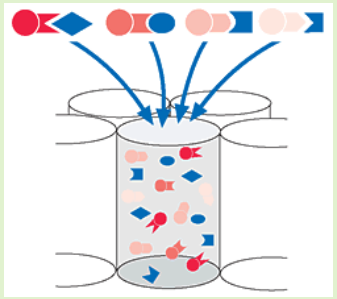


Raterman HG, Vosslamber S, et al Arthritis Res Ther. 2012 Apr 27;14(2):R95

Only baseline expression of IFN response genes relate to clinical outcome

Integrated characterization of the rheumatoid factor response and associated autoantibody responses for prediction of disease (course) and response to treatment in rheumatoid arthritis





Multiplex platform for integrated and comprehensive analysis of:

- **Initiating and amplifying auto-antibodies: Rheumatoid Factor, Anti-hinge antibodies, ACPAs**
- **Antibody characteristics: Isotype (IgM/IgA/IgG), subclass- and allotype fine-specificity, avidity, glycosylation status**
- **Immune complexes**

Diagnosis

Disease course

Response to treatment

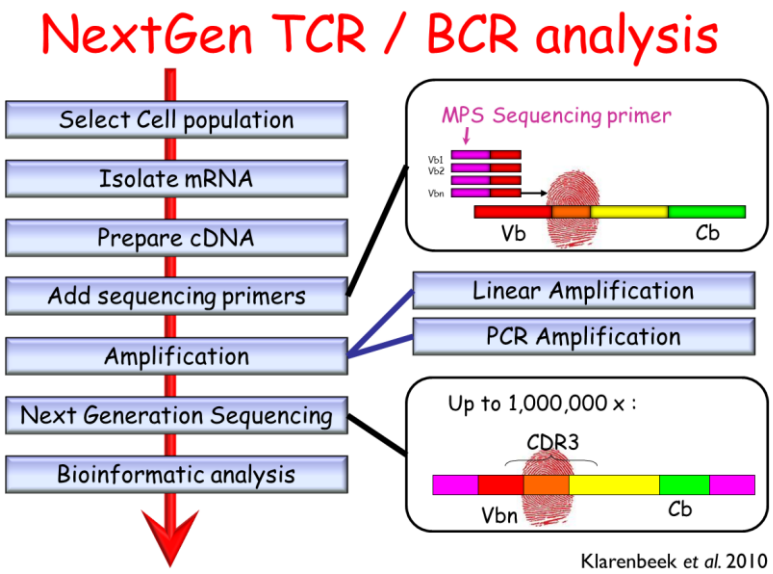
Innovation

Measuring **pathophysiological agents** in a ***qualitative*** instead of just a quantitative way.

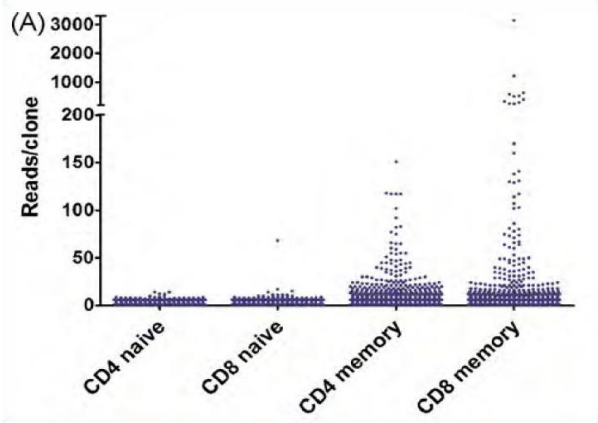
Milestones

2015: Development of individual assays.
2016: Integrating relevant assays into a comprehensive chip- or bead based multiplex platform. Validation of the platform in existing patient cohorts.
2017: Finalizing multiplex platform in format practical for use in clinical settings and validating the platform in the new multi-center cohort.

BCR analysis in at risk patients



Klarenbeek *et al.* 2010

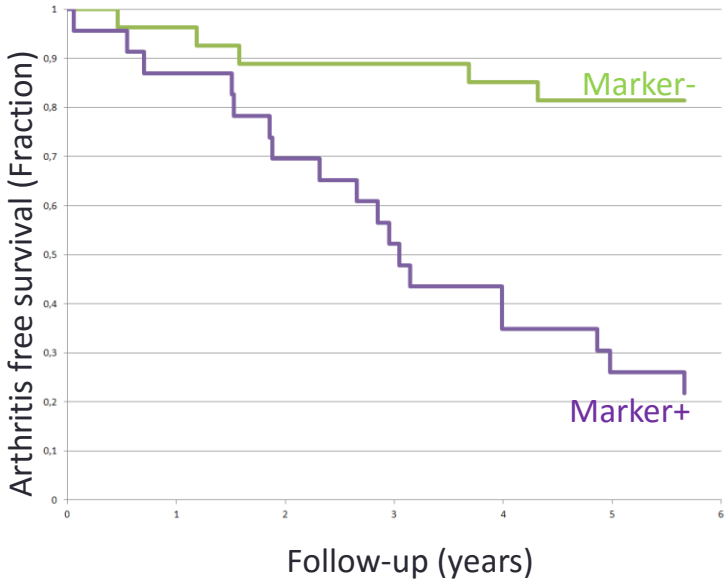


Test at baseline in patients at risk:
- No arthritis
- CCP positive

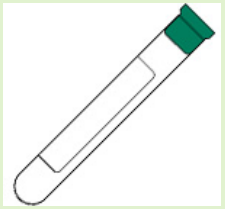
Time

Arthritis

No arthritis

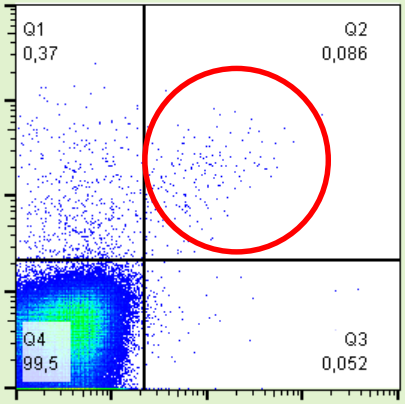


WP1/2.4 Pathogenic B cells

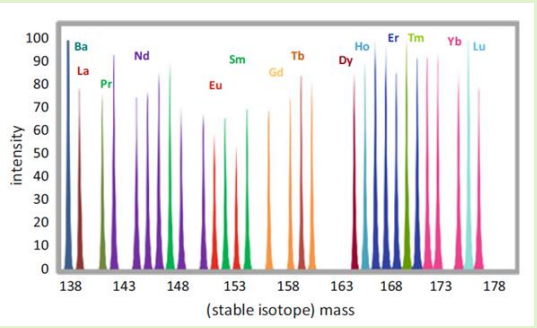


peripheral blood/
synovial fluid

citrulline-specific B cells

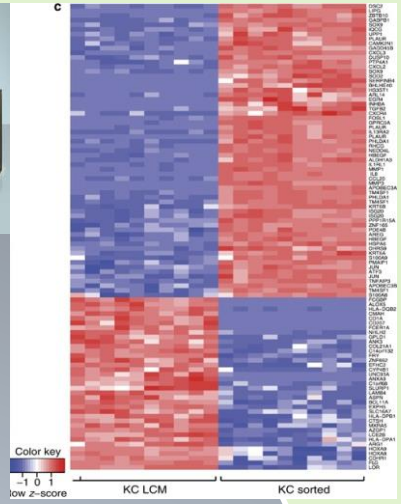


antigen-specific
isolation



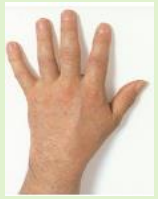
multiparameter phenotyping (CyTOF)

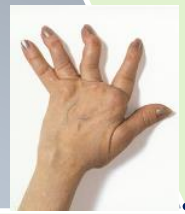
molecular profiling (mRNA)



WP 2

biomarker identification/
validation





healthy

"at-risk"

undifferentiated
arthritis

rheumatoid
arthritis

treatment

WP1.2 Pathogenic antibodies

Characterization of auto-antibody profiles and features F(ab) glycosylation