Biomarkers for Giant Cell Arteritis
& Polymyalgia Rheumatica
From immunopathology towards clinical relevance

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Disclosure slide

Conflict of interests	None
Relevant relationship with companies	NA
• Sponsoring or research money • Fee or other reimbursement • Shareholder • Other relationship, namely …	• • • •

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Today's presentation

- Why do we need biomarkers?
- What biomarkers can we use?

- Based on publications
- Ongoing work in our group

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JOURNAL ARTICLE

High angiopoietin-2 levels associate with arterial inflammation and long-term glucocorticoid requirement in polymyalgia rheumatica

Yannick van Sleen, Annemieke M H Boots, Wayel H Abdulahad, Johan Bijzet, Maria Sandovici, Kornelis S M van der Geest, Elisabeth Brouwer   Author Notes

Rheumatology, Volume 59, Issue 1, January 2020, Pages 176–184, https://doi.org /rheumatology/kez261

Published: 10 July 2019   Article history ▾

Markers of angiogenesis and macrophage products for predicting disease course and monitoring vascular inflammation in giant cell arteritis

Yannick van Sleen, Maria Sandovici, Wayel H Abdulahad, Johan Bijzet, Kornelis S M van der Geest, Annemieke M H Boots, Elisabeth Brouwer

Rheumatology, Volume 58, Issue 8, August 2019, Pages 1383–1392, https://doi.org /10.1093/rheumatology/kez034

Published: 25 February 2019   Article history ▾

Home > Arthritis Research & Therapy > Article

Angiopoietin-2/-1 ratios and MMP-3 levels as an early warning sign for the presence of giant cell arteritis in patients with polymyalgia rheumatica

Research | Open access | Published: 07 March 2022
Volume 24, article number 65, (2022)   Cite this article

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Yannick van Sleen, Philip Therkildsen, Berit Dalsgaard Nielsen, Kornelis S. M. van der Geest, Ib Hansen, Peter Heeringa, Marcel D. Posthumus, Maria Sandovici, Erik J. M. Toonen, Jannik Zijlstra, Annemieke M. H. Boots, Ellen-Margrethe Hauge & Elisabeth Brouwer

REVIEW article

Front. Immunol., 15 June 2023   This article is part of the Research Topic
Sec. Autoimmune and Autoinflammatory Disorders : Autoimmune Disorders   Novel Therapeutic Options in Large Vessel Vasculitis
Volume 14 - 2023 | https://doi.org/10.3389/fimmu.2023.1202160   View all 8 Articles >
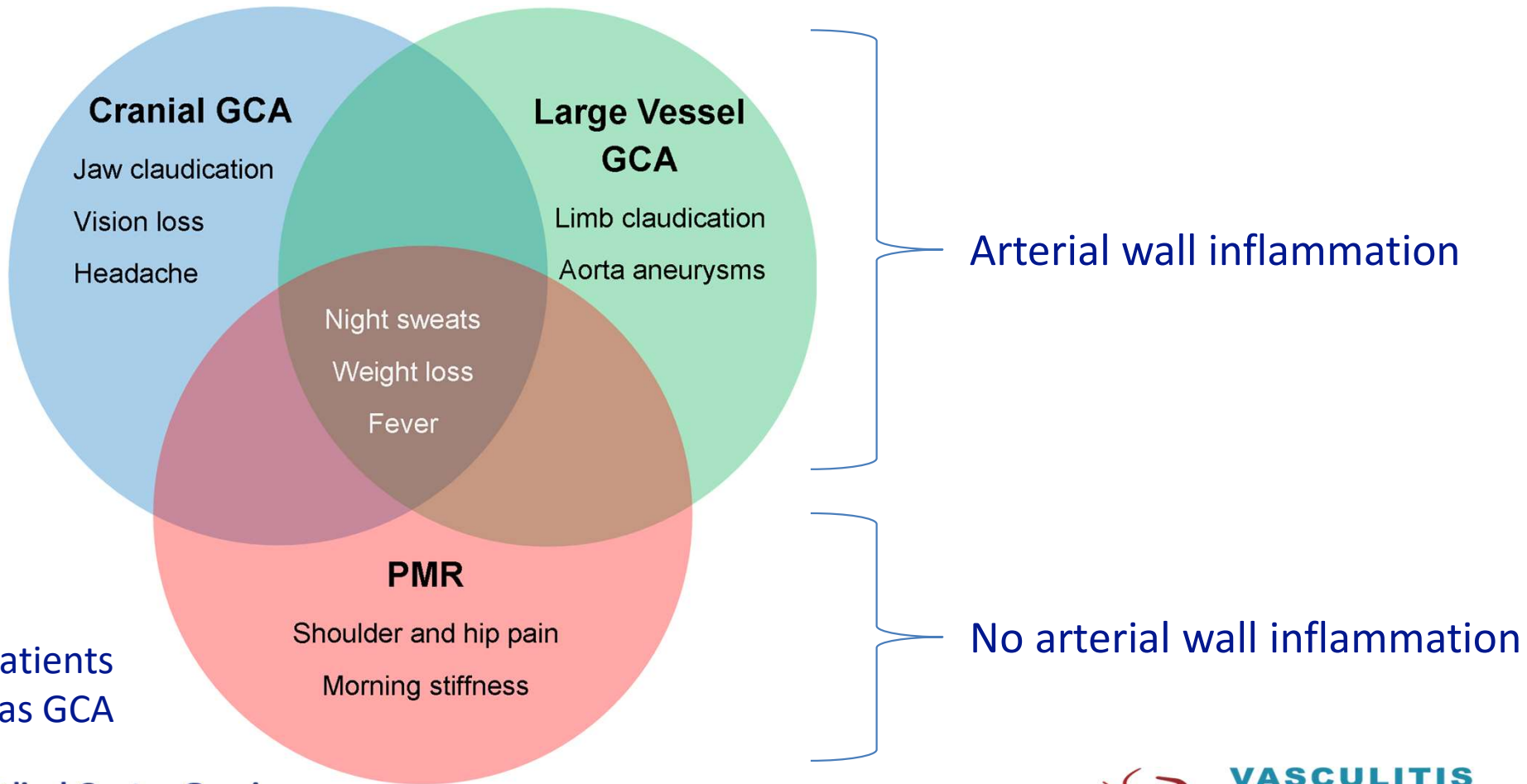
Biomarkers in the era of targeted therapy in giant cell arteritis and polymyalgia rheumatica: is it possible to replace acute-phase reactants?

Guillermo Carvajal Alegria, Mathilde Nicolas, Yannick van Sleen

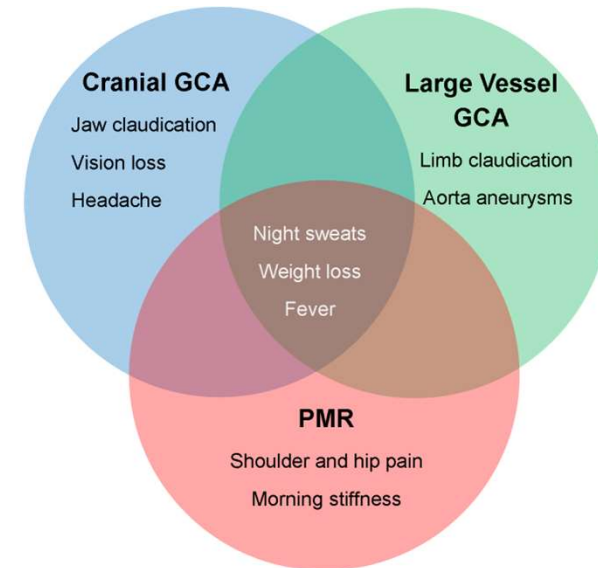# GPSD: GCA-PMR Spectrum Disease

Clinical need I:
Isolated PMR or overlapping GCA?

- Patient presenting with PMR symptoms
  - *No headache? Then it is just isolated PMR*
  - *Patient looks feverish, must be overlapping GCA*
  - *Ultrasound of temporal artery is normal, so clearly just PMR*
  - *High CRP = high risk of GCA*

- Why is it important to know the difference?
  - Complications of GCA
  - Side-effects of high-dose glucocorticoids
  - Different new treatment options

Cranial GCA
Jaw claudication
Vision loss
Headache

Large Vessel GCA
Limb claudication
Aorta aneurysms

Night sweats
Weight loss
Fever

PMR
Shoulder and hip pain
Morning stiffness

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Improving diagnosis for GCA and PMR

- Ideal situation: one easy biomarker that confidently identifies overlapping GCA in PMR patients
  - High sensitivity: identifies most GCAs
  - High specificity: does not select many isolated PMR

- PMR patients with high risk of GCA can be subjected to further diagnostic tests

- Which biomarker would be suited to aid the diagnosis?
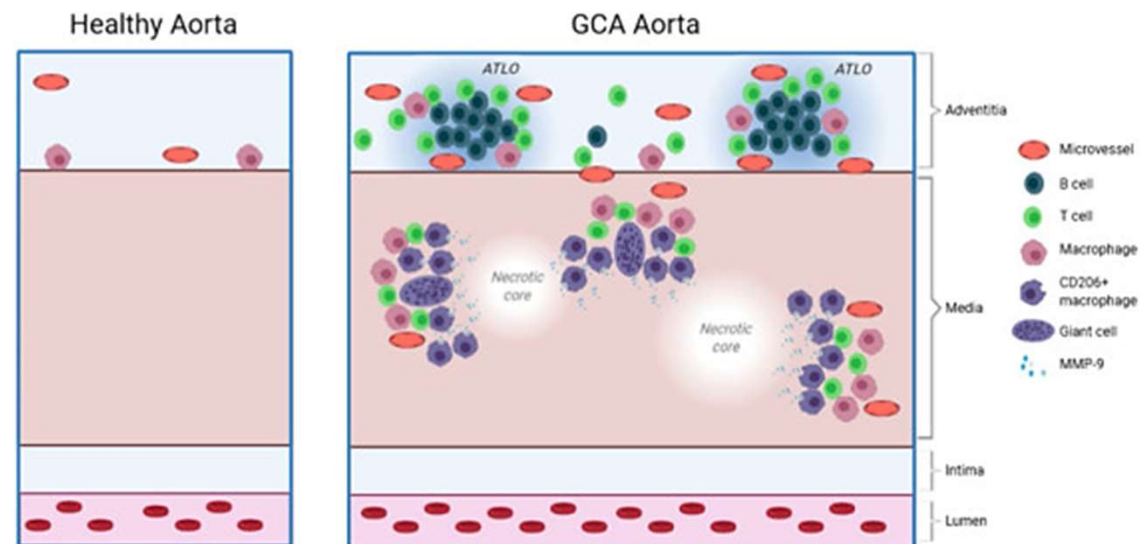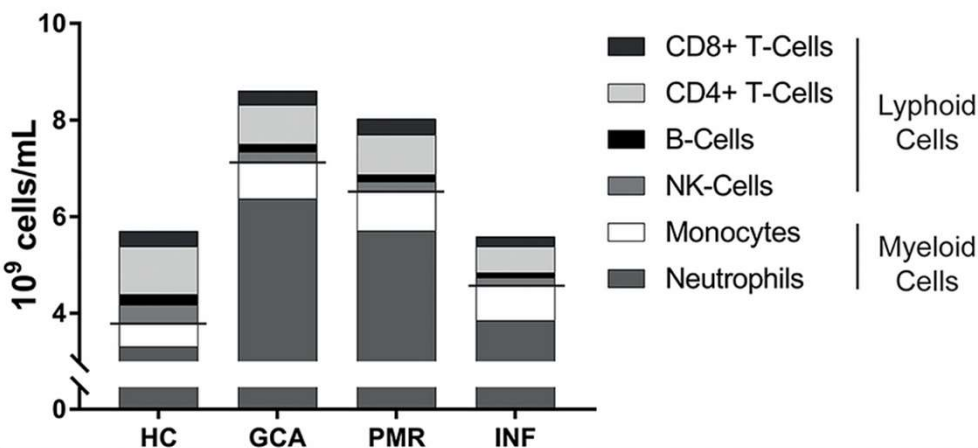
Immunopathology of GCA and PMR

- ## In the blood
  - 'Myeloid shift'
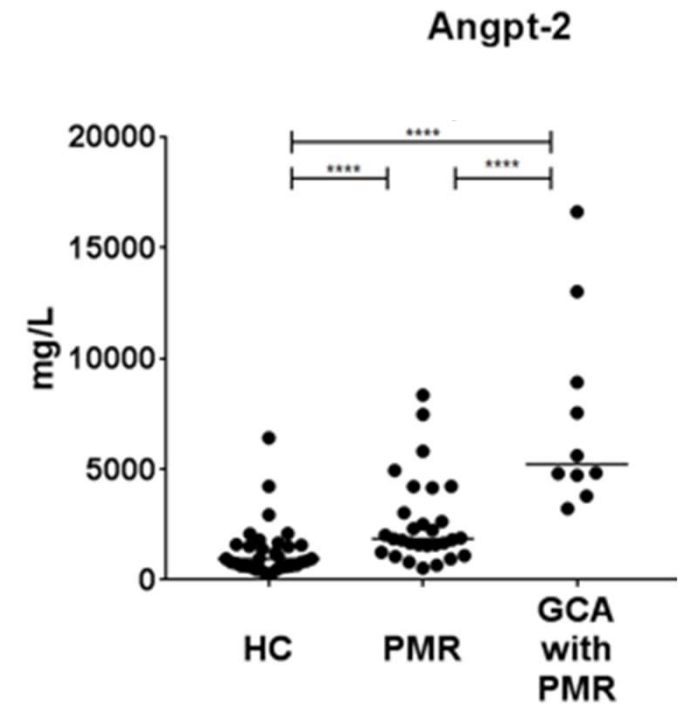 - Acute-phase response

- ## In the tissues
  - Immune cell infiltration
 - New small vessel formation

Isolated PMR or overlapping GCA: First results

- Comparing isolated PMR with GCA+PMR patients
  - All treatment-naïve
  - PET-CT, ultrasound and long-term follow-up
  - Quite a small population
    - Isolated PMR n=29
    - GCA+PMR n=10

Angpt-2

Isolated PMR or overlapping GCA: First results

- **Comparing isolated PMR with GCA+PMR patients**
  - All treatment-naïve
  - PET-CT, ultrasound and long-term follow-up
  - Quite a small population
    - Isolated PMR n=29
    - GCA+PMR n=10

- **CRP does not help at all**

- **High ESR associates with overlapping GCA**

- **Angiopoeitin-2 performs much better!**

- **Still preliminary → validation is needed!**

ROC curves

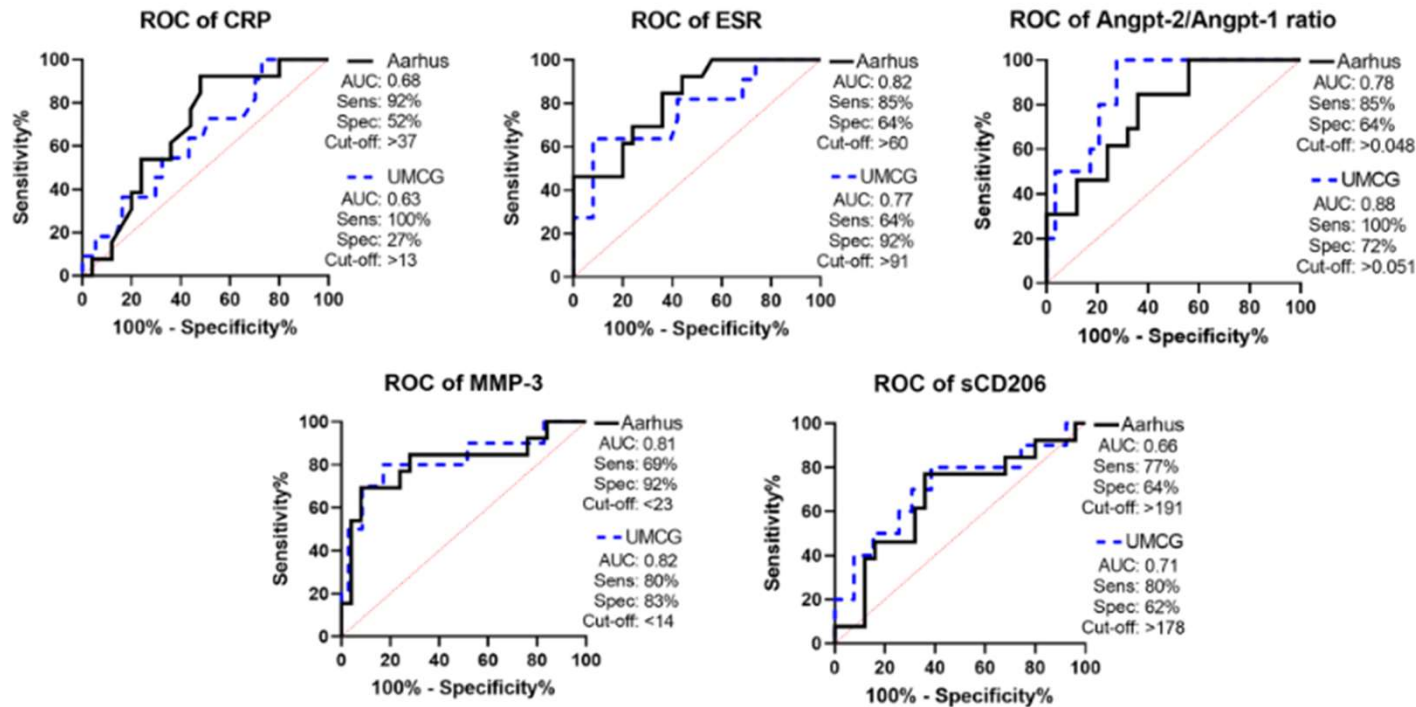*van Sleen et al, 2020, Rheumatology*
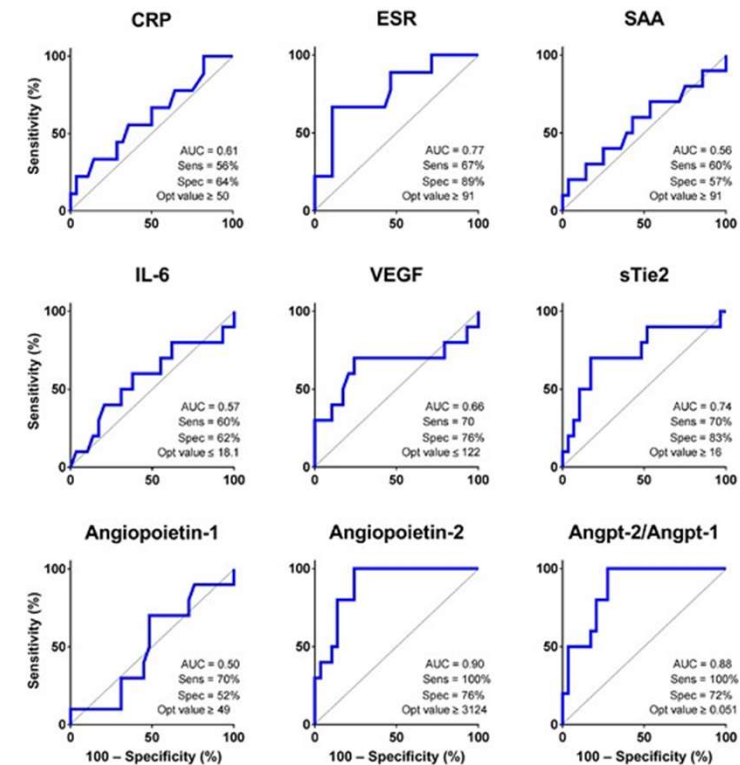
Validation cohort / *Valideringskohorte*

- **GCA/PMR cohort in Aarhus, Denmark**
  - Treatment-naïve
  - Extensive PET-CT examination
  - Relatively comparable population

- **Measurements of biomarkers in serum**
  - Repeat of previous data
  - Selection of new biomarkers
    - Also measured in Groningen

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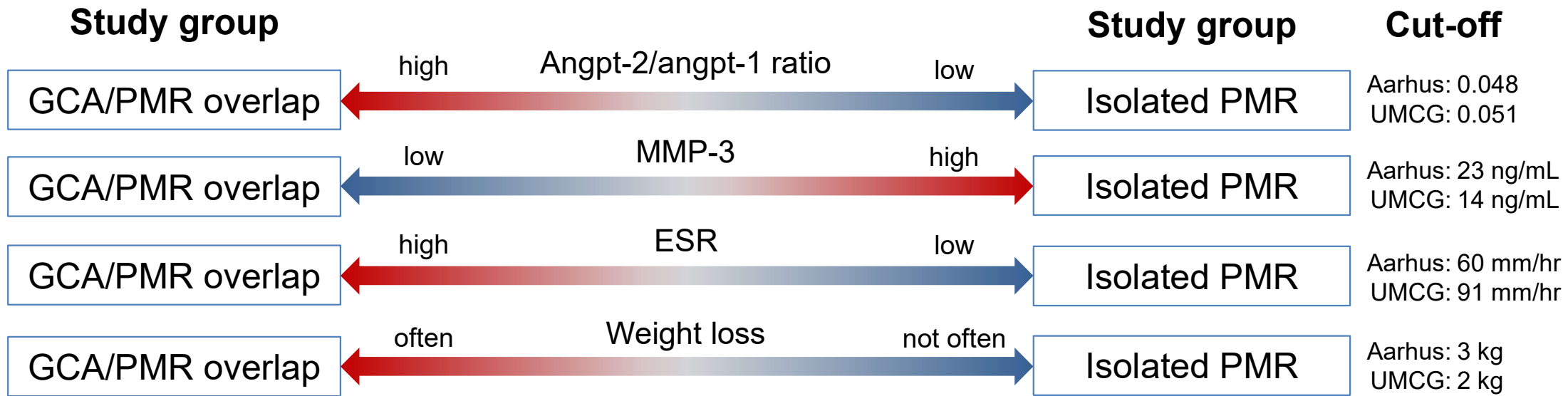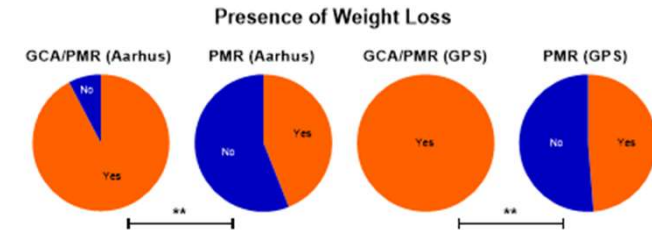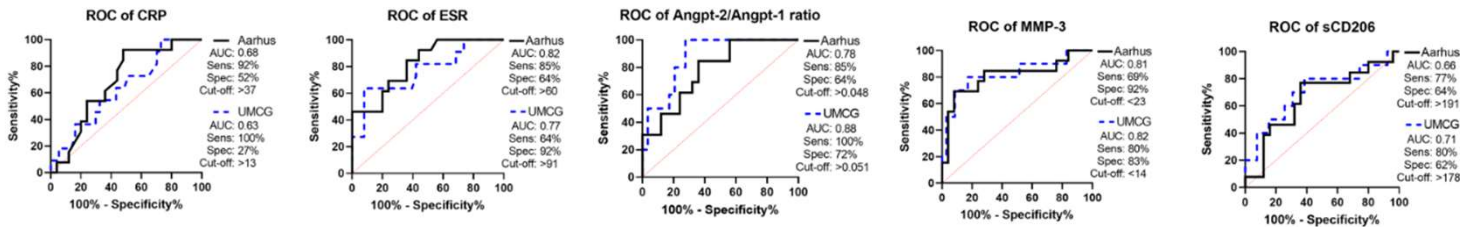
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Which biomarker works well to detect GCA in Groningen ánd in Aarhus?

- High ESR, high Angiopoietin-2/1 ratio, high sCD206
- Low MMP-3

Which biomarker or symptom works well to detect GCA in Groningen ánd in Aarhus?

Study group			Study group	Cut-off
	high	Angpt-2/angpt-1 ratio low		Aarhus: 0.048
GCA/PMR overlap		→	Isolated PMR	UMCG: 0.051
	low	MMP-3 high		Aarhus: 23 ng/mL
GCA/PMR overlap		→	Isolated PMR	UMCG: 14 ng/mL
	high	ESR low		Aarhus: 60 mm/hr
GCA/PMR overlap		→	Isolated PMR	UMCG: 91 mm/hr
	often	Weight loss not often		Aarhus: 3 kg
GCA/PMR overlap		→	Isolated PMR	UMCG: 2 kg

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van Sleen et al, 2022, Arthritis Research & Therapy

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Clinical need II:
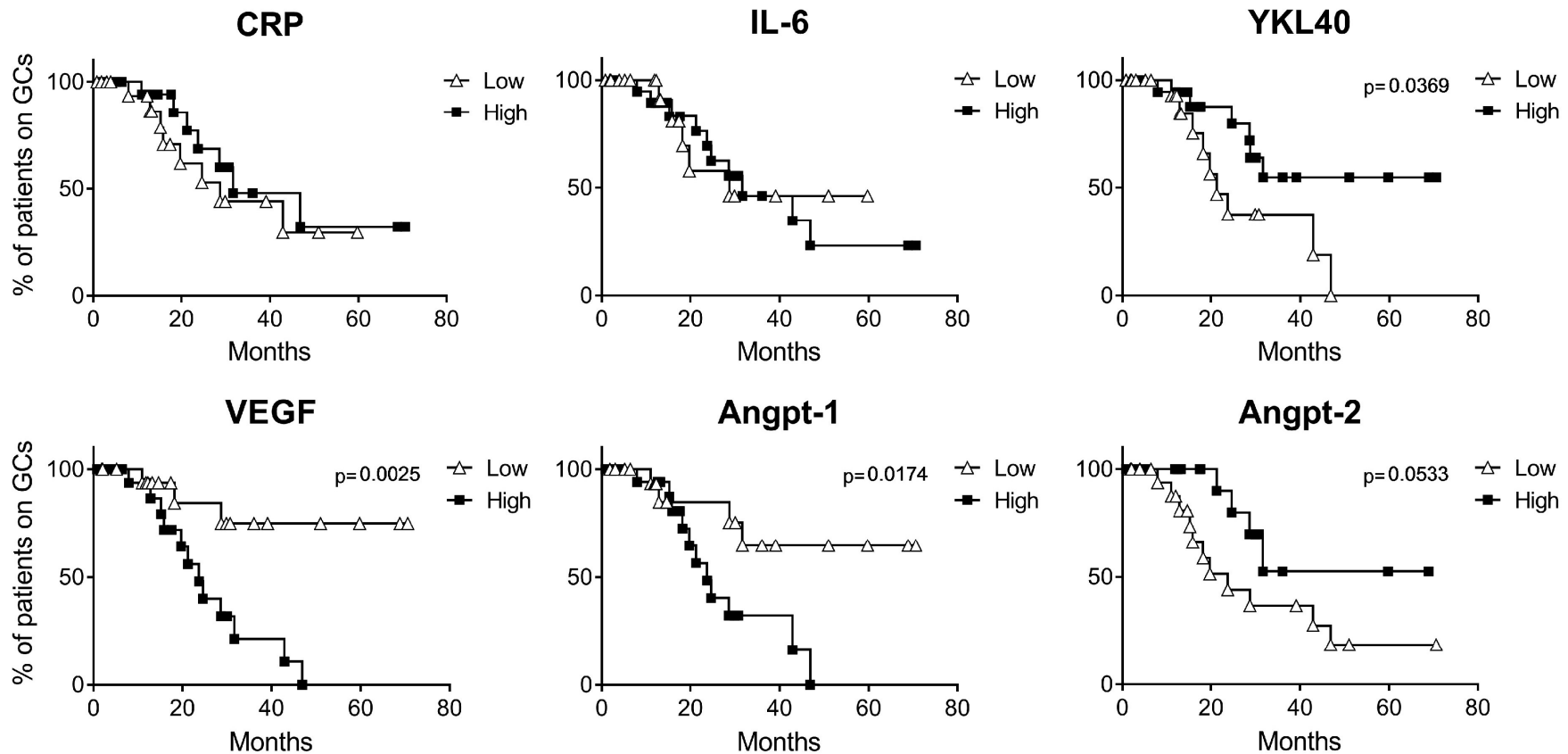# Can we predict which patients respond well to treatment?

- There is a wide variation in treatment responses for GCA and PMR patients
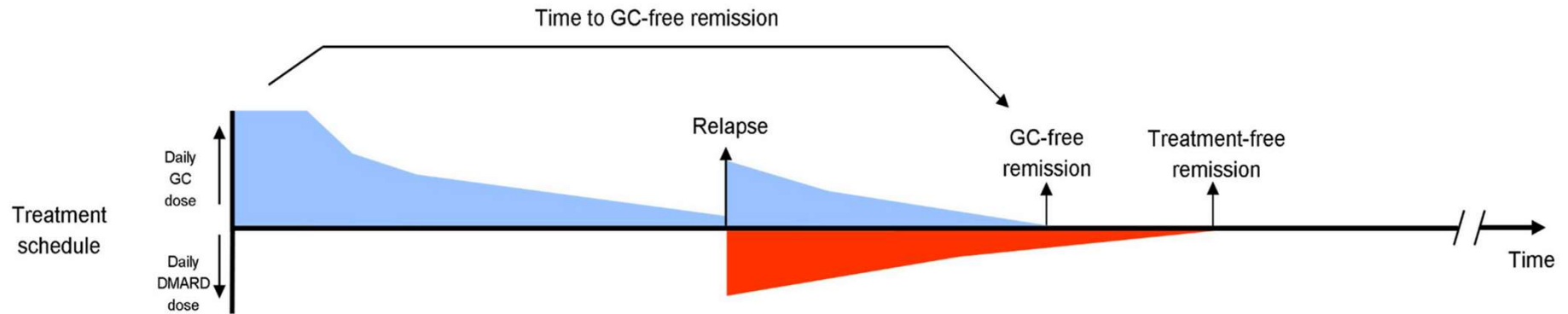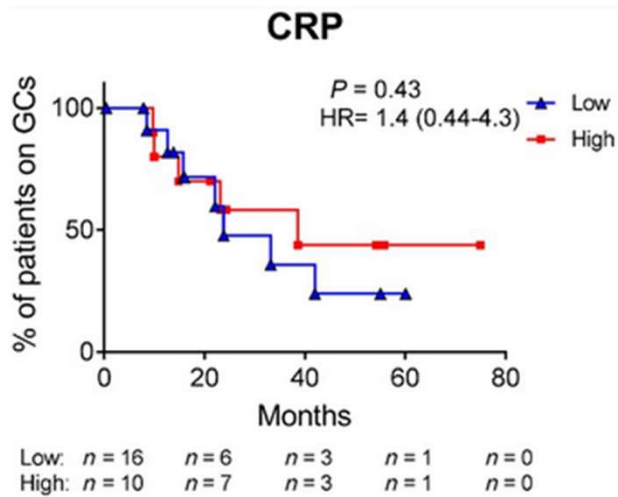

- Can we, at diagnosis, identify patients with favourable or unfavourable disease course?
  - Reducing GC use
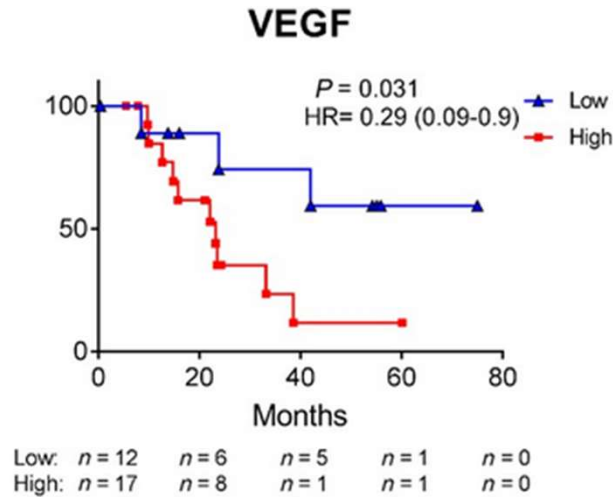 - Selecting patients for other/additional treatment options

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Predicting time to glucocorticoid-free remission at GCA diagnosis

van Sleen et al, 2019, Rheumatology

Similar patterns in PMR

van Sleen et al, 2020, Rheumatology
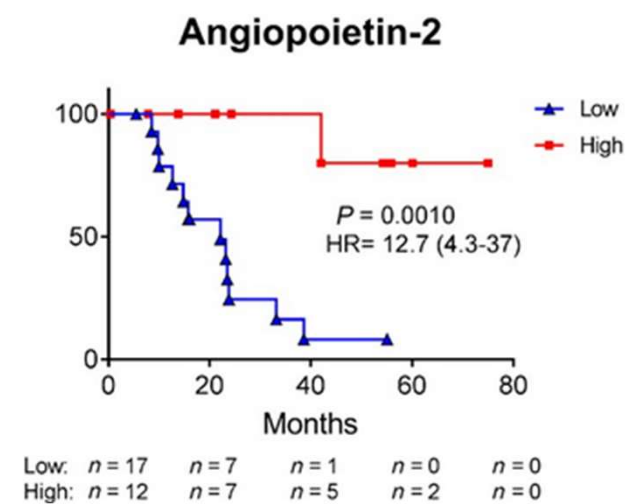
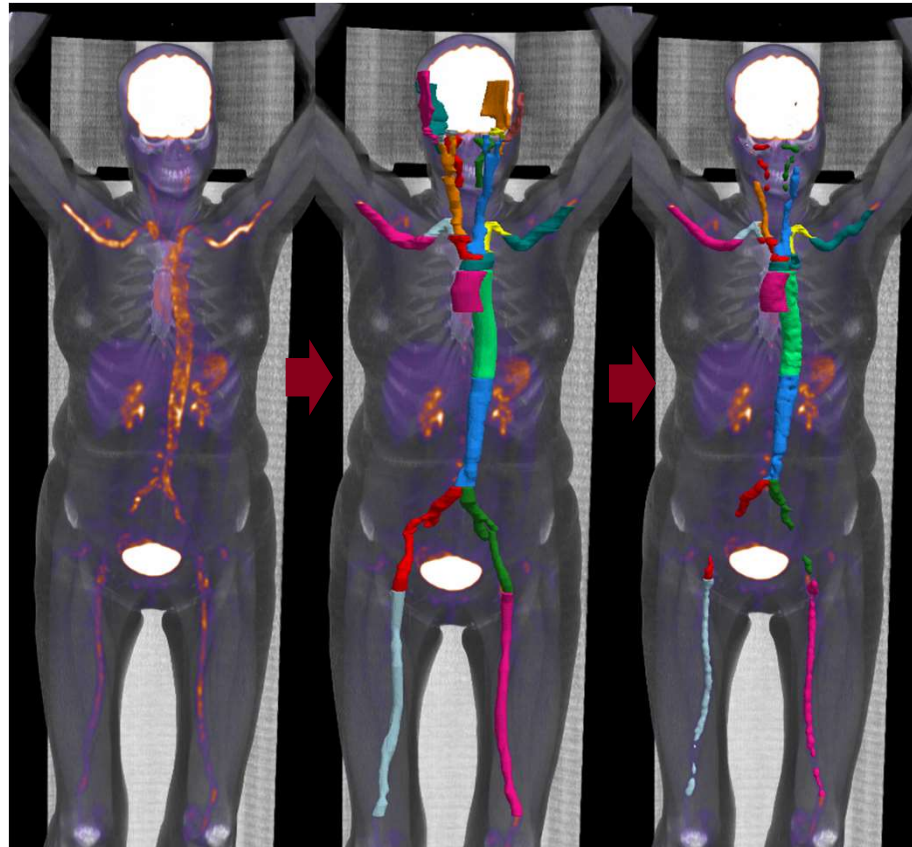# Markers of angiogenesis and innate immune activation are useful diagnostic and prognostic biomarkers

- Clinical need I: Isolated PMR or overlapping GCA?
  - High Angiopoietin-2/1 ratio, ESR
  - Low MMP-3
- Clinical need II: Can we predict which patients respond well to treatment?
  - High VEGF, Angiopoietin-1 levels
  - Low YKL-40, Angiopoietin-2 levels

- What's next?

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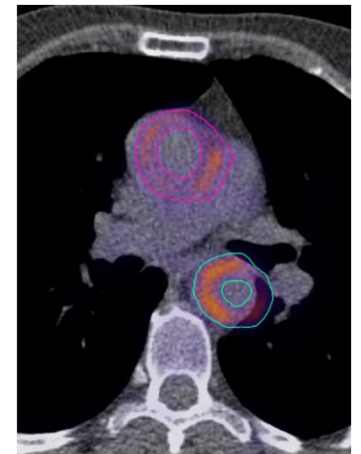**VASCULITIS EXPERTISE CENTER GRONINGEN**

# Measuring Arterial Inflammation on PET-CT: Total lesion glycolysis

- Quantification of inflamed arteries on FDG-PET-CT in GCA patients

- Calculates a score that both indicates:
  - How much of the arteries is inflamed
  - How strongly those parts are inflamed

Metabolic Activity x Lesion Volume

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Low total lesion glycolysis (TLG) at diagnosis predicts an unfavorable treatment response in GCA patients
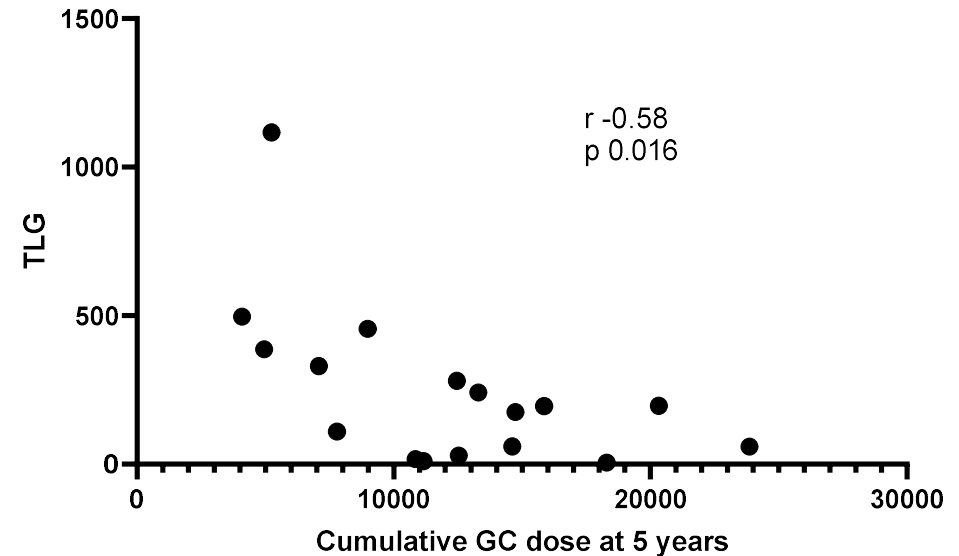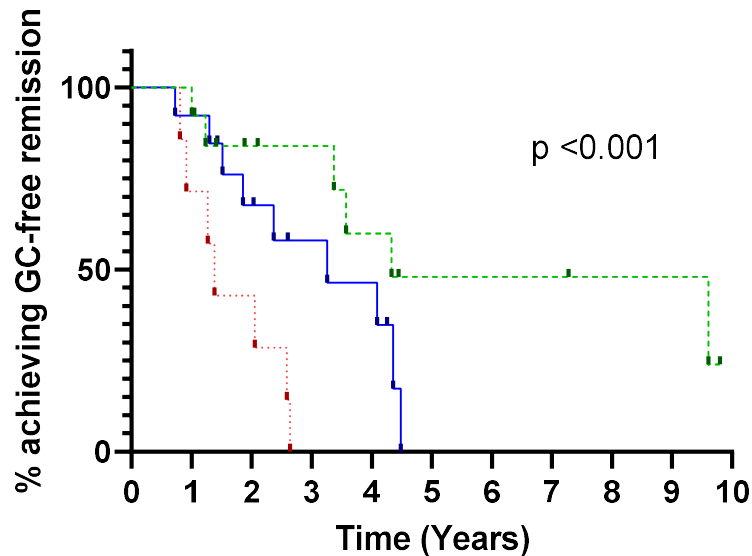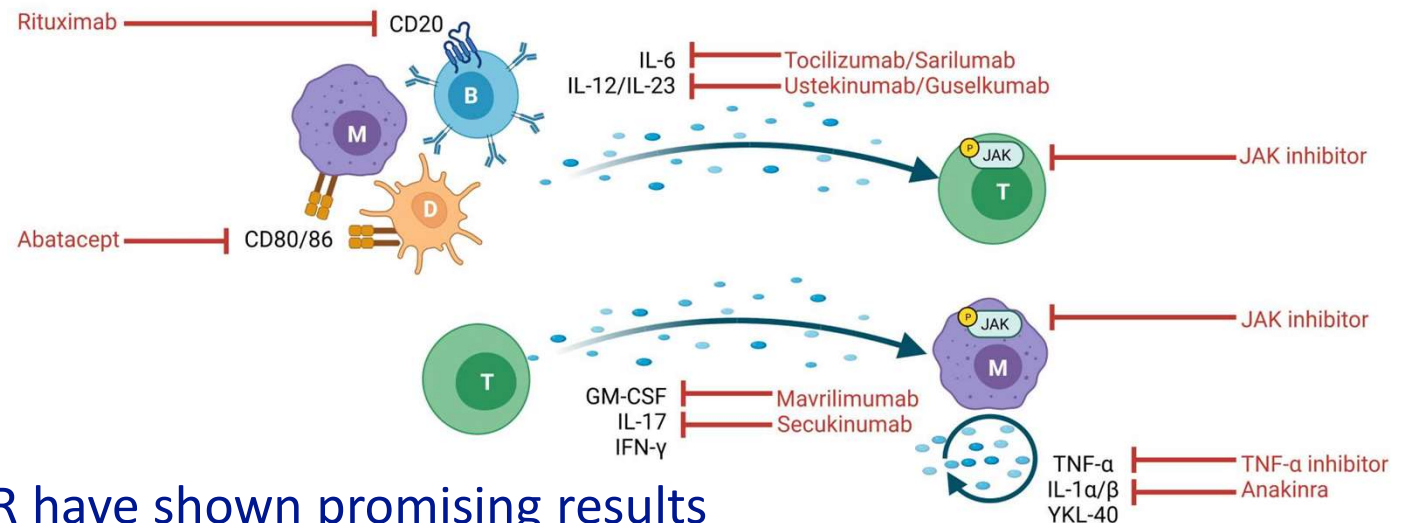

- Counterintuitive finding: more inflammation at diagnosis predicts favourable response to glucocorticoids
  - Highly inflammatory disease vs smouldering, tissue remodeling disease?

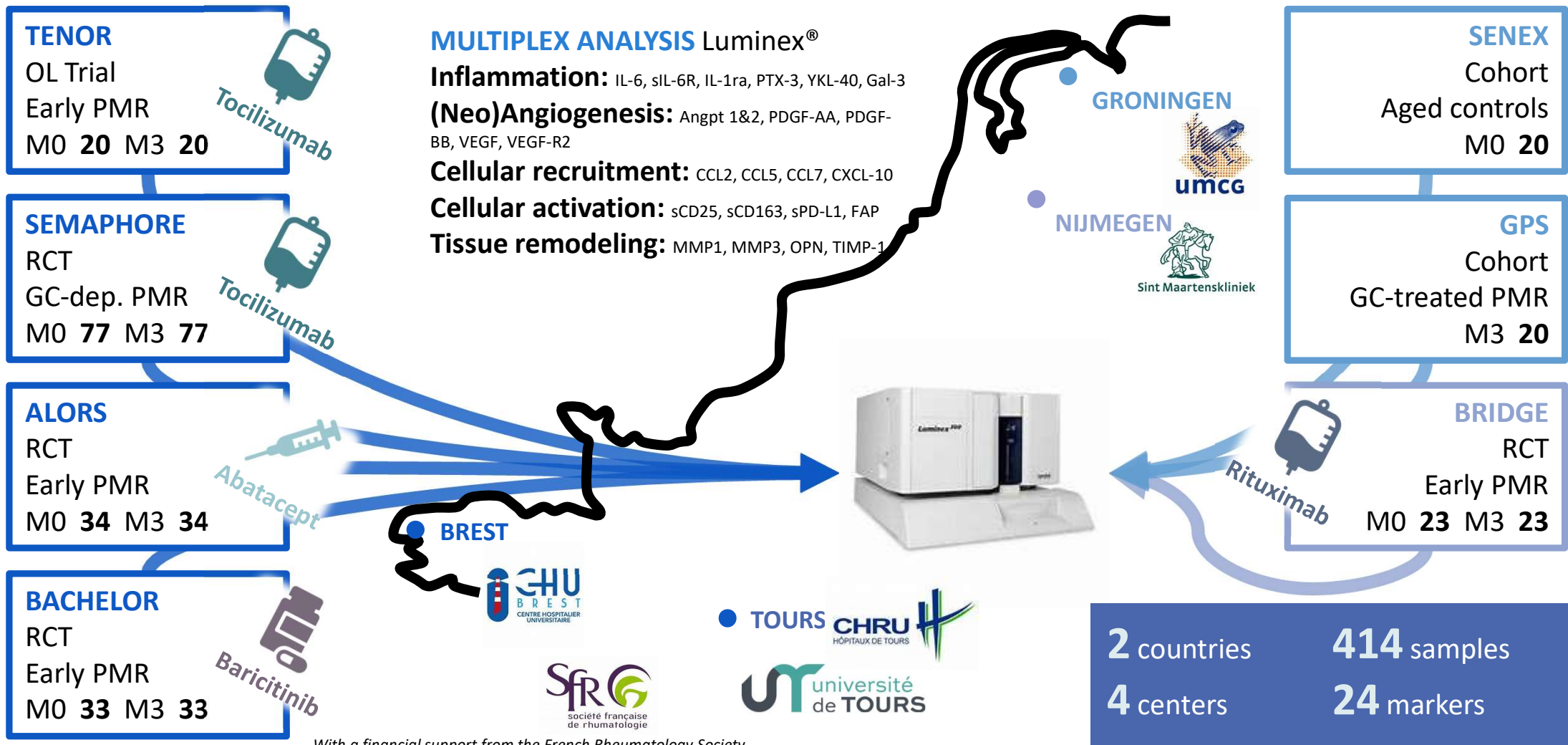# Biomarkers in the era of targeted therapy in GCA and PMR

- New biological therapies are becoming available for both GCA and PMR

- Clinical trials on PMR have shown promising results
- Can biomarker help us here too?
  - Predicting treatment response
  - Monitoring effect of treatment on inflammation

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Sandovic et al, 2022, RMD Open

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BIOPICA: Biomarkers for polymyalgia rheumatica

TENOR
OL Trial
Early PMR
M0 **20** M3 **20**
Tocilizumab

SEMAPHORE
RCT
GC-dep. PMR
M0 **77** M3 **77**
Tocilizumab

ALORS
RCT
Early PMR
M0 **34** M3 **34**
Abatacept

BACHELOR
RCT
Early PMR
M0 **33** M3 **33**
Baricitinib

MULTIPLEX ANALYSIS Luminex®
Inflammation: IL-6, sIL-6R, IL-1ra, PTX-3, YKL-40, Gal-3
(Neo)Angiogenesis: Angpt 1&2, PDGF-AA, PDGF-BB, VEGF, VEGF-R2
Cellular recruitment: CCL2, CCL5, CCL7, CXCL-10
Cellular activation: sCD25, sCD163, sPD-L1, FAP
Tissue remodeling: MMP1, MMP3, OPN, TIMP-1

GRONINGEN
umcg

NIJMEGEN
Sint Maartenskliniek

SENEX
Cohort
Aged controls
M0 **20**

GPS
Cohort
GC-treated PMR
M3 **20**

BRIDGE
RCT
Early PMR
M0 **23** M3 **23**
Rituximab

BREST
CHU BREST
CENTRE HOSPITALIER UNIVERSITAIRE

TOURS
CHRU HÔPITAUX DE TOURS

SFR
société française de rhumatologie

université de TOURS

With a financial support from the French Rheumatology Society

2 countries   **414** samples
4 centers   **24** markers

BIOPICA: First results

2. Five different patterns

1. Reliable data

A strong correlation between Multiplex and ELISA for the IL-6

IL-6 in ELISA and LUMINEX in the TENOR study
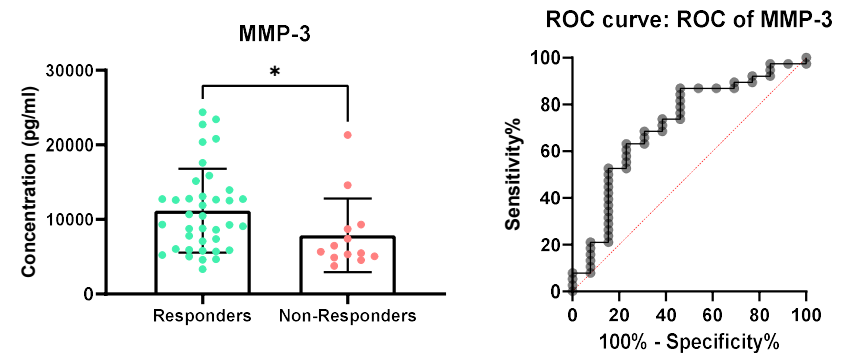
r = 0.835
p < 0.0001

The results replicate some previous observations (IL-6, VEGF, MMP-3, YKL-40, Angpt-2...)
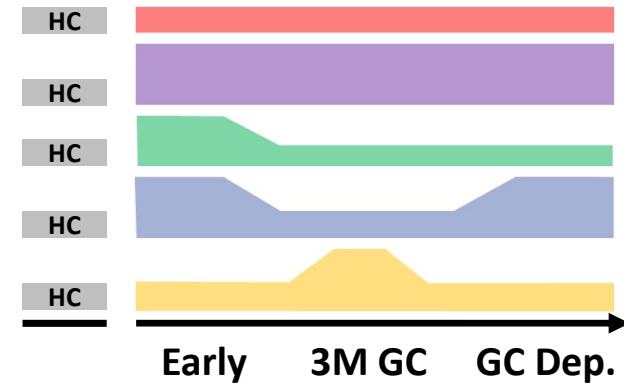
3. First candidate for predictive biomarker


More results to come...

Designing future biomarker studies for GCA and PMR: Points to consider

- Scientific question: what is the aim of the study
  - Diagnosis
  - Prognosis
    - GCs or targeted drugs?
    - Risk of complications
  - Monitoring of disease activity / drug monitoring
    - Relapse definition
- Biomarkers to chose
  - One, more or many
  - Based on pathogenesis

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Designing future biomarker studies for GCA and PMR: Points to consider

- **Choice of material**

- **Study population**
  - Treatment-naïve?
  - Controls: healthy, infection, look-alike
  - Study size

- **Validation**
  - Splitting cohorts
  - Separate cohorts

- **GCA and PMR patients deserve better!**

Physical functioning

Carvajal Alegria et al, 2023, Frontiers in Immunlogy
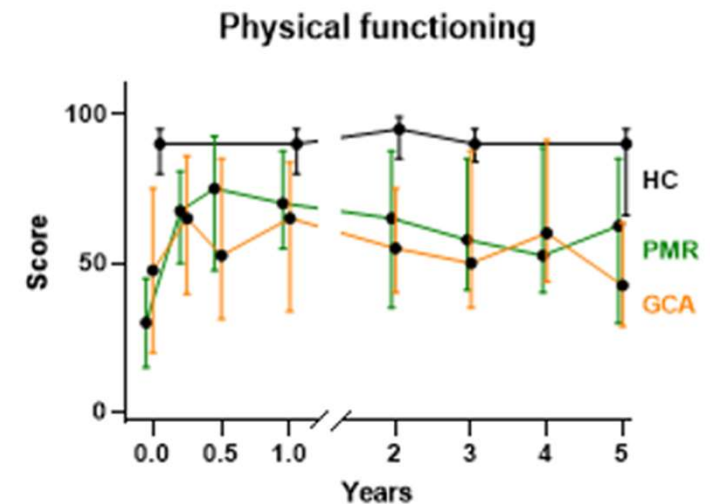
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