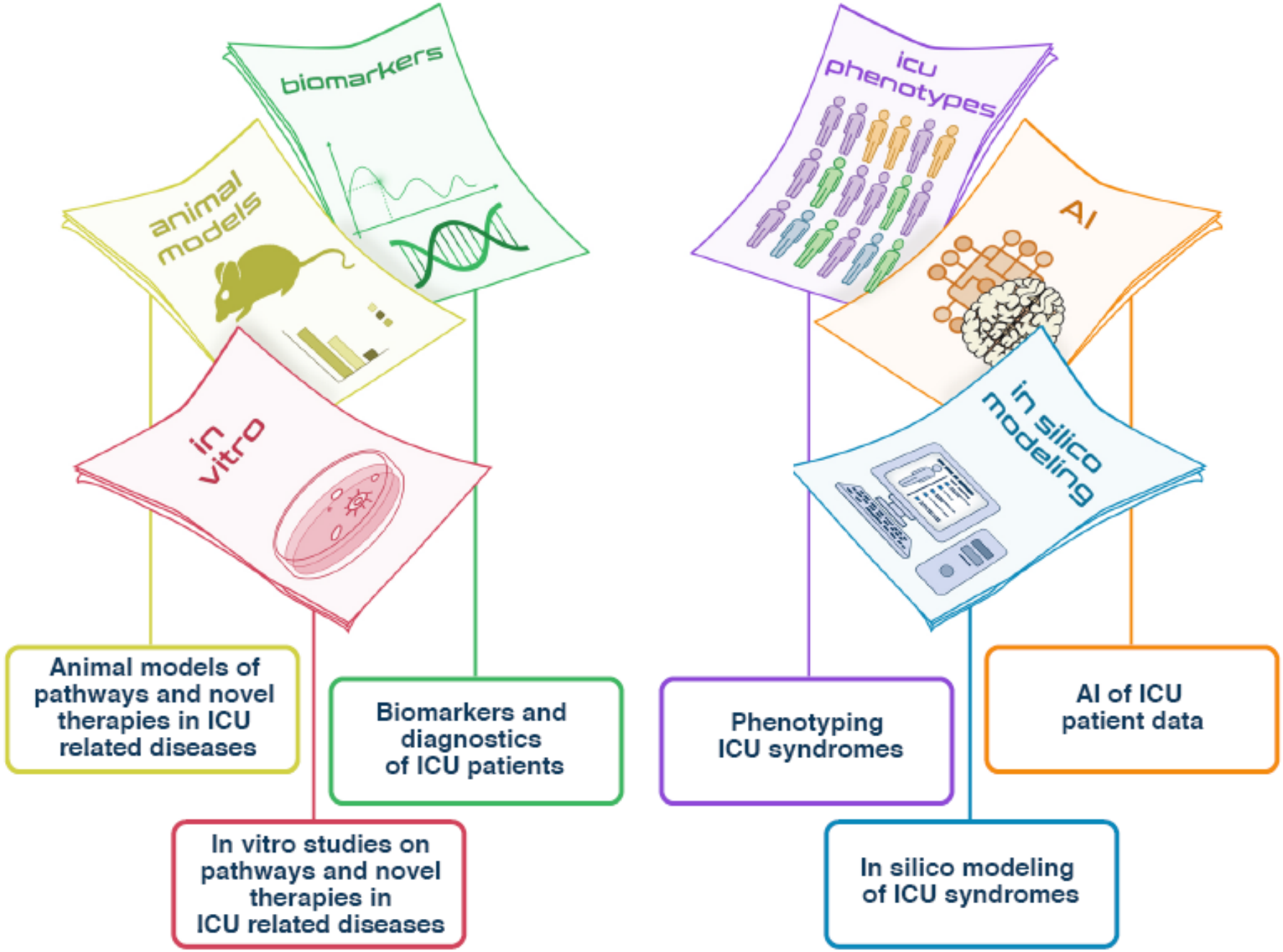
Year in review ‘experimental’
NVIC 2023

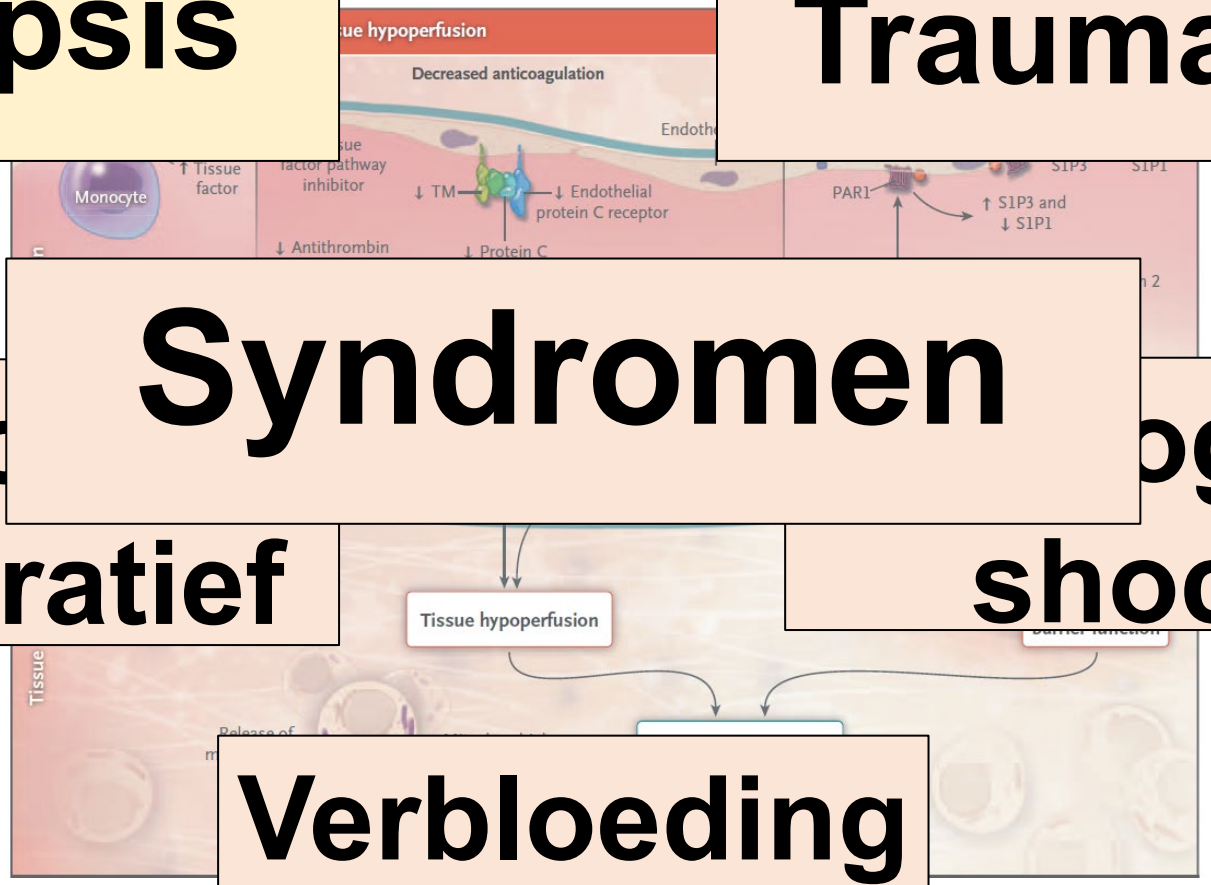
Disclosure belangen spreker	
Geen (potentiële) belangenverstrengeling	N.v.t.
Voor bijeenkomst mogelijk relevante relaties	N.v.t.
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk…	N.v.t.


biomarkers
animal models
in vitro
icu phenotypes
AI
in silico modeling
Animal models of pathways and novel therapies in ICU related diseases
Biomarkers and diagnostics of ICU patients
In vitro studies on pathways and novel therapies in ICU related diseases
Phenotyping ICU syndromes
AI of ICU patient data
In silico modeling of ICU syndromes

Mijn eerste benoeming

Sepsis

Trauma



Syndromen

Po operatief

ogene shock

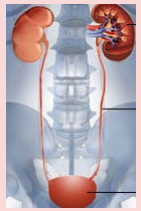
Verbloeding

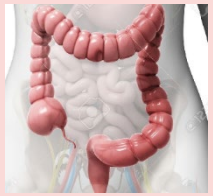
Gram-neg

Gram-pos

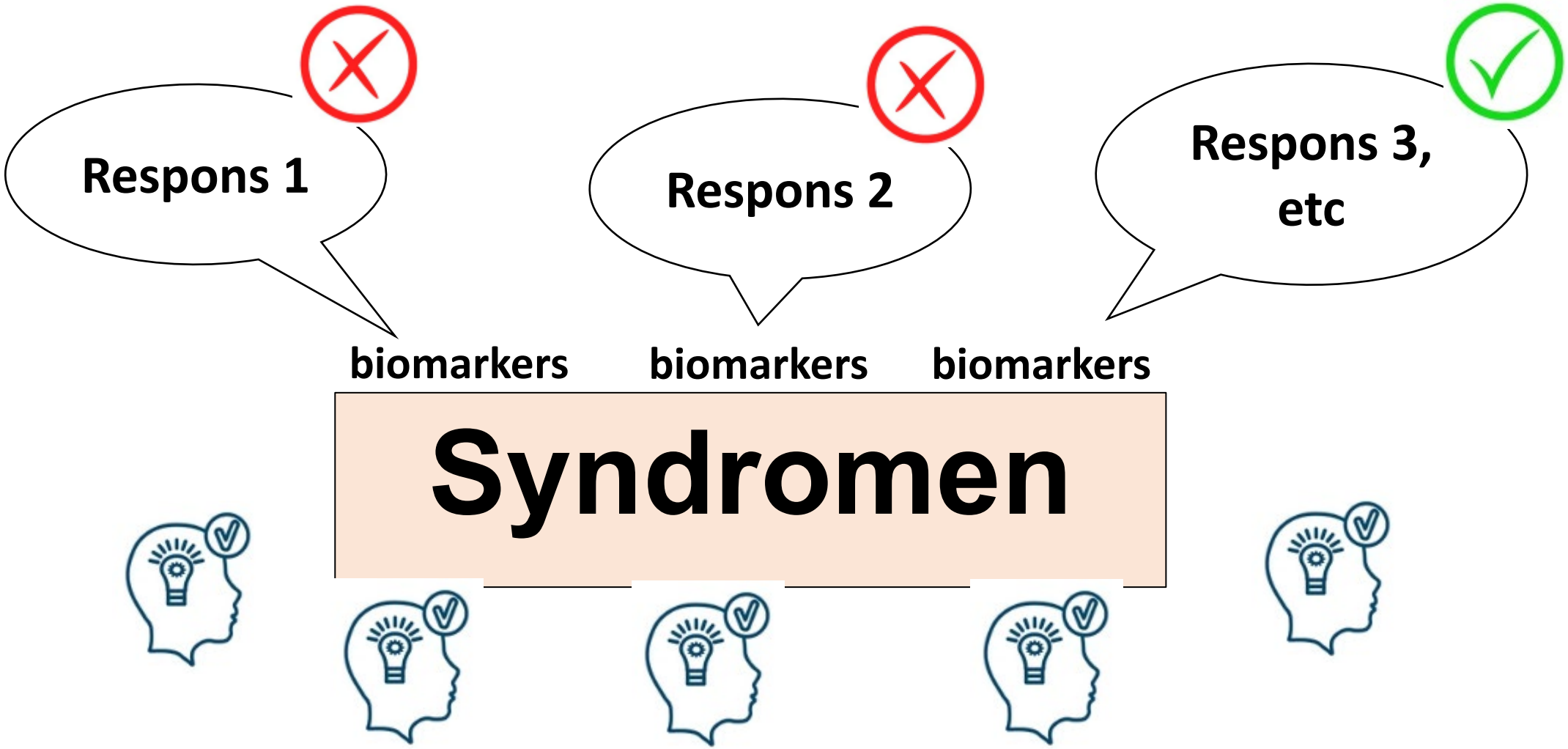
Fungus

Sepsis





Nieuwe therapie



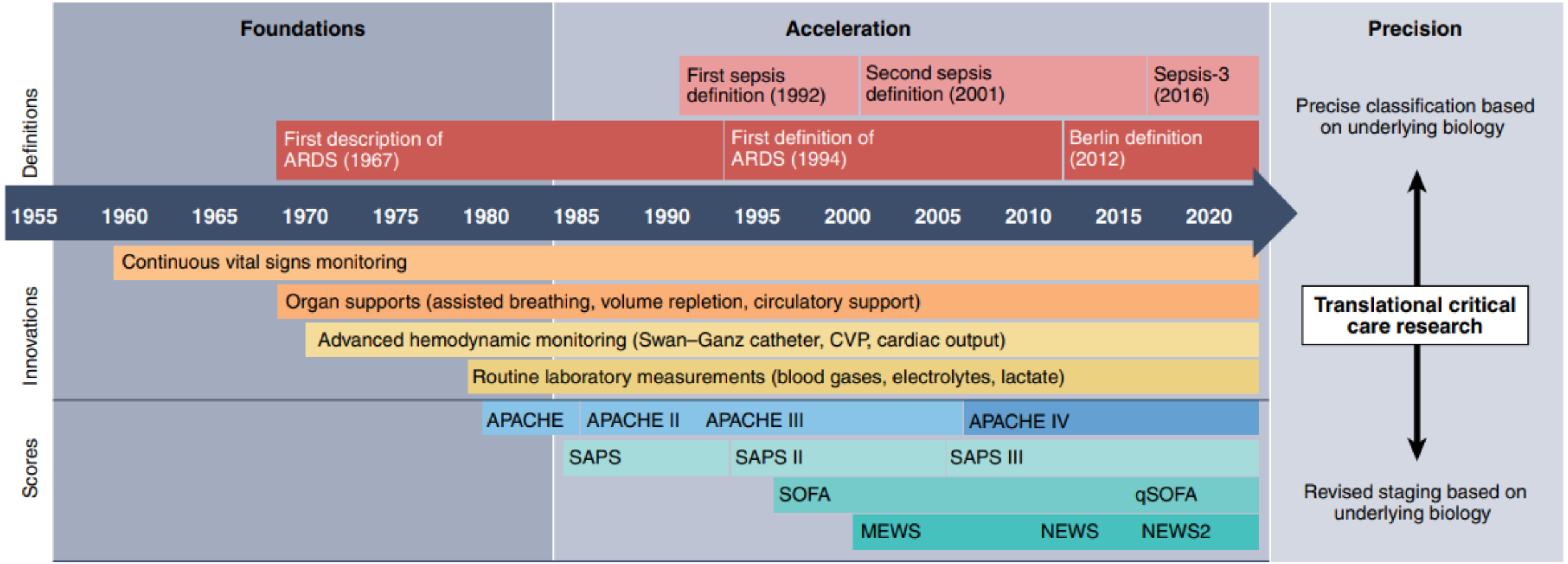
nature medicine

PERSPECTIVE

https://doi.org/10.1038/s41591-022-01843-x

Redefining critical illness

2022

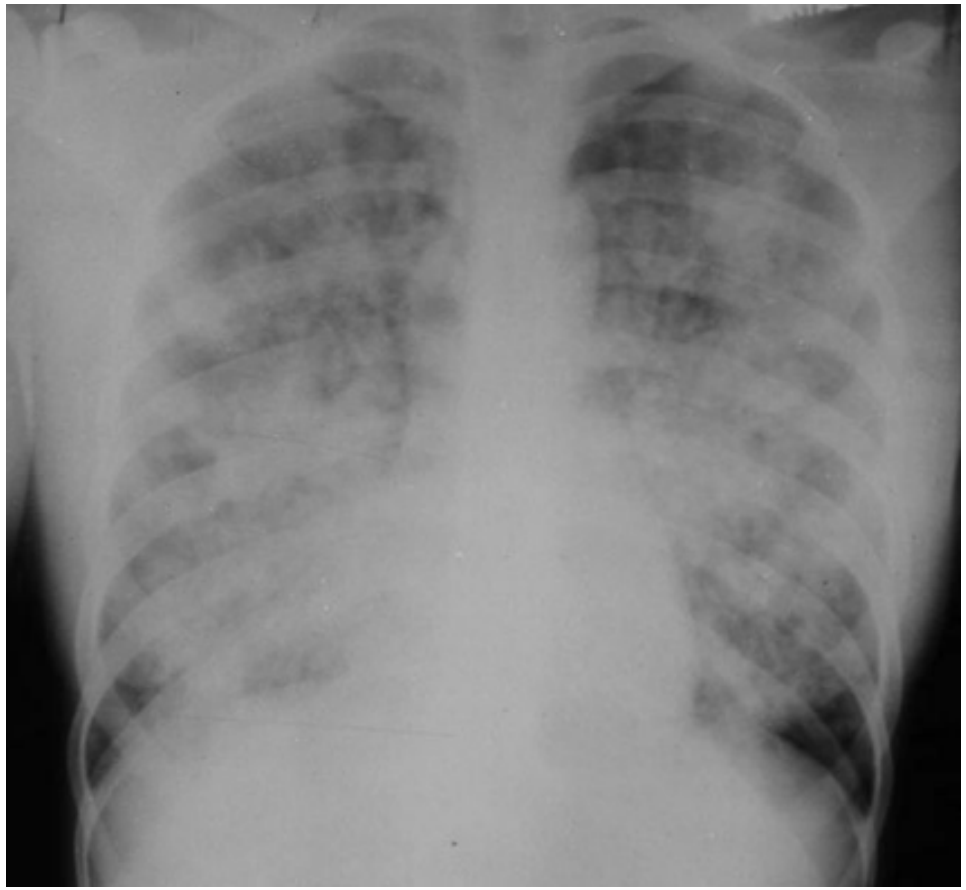

Foundations
Acceleration
Precision
Definitions
Innovations
Scores
First sepsis definition (1992)
Second sepsis definition (2001)
Sepsis-3 (2016)
First description of ARDS (1967)
First definition of ARDS (1994)
Berlin definition (2012)
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
2020
Continuous vital signs monitoring
Organ supports (assisted breathing, volume repletion, circulatory support)
Advanced hemodynamic monitoring (Swan–Ganz catheter, CVP, cardiac output)
Routine laboratory measurements (blood gases, electrolytes, lactate)
APACHE
APACHE II
APACHE III
APACHE IV
SAPS
SAPS II
SAPS III
SOFA
qSOFA
MEWS
NEWS
NEWS2
Precise classification based on underlying biology
Translational critical care research
Revised staging based on underlying biology

2019

- Woman 65 yo
- Fever, cough, dyspnea
- Hypoxemia

Treatment:

- Antibiotics, OK.
- Any other thoughts….?
  - How much fluid?
  - Steroids?
  - Anti-biologicals?

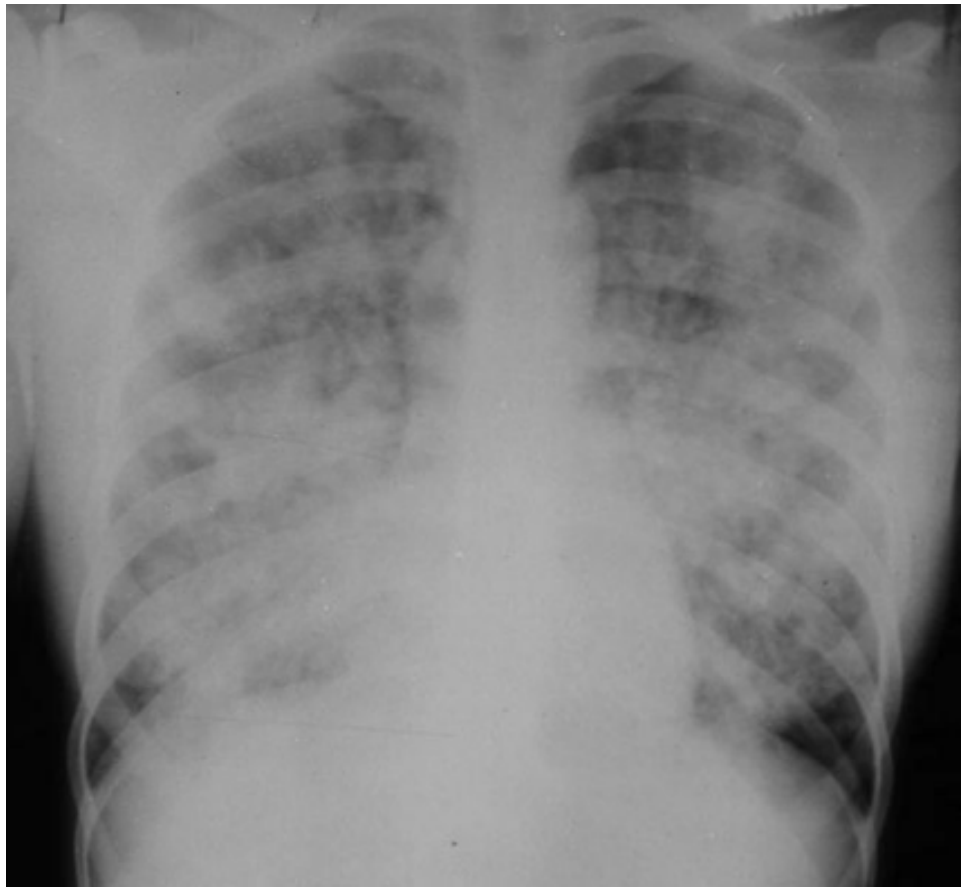


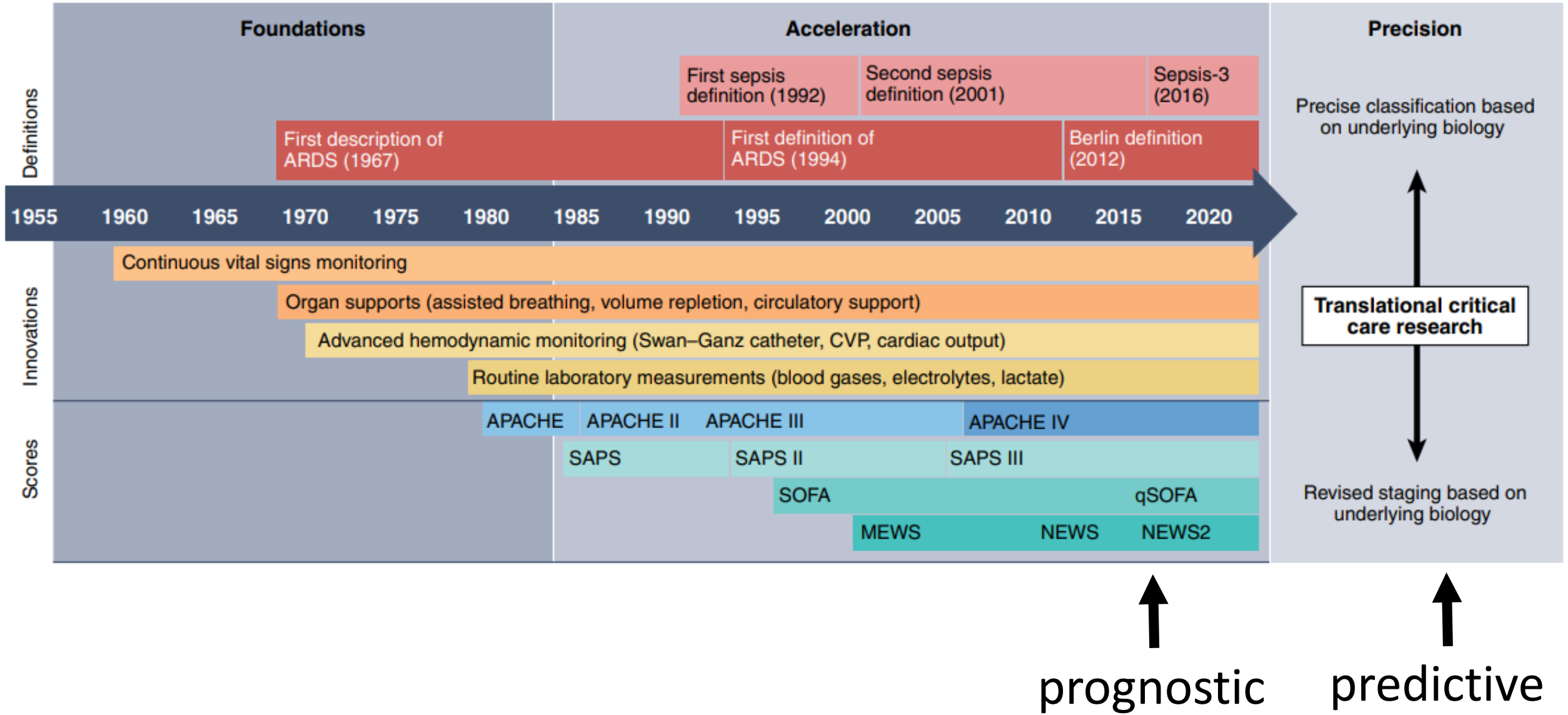
2021

- Woman 65 yo
- Fever, cough, dyspnea
- Hypoxemia

COVID +

- Steroids
- Anti-IL6
- No remdesivir
- No heparin

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APACHE II
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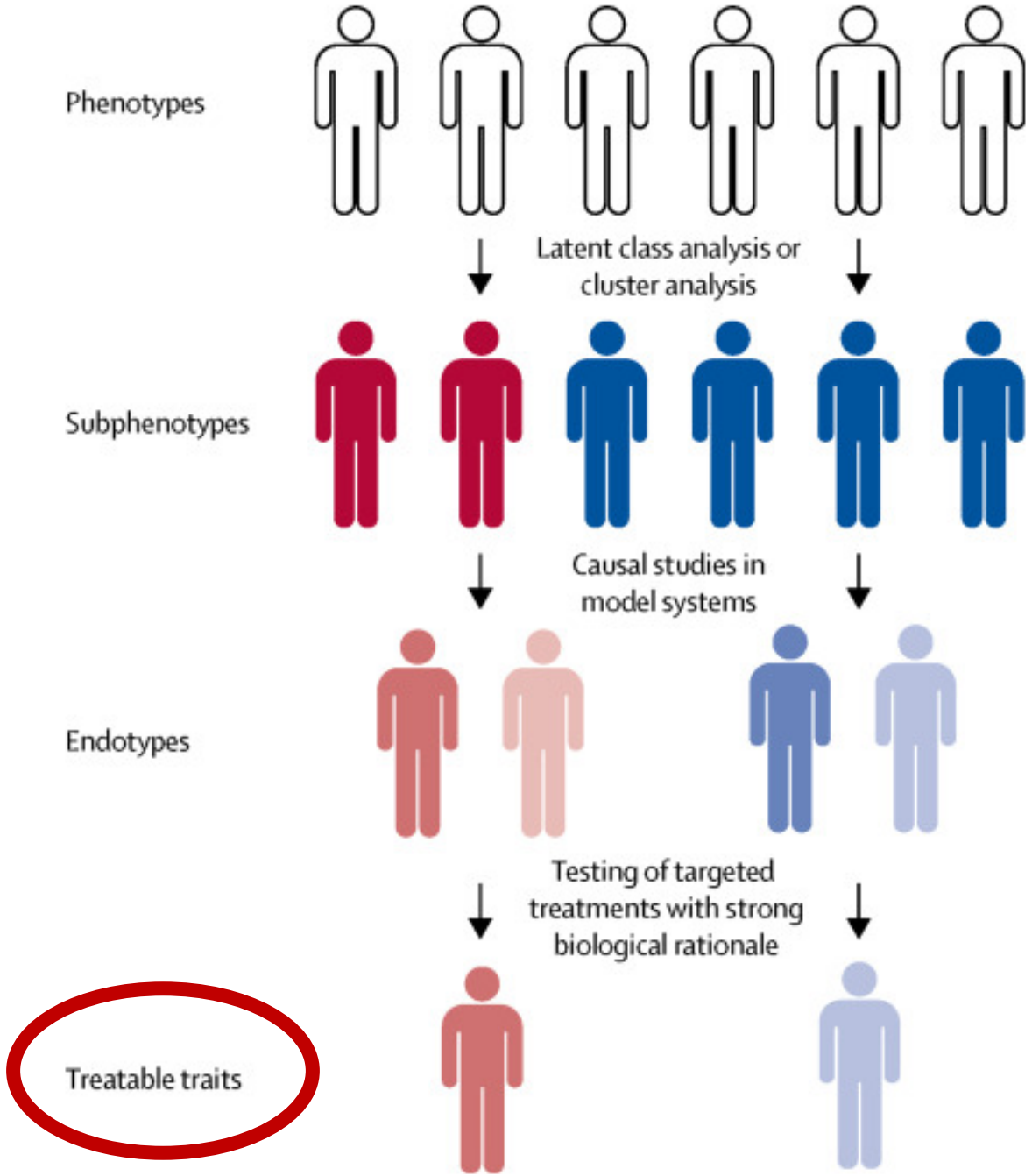
SAPS
SAPS II
SAPS III
SOFA
qSOFA
MEWS
NEWS
NEWS2
Precise classification based on underlying biology
Translational critical care research
Revised staging based on underlying biology
prognostic
predictive



Statistiek

COVID **DM**

Karakteristiek

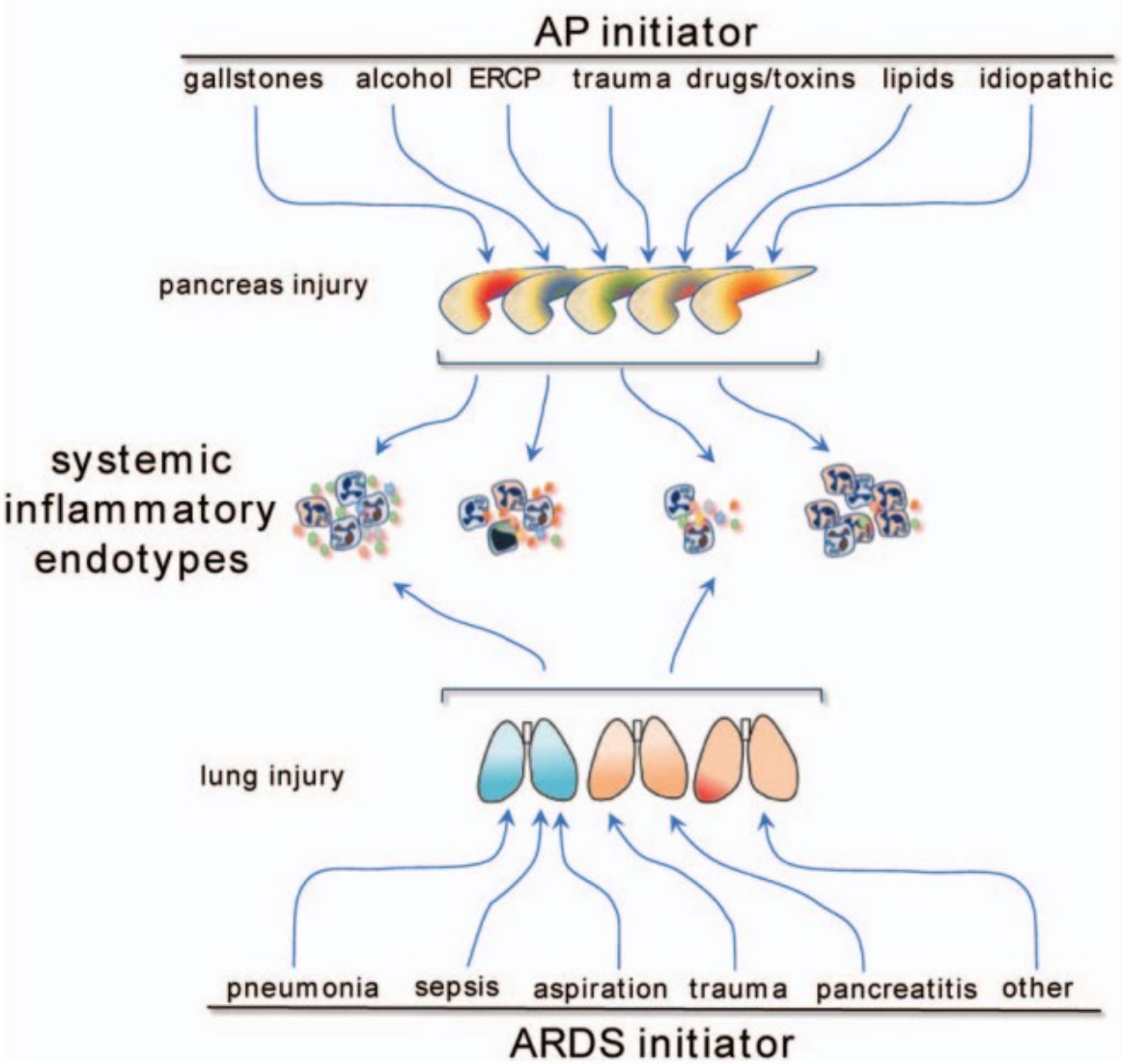
Mechanismen van ziekte

IL-6 **obesitas**

Therapie

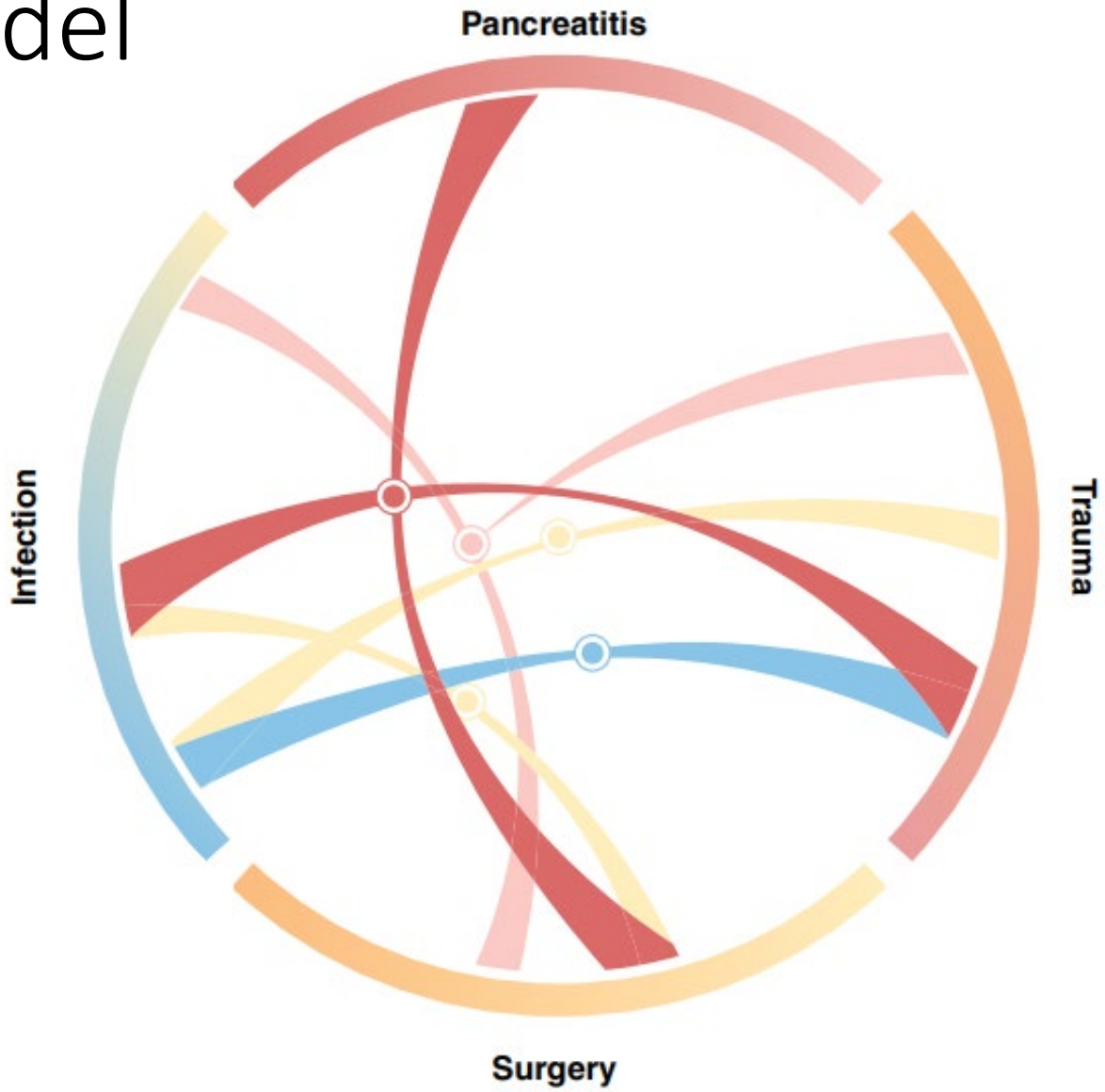
Toci **dieet**

Pancreatitis heeft dezelfde endotypes als ARDS



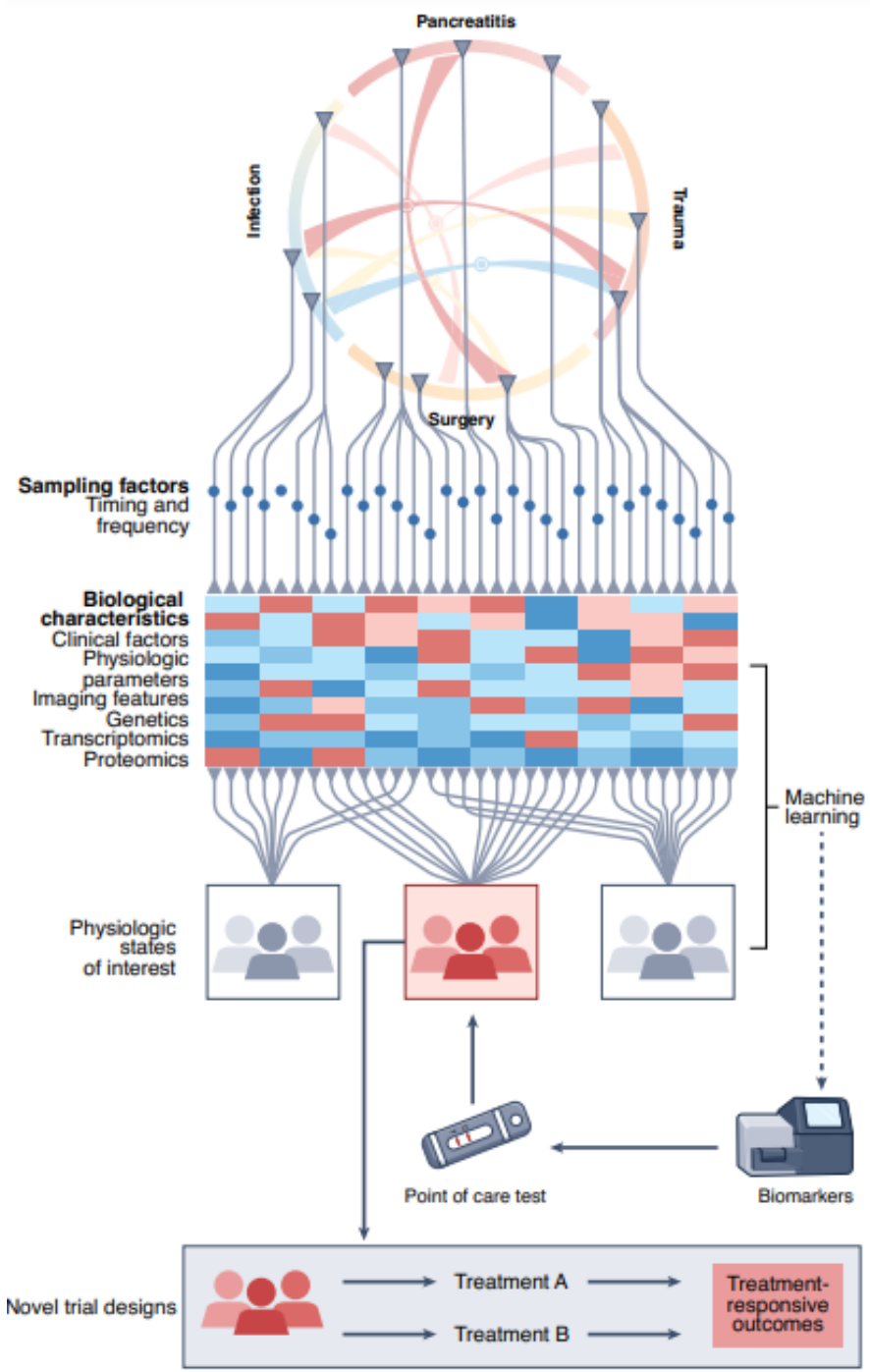
Ann Surg 2022

Nieuw model



Recruitment into trials based on treatable trait…

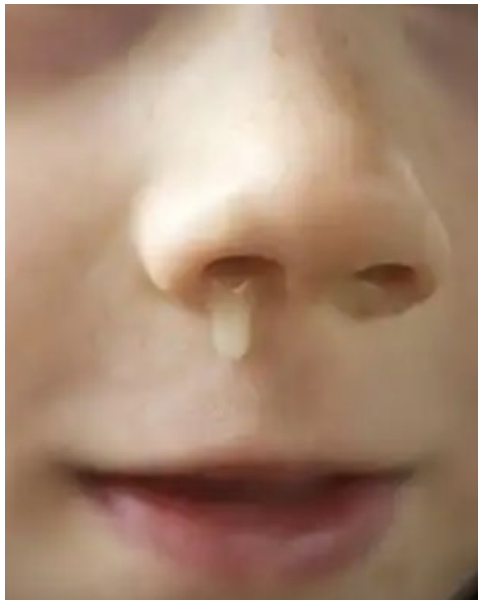
Nat Med 2022

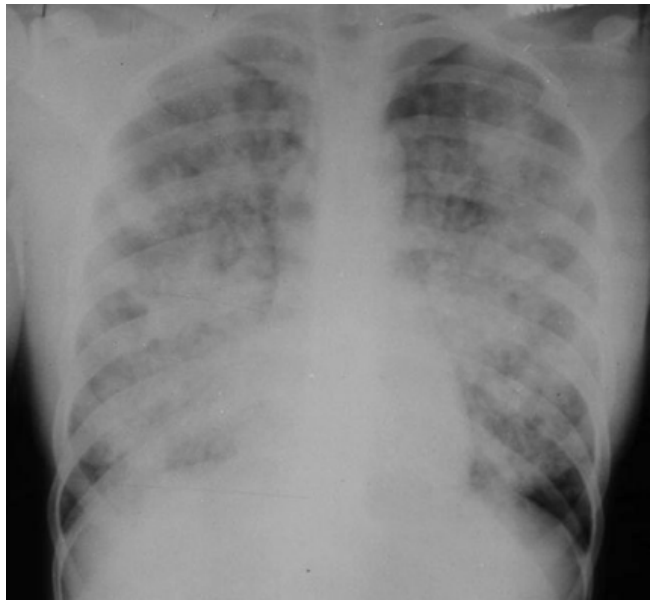

Pancreatitis
Infection
Trauma
Surgery
Sampling factors
Timing and frequency
Biological characteristics
Clinical factors
Physiologic parameters
Imaging features
Genetics
Transcriptomics
Proteomics
Machine learning
Physiologic states of interest
Point of care test
Biomarkers
Novel trial designs
Treatment A
Treatment B
Treatment-responsive outcomes

SARS-CoV-2 pathogenesis

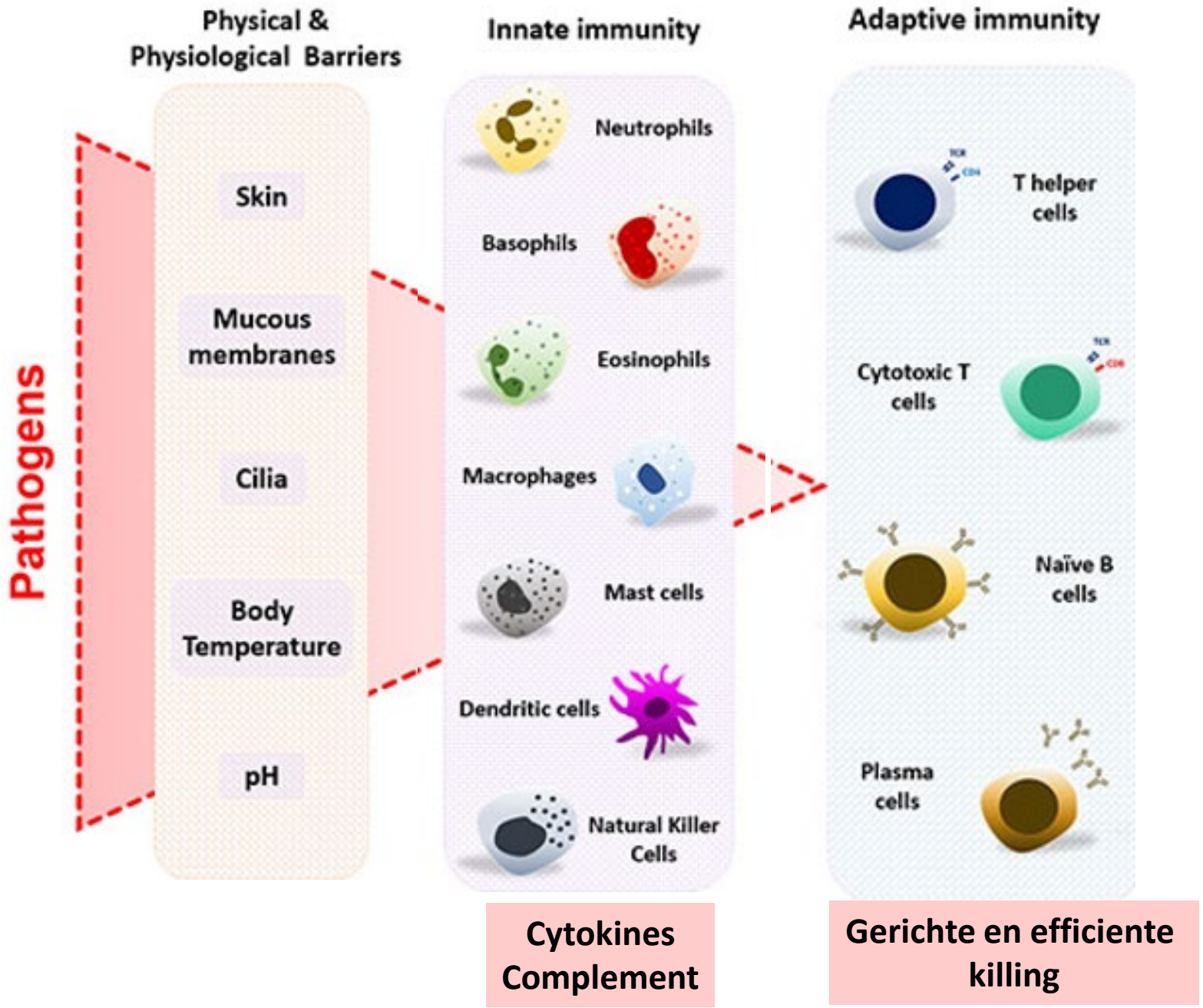
Mart M. Lamers and Bart L. Haagmans ✉

nature REVIEWS MICROBIOLOGY

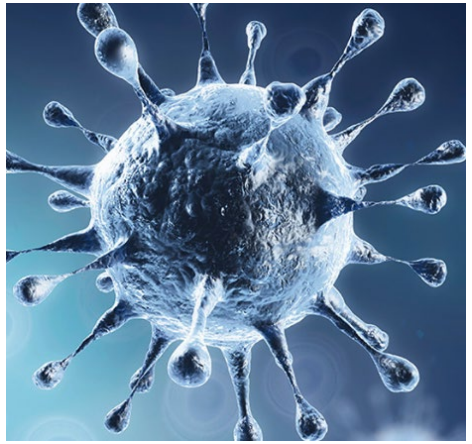


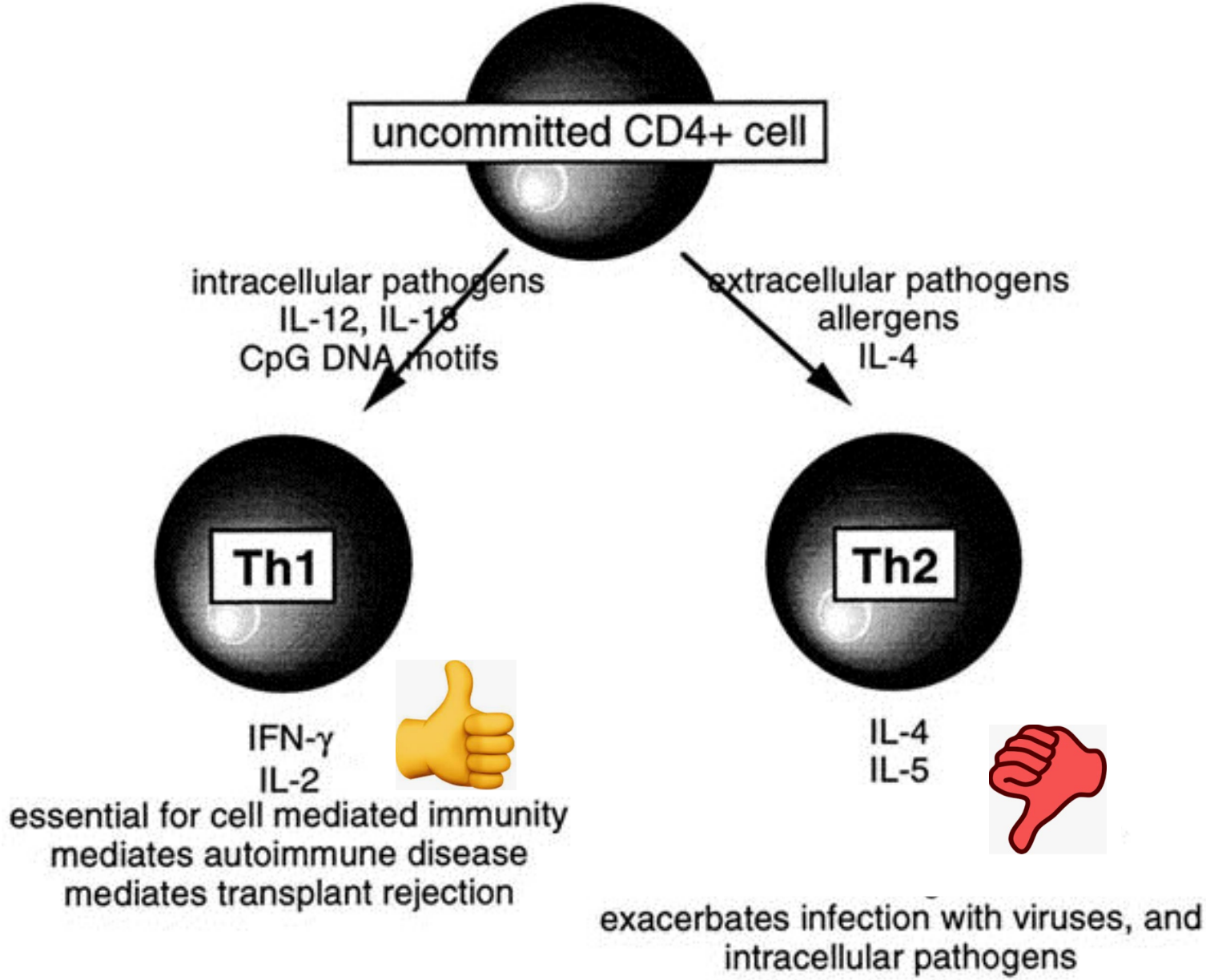


Nat Rev 2022

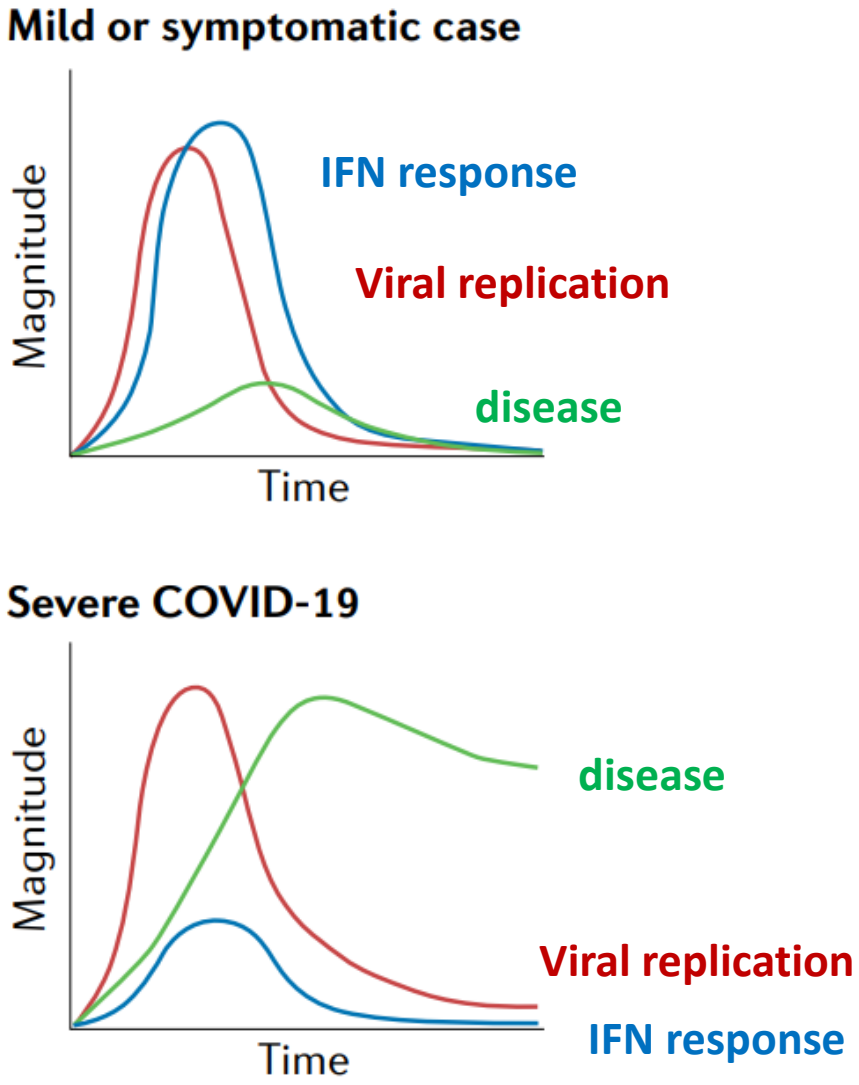

Physical &
Physiological Barriers
Innate immunity
Adaptive immunity
Pathogens
Skin
Mucous membranes
Cilia
Body Temperature
pH
Neutrophils
Basophils
Eosinophils
Macrophages
Mast cells
Dendritic cells
Natural Killer Cells
T helper cells
Cytotoxic T cells
Naïve B cells
Plasma cells
Cytokines
Complement
Gerichte en efficiente killing

T helper cells





Defective interferon response in COVID is detrimental



Auto-Abs to IFN
Mutations in IFN receptor
Delayed/poor IFN response

Nat Rev 2022

Anti auto-Abs against IFN

COVID:
Found in ~20%
Mortality ~80%

ICM 2021

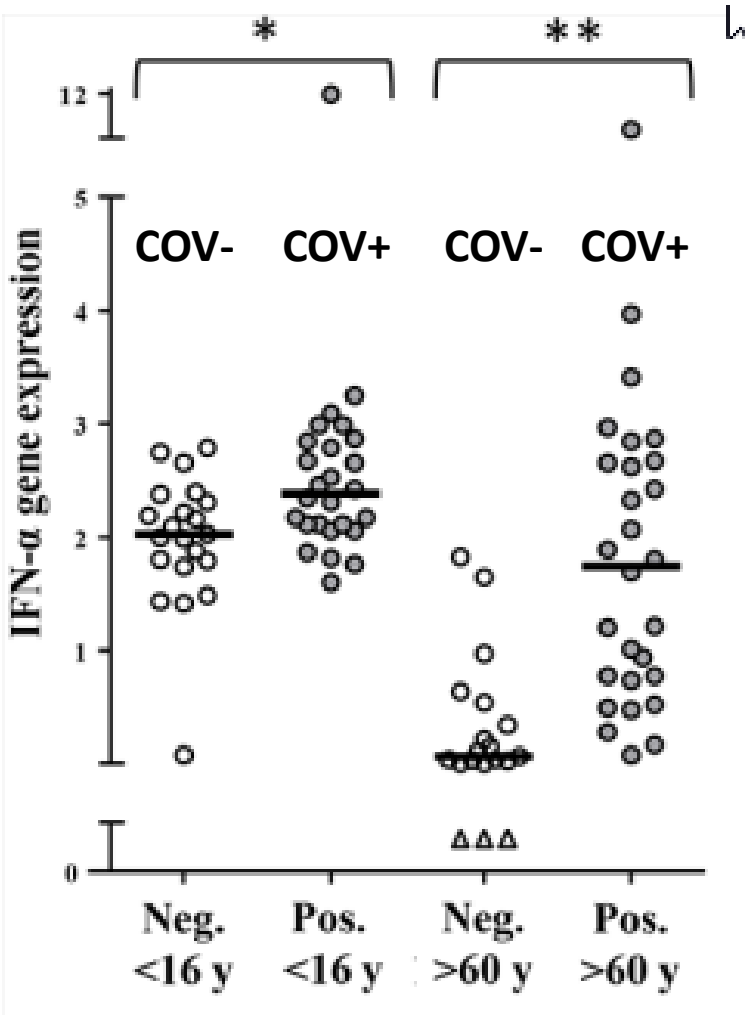
Influenza:
Found in ~5%

JEM 2022

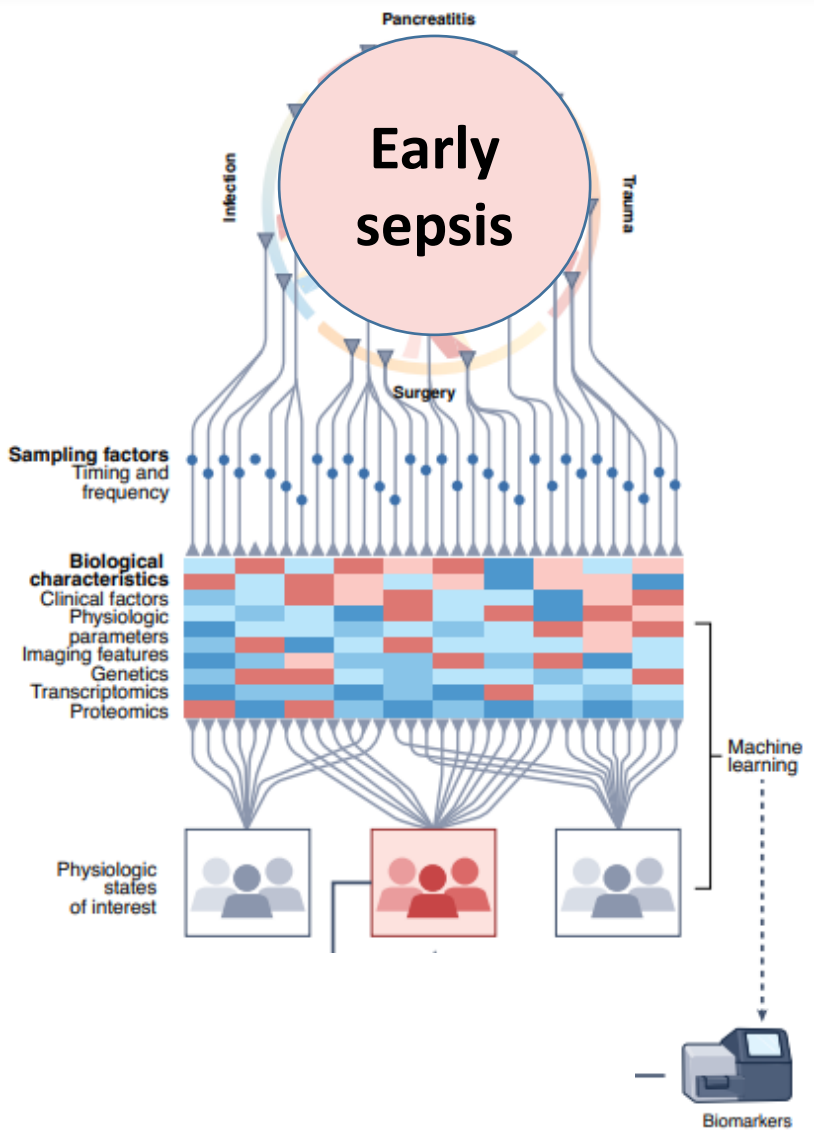
Dissemin TB
Salmonella

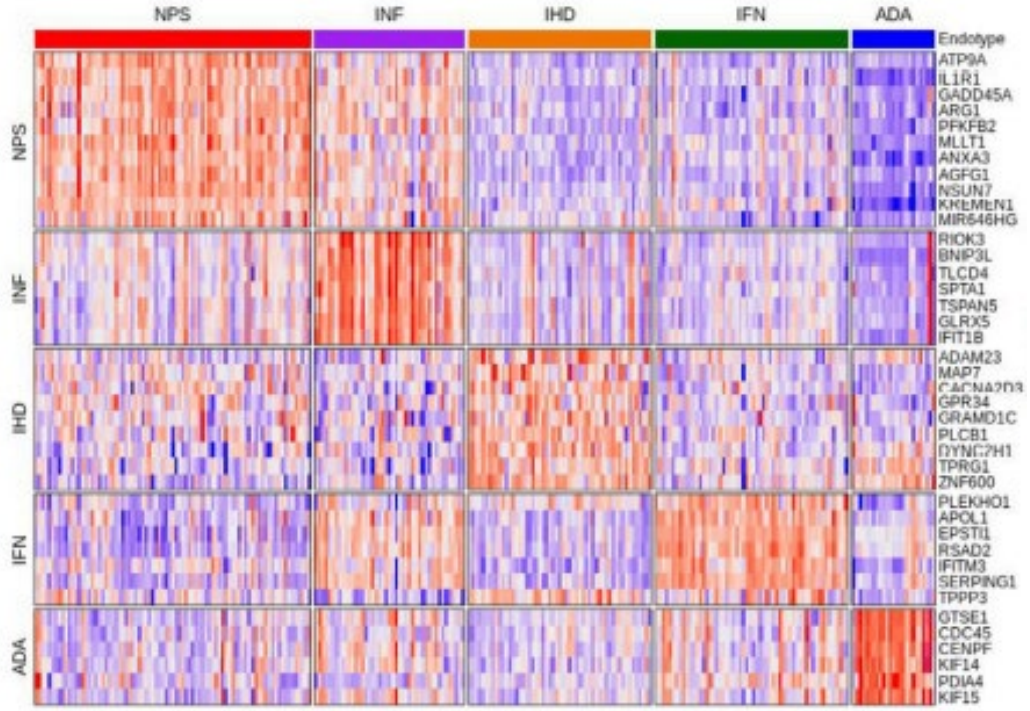
JEM, Sci Rep 2022

Higher age comes with slow IFN response in COVID



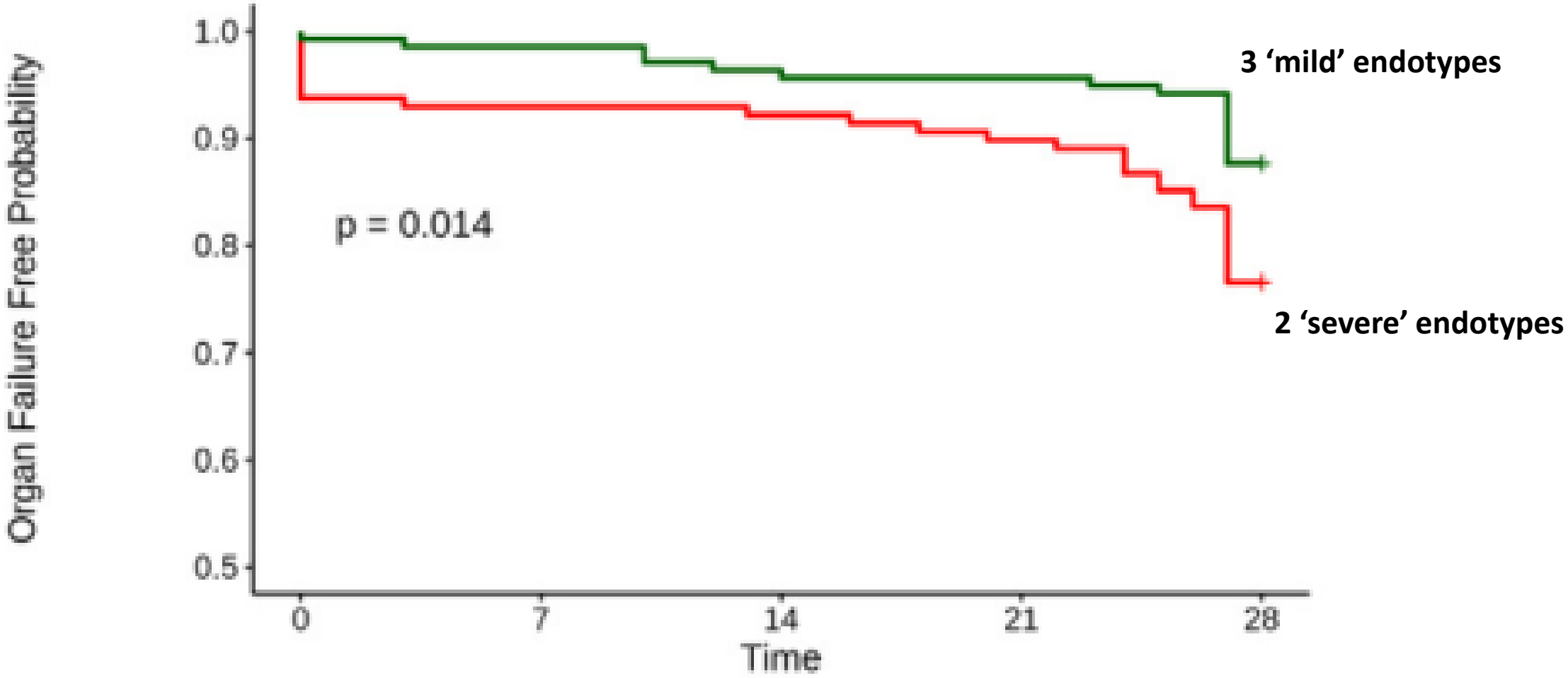
Front Immunol 2022





eBiomed 2022

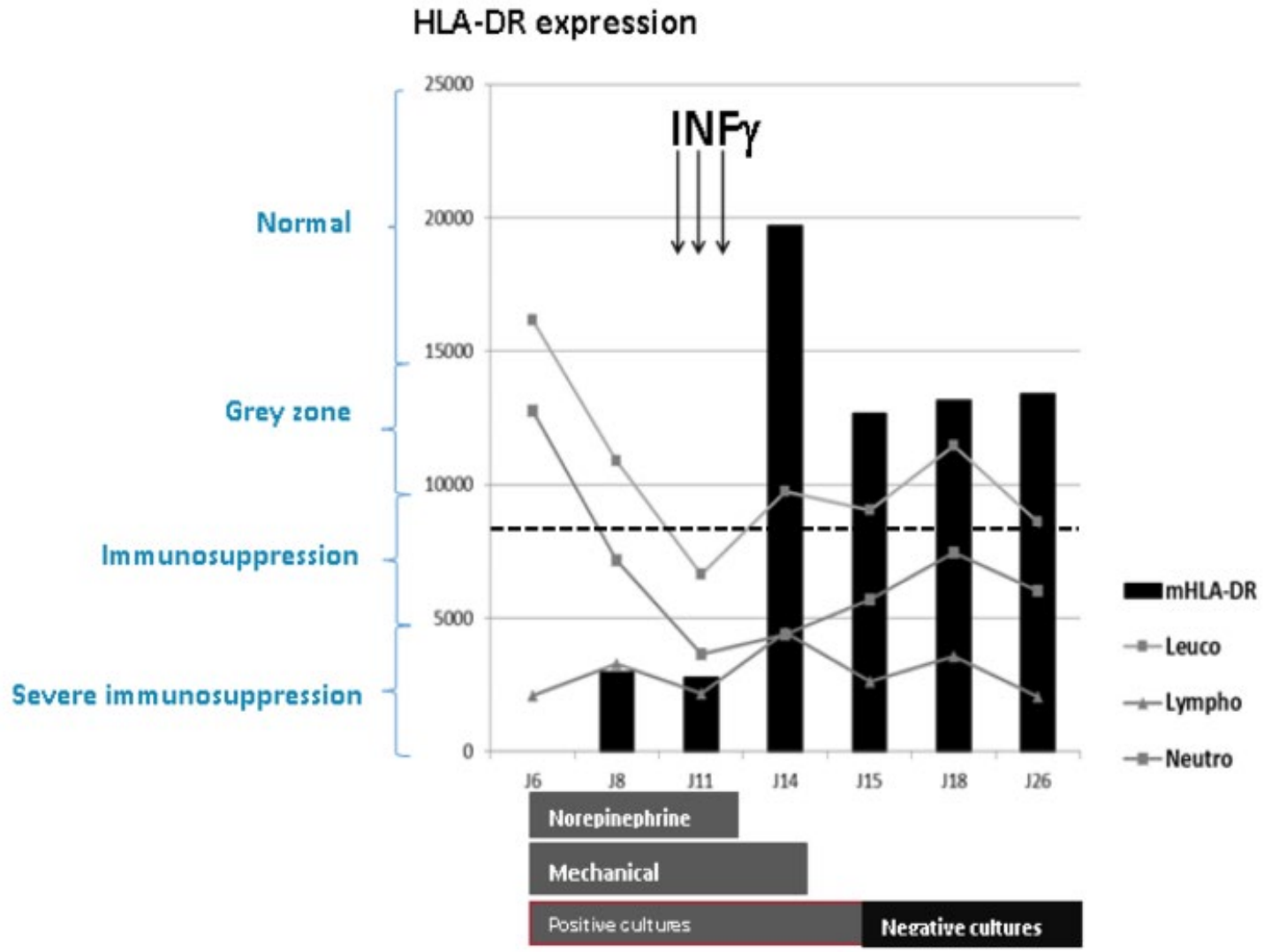
Endotypes have distinct survival patterns



Severe endotype 1:
‘defective’ response in sepsis

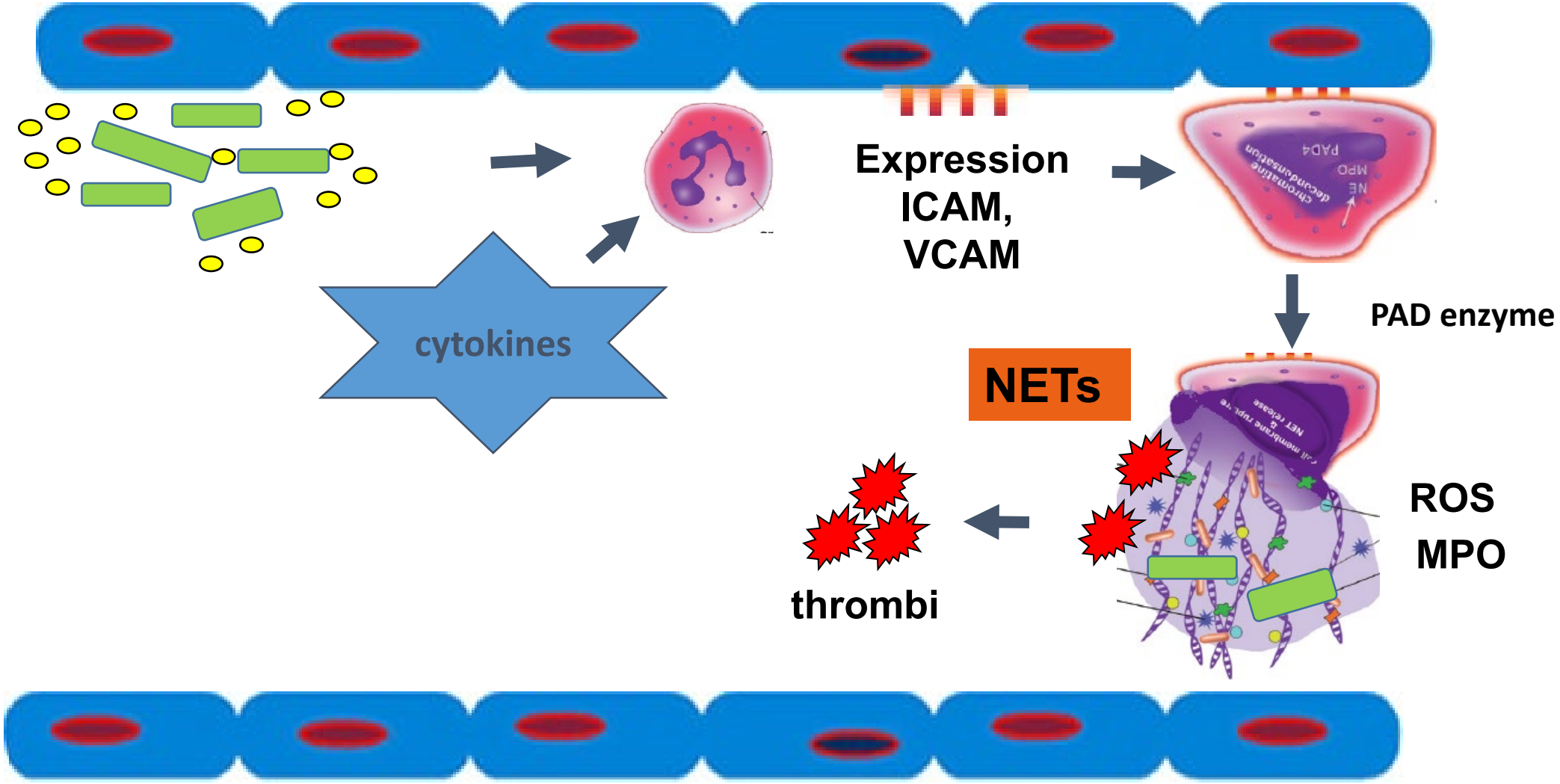
- Low IFNα, β response
- High neutrophil count, with degranulation -> dysfunctional ?
- Reduced phagocytosis

IFN therapy improves host response in sepsis (case series)



BMC Inf 2019

Neutrophil degranulation



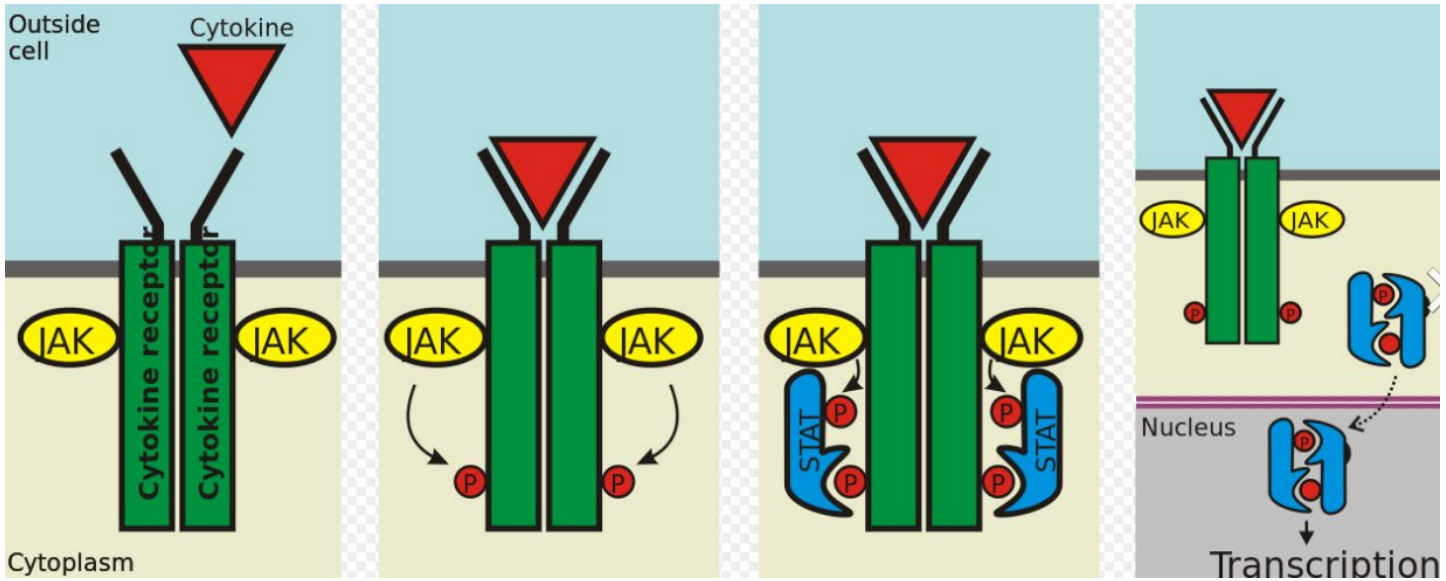
Look out for work on these potential treatable traits

- MPO as biomarker (PoC device already trialled in cardiology)

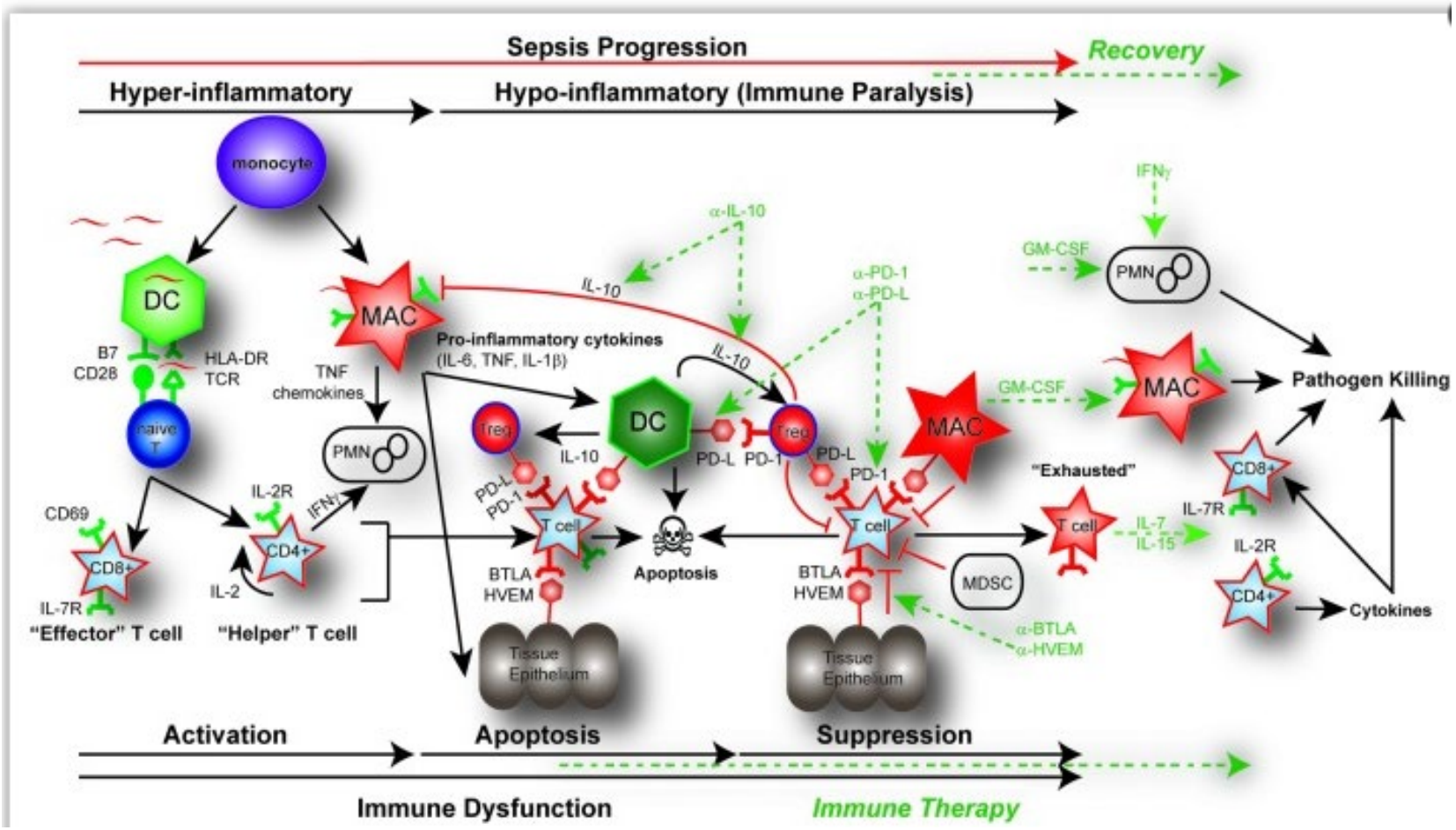
- Treatments:
  - PAD inhibitors
  - Aspirin
  - DNAse
  - Heparin
  - Etc…….

Severe endotype 2: pro-inflammatory response

- High IL-1
- High IL-6
- High IFNγ
- JAK/STAT pathway



Endotypes trajectory ?



The end of ‘pragmatic’ trials ?!!

- we lump patients together
  …’because blood sampling is too difficult’
  ….’the intervention is aimed to be widely applicable..’

- we compare strategies we dont understand…
  …‘because it is standard of care’

- we taken 90D mortality as an outcome
  …’because it is relevant’

The end of ‘patient centered’ outcomes ?!!

‘welke treatable trait vind u belangrijk…’

‘heeft u liever een interventie gericht op stimulatie of op suppressie van uw immuunsysteem ‘

De toekomst

- We gaan gerichte therapie krijgen voor endotypes/traits/‘profielen’
- We gebruiken syndromen niet meer om te behandelen
- Het zal snel gaan