HELLENIC REPUBLIC
National and Kapodistrian University of Athens
EST. 1837

European Sepsis Alliance

Empowering Precision-medicine approach through NETs Plasma Biomarker-driven personalized treatment

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President: Hellenic Society for Chemotherapy

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HELLENIC INSTITUTE FOR THE STUDY OF SEPSIS

https://sepsis.gr/

CONFLICT OF INTEREST DISCLOSURE

- Honoraria (paid to the University of Athens): Abbott Products Operations AG, bioMérieux France, Brahms ThermoFisher GmbH Germany, and Swedish Orphan BioViotrum
- Consultation fees (paid to the University of Athens): Abbott Products Operations AG, Abionic SA, Biorad, and Swedish Orphan BioViotrum
- Independent educational grants (paid to the University of Athens): AbbVie USA, InCyte, Novartis, Sanofi, UCB
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- Funding by the Horizon 2020 ITN European Sepsis Academy (granted to the University of Athens), by the Horizon 2020 ImmunoSep and RISKinCOVID (granted to the Hellenic Institute for the Study of Sepsis) and by the Horizon Europe EPIC-CROWN-2, POINT and Homi-Lung (granted to the Hellenic Institute for the Study of Sepsis)

HIGH HiSCR PLACEBO RESPONSES IN MOST TRIALS: UNDENIABLE SITUATION

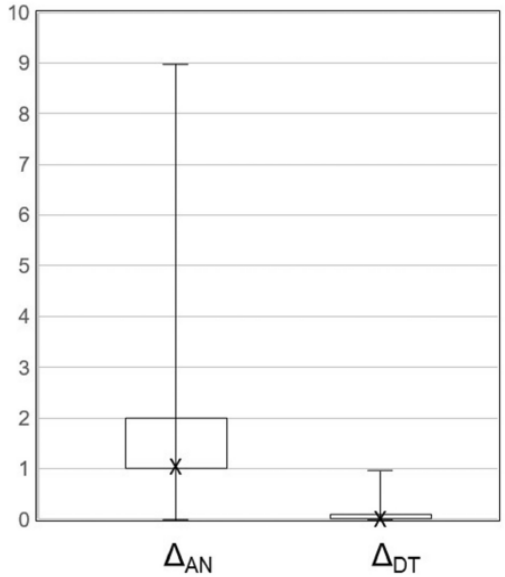
Ref.	Trial acronym (patients under placebo)	Active drug	Week of assessment	HiSCR of placebo (%)	Upper 95% CI
1	PIONEER I (154)	Adalimumab	12	26.0	**33.4**
	PIONEER II (163)	Adalimumab	12	27.6	**34.9**
2	SHARPS (103)	Adalimumab	12	34.0	**43.6**
3	SUNSHINE (180)	Secukinumab	16	34.0	**41.1**
	SUNRISE (183)	Secukinumab	16	31.0	**38.2**
4	HOVA (62)	Guselkumab	16	38.7	**51.1**
5	BE-HEARD I (72)	Bimekizumab	16	29.0	**40.5**
	Be-HEARD II (74)	Bimekizumab	16	32.0	**43.7**
6	SHINE (36)	Vilobelimab	16	47.1	**64.9**

CI: confidence interval
HiSCR: hidradenitis suppurativa clinical response

1. Kimbal AB, et al. *N Engl J Med* 2016; 375, 422-434
2. Bechara FG, et al. *JAMA Dermatol* 2021; 156: 1001-1009
3. Kimball AB, et al. *Lancet* 2023; 401, 747-761
4. Kimbal AB, et al. *J Eur Acad Dermatol Venereol* 2023; 37: 2098-2108
5. Kimbal AB, et al. *Lancet* 2024; 403: 2504-2519
6. Giamarellos-Bourboulis EJ, et al. *Br J Dermatol* 2026; 194: 254-263

HIGH HiSCR PLACEBO RESPONSES IN MOST TRIALS: PROBABLE EXPLANATIONS

- High variability of the disease
- Inter-rater/intra-rater variability[1]



BUT….
HiSCR never exceeds 60%

How about that
not all patients are same?

AN: inflammatory lesions
DT: draining tunnels
HiSCR: Hidradenitis suppurativa clinical response

1. Zouboulis CC, et al. *J Eur Acad Dermatol Venereol* 2024; 38: e716-e718

THE MAIN QUESTION

How are neutrophils recruited to the affected skin lesion to produce pus?

This process may be mediated by anaphylatoxins produced during complement activation

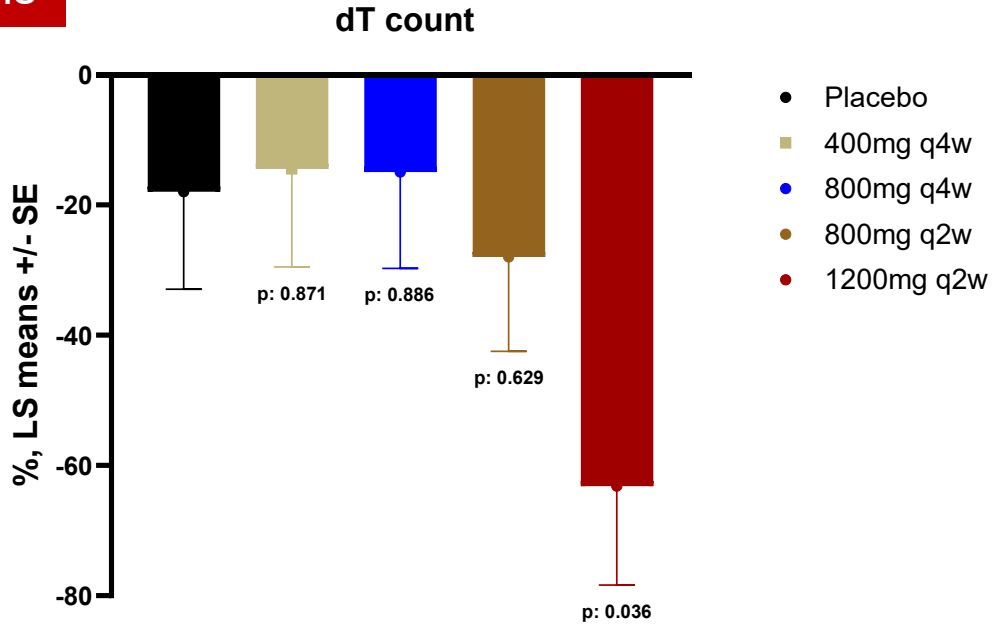
(C3a, C5a, C5b-9)

VILOBELIMAB BLOCKS COMPLEMENT FACTOR C5a AND DECREASES THE dT COUNTS

(Giamarellos-Bourboulis EJ, et al. *Br J Dermatol* 2026; 194: 254-263)

Main teaching

- Neutrophil efflux and activation
- Major components of HS pathogenesis



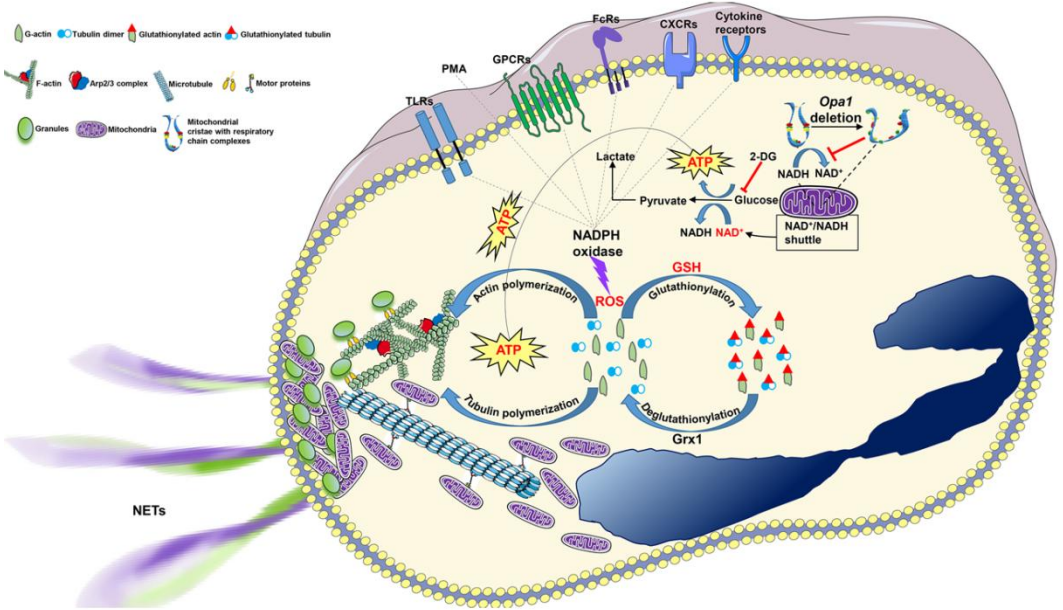
dT: draining tunnel
HS: hidradenitis suppurativa
q: every
w: week

WHAT ARE THE CRITERIA FOR A NEUTROPHIL DISORDER?

Classification criteria

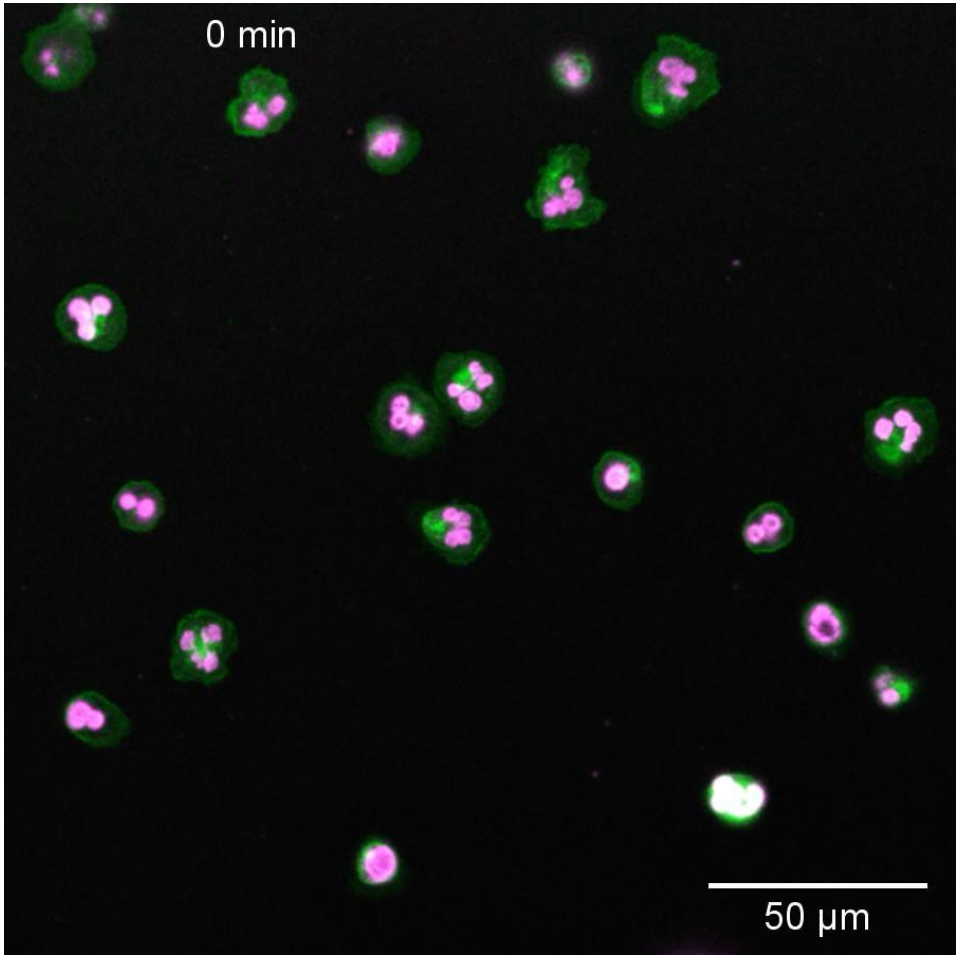
- Priming by IL-1β
- Neutrophil infiltration
- NET formation (antimicrobial peptides)

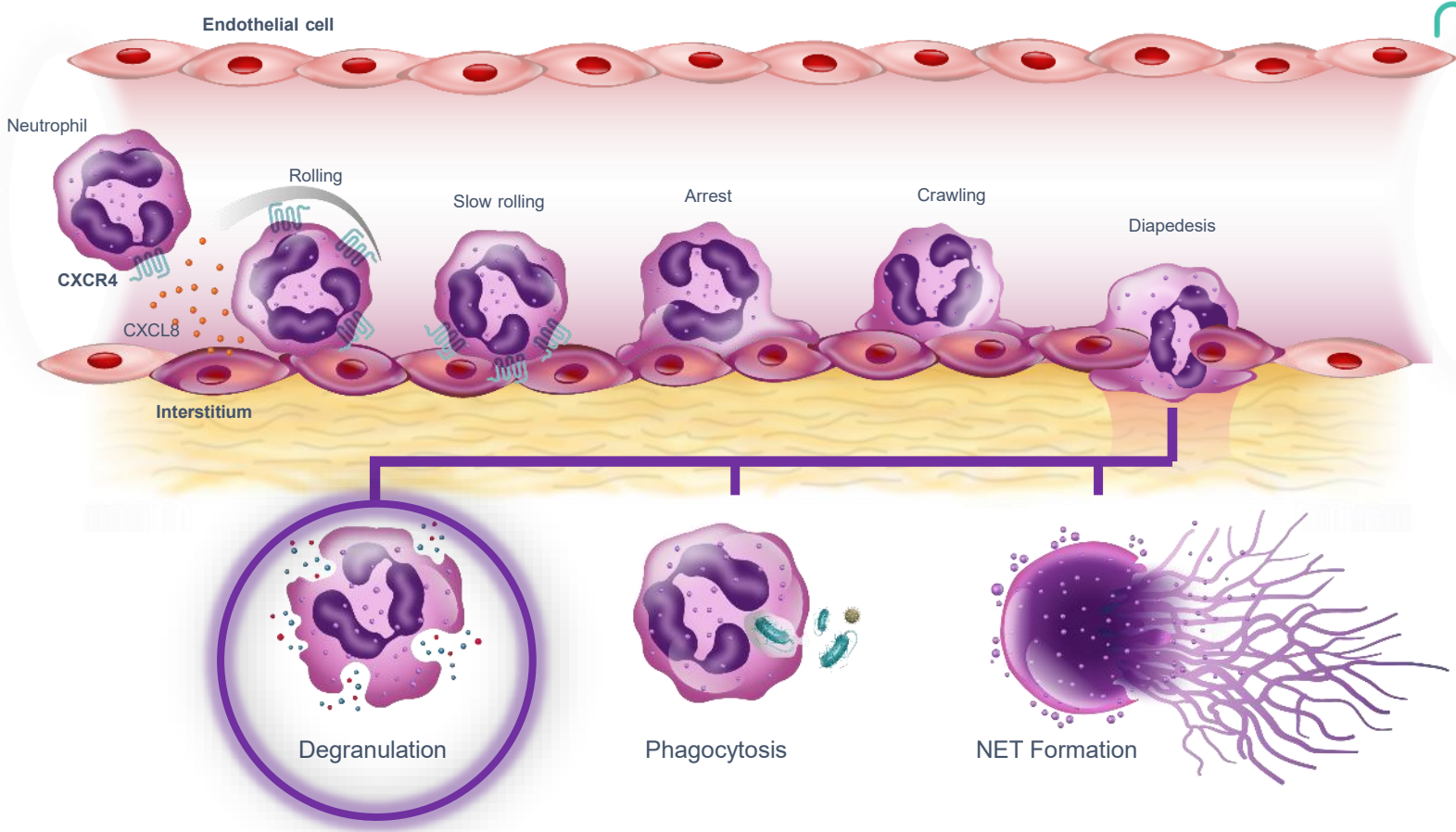
Satoh TK, et al. *Br J Dermatol* 2018; 178: 603



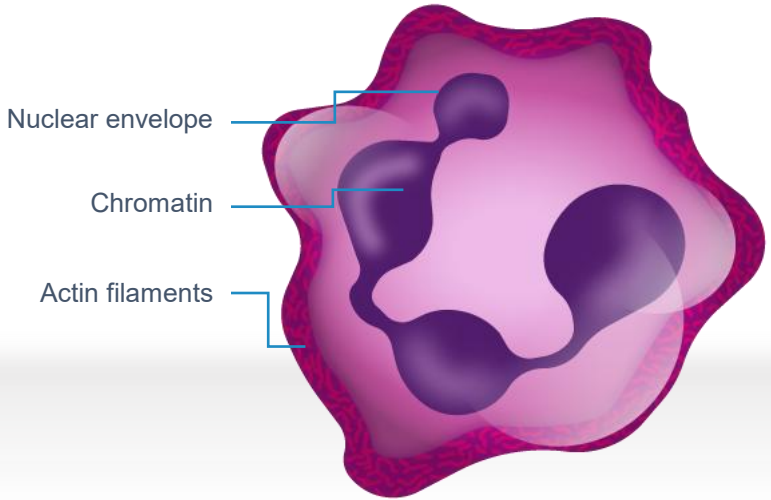
NET: neutrophilic extracellular traps

Yousefi S, et al. *Eur J Immunol* 2019; 49: 221

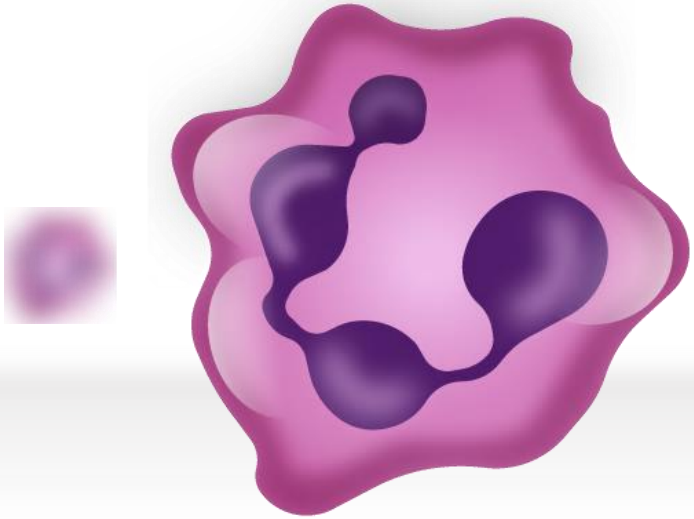

0 min
50 µm


Endothelial cell
Neutrophil
CXCR4
CXCL8
Rolling
Slow rolling
Arrest
Crawling
Diapedesis
Interstitium
Degranulation
Phagocytosis
NET Formation

Resting Neutrophil

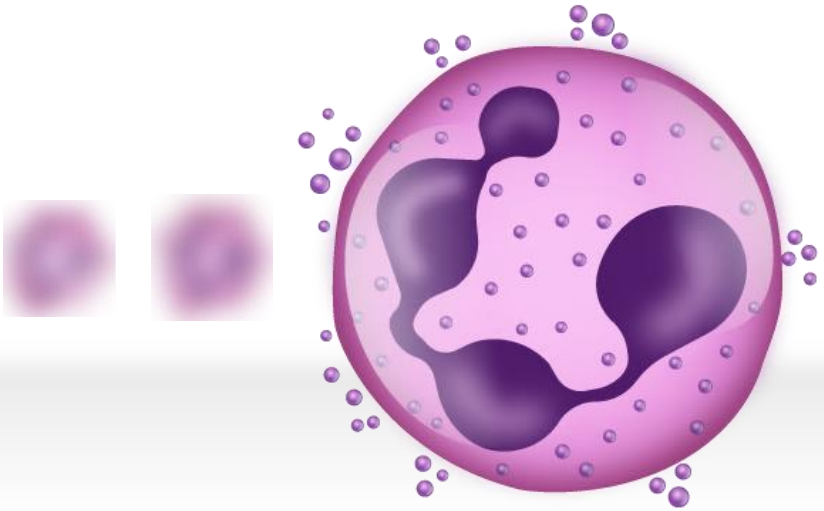


Activated Neutrophil



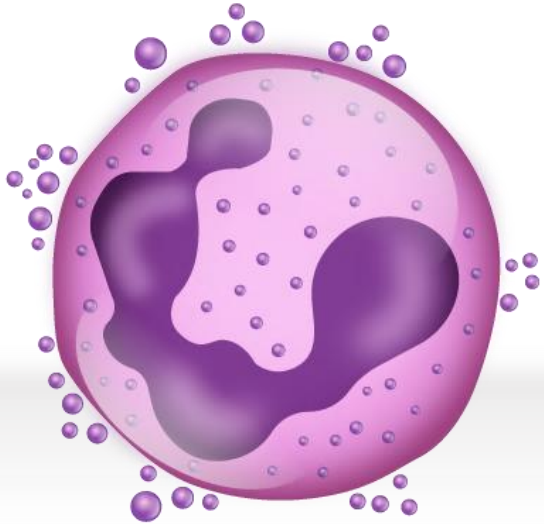
Actin filament disassembly

Activated Neutrophil



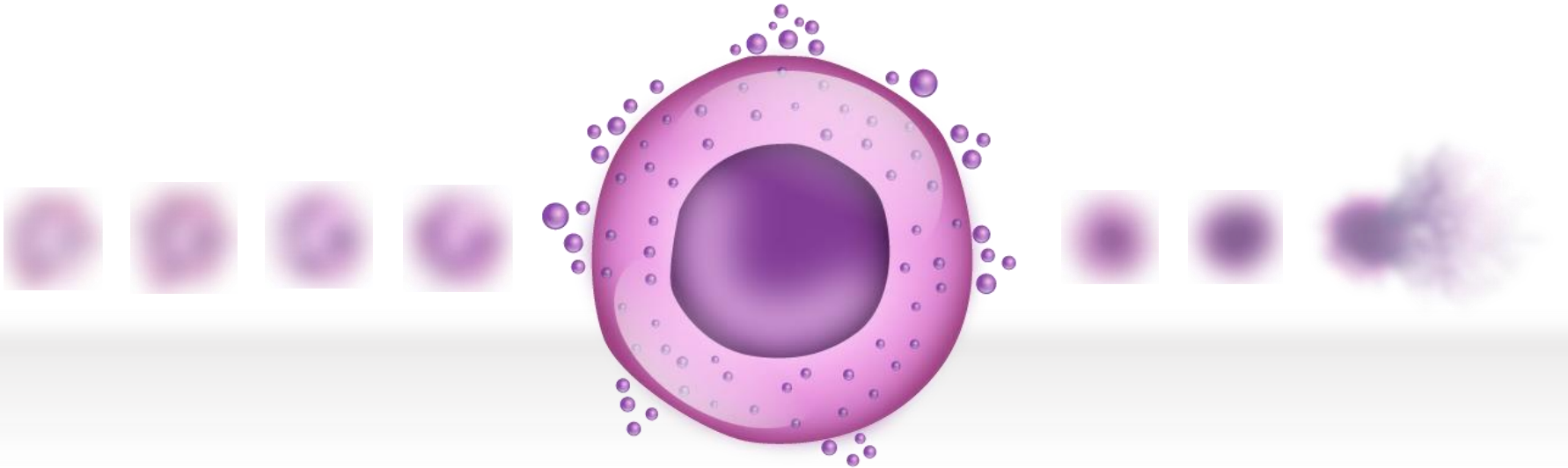
Plasma membrane microvesicle shedding

Activated Neutrophil



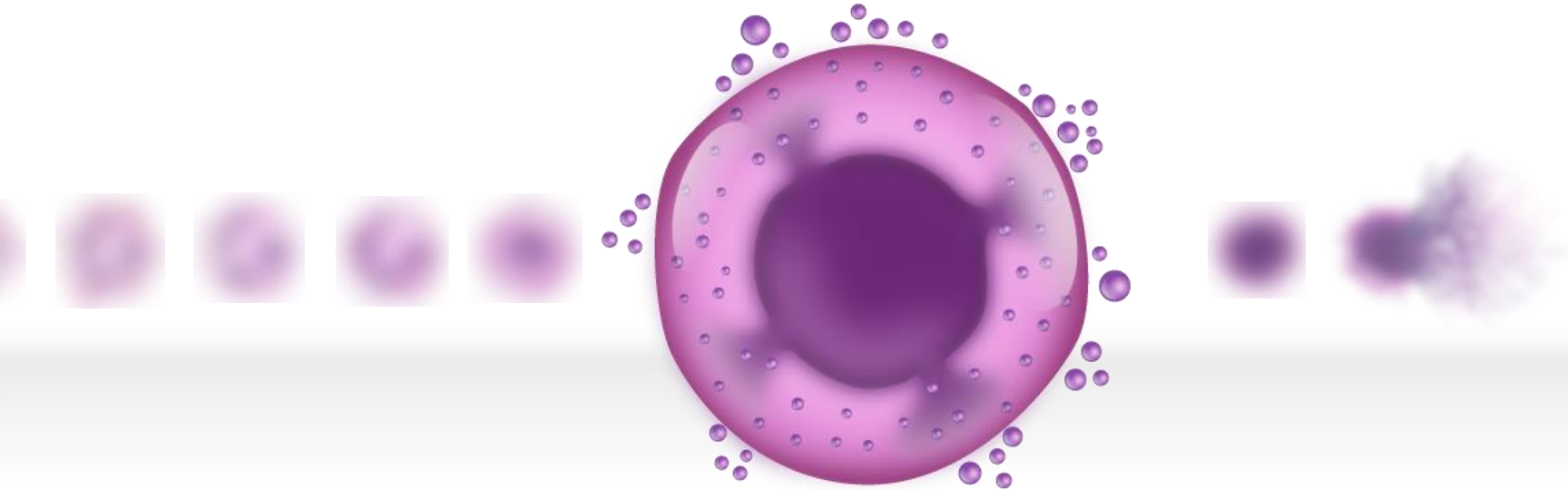
Chromatin decondensation

Activated Neutrophil



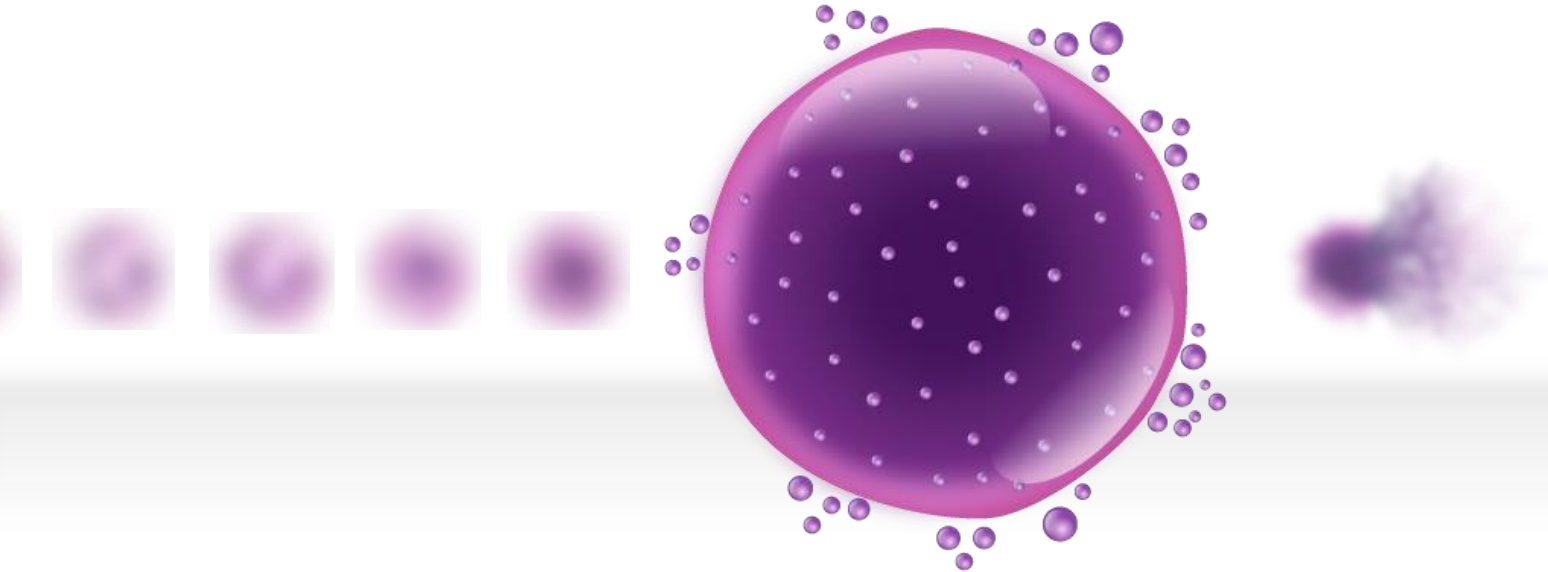
Nuclear rounding and plasma membrane
and nuclear envelope permeabilization

Activated Neutrophil

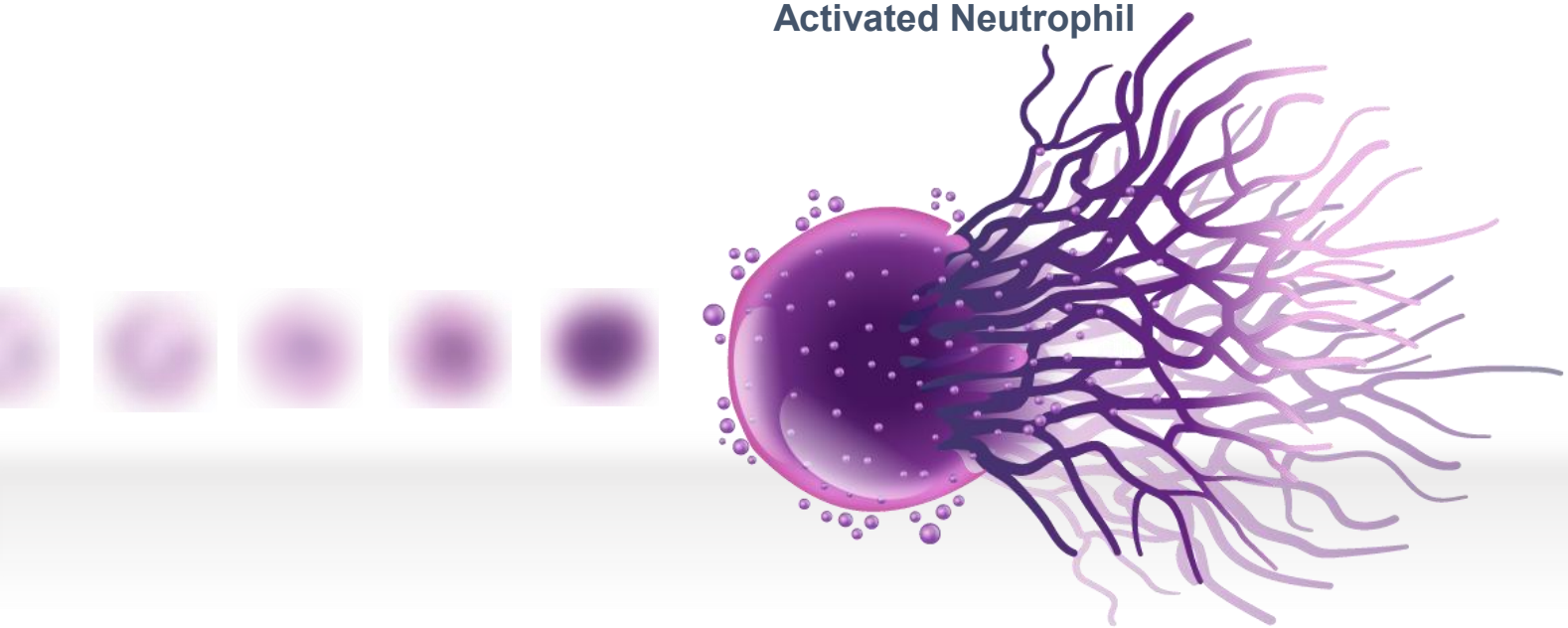


Rupture of nuclear envelope

Activated Neutrophil



Chromatin expansion into the cytoplasm



Plasma membrane rupture
and NET release

MAIN NET COMPONENTS & ASSOCIATED DISEASES (Shahzad A, et al. *Mol Med* 2025; 6: 30)

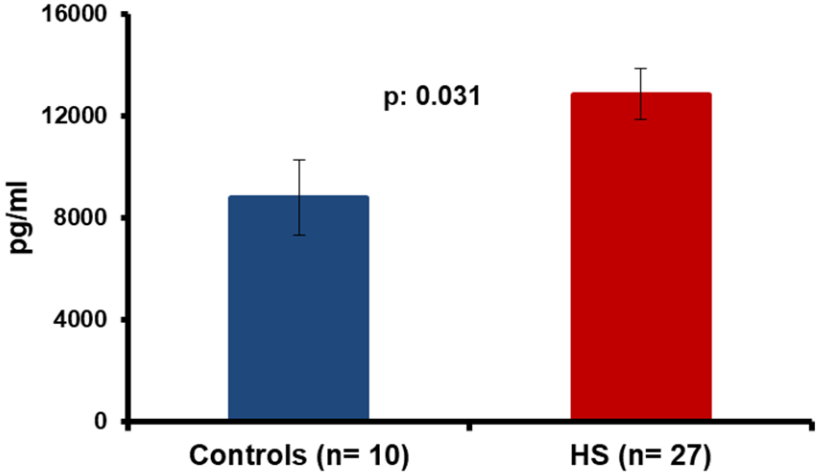
Components	Triggers	Localization	Diseases	Mechanism of action
DNA (chromatin)	Oxidative burst, bacterial toxins	Nuclear chromatin into extracellular fibers	Liver metastases SLE, infections	Autoantibodies, bacterial entrapment
Histone H2A	Cellular stress	Chromatin released	Infections	Bacteria disruption
Histones H2B	Bacterial stimulation	Nuclear chromatin fibers	*Leismania spp.*	Immune dysregulation
Histones H4	Pro-inflammatory stressors, toxins	Nuclear protein integrated into NETs	Bacteria, influenza A, SARS-CoV-2	Immune response viral neutralization
Neutrophil elastase	Bacterial toxins	Azurophilic granules, extracellular space	*Shigella* spp, *C.albicans*, RSV ANCA-vasculitis	Bacterial and fungal cell degradation, viral clearance
Myeloperoxidase	Microbial triggers	Azurophilic granules, NETs structures	Bacterial infection	Reactive oxygen species production
Defensins	Pathogens	Cytoplasmic granules	Bacteria, SLE, HIV	Immune response
Calprotectin	Infection-induced	Cytoplasm	*C.albicans*	Antifungal activity

EXAMPLES OF CHRONIC INFLAMMATORY DISORDERS WITH NETs FOR DIAGNOSIS/PROGNOSIS (Torfs K, et al. *Cell Mol Immunol* 2026; 23: 123-149)

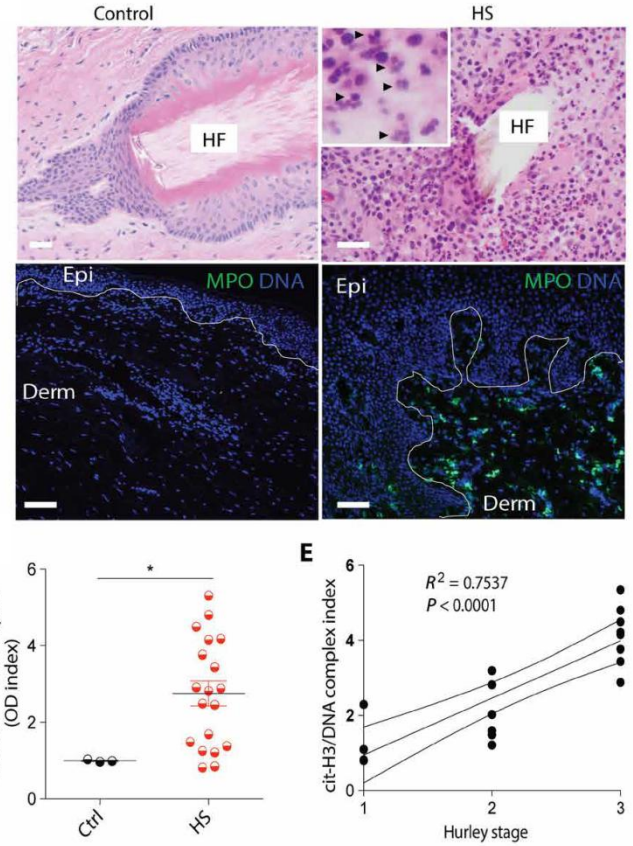
Disease	Sample type	Findings concerning neutrophils
Rheumatoid arthritis	Plasma	Cell-free nucleosomes as a potential diagnostic biomarker Carbamylated NET proteins are increased
	Synovial fluid	Cell-free nucleosomes as a potential diagnostic biomarker
Atherosclerosis	Plasma	Increased S100A12 correlating with increased risk of major cardiovascular events
Inflammatory bowel disease	Feacal samples	S100A8/A9 used as a biomarker for disease activity
Systemic Lupus Erythematosus	Whole blood and plasma	Improvement of neutropenia, attenuation of apoptosis and NETosis

EVIDENCE FOR HS AS NEUTROPHLIC DISORDER

β-defensin production by whole blood[1]



NET formation[2]



1. Giamarellos-Bourboulis EJ, et al. *J Invest Dermatol* 2016, 136: 1592
2. Byrd AS, et al. *Sci Transl Med* 2019; 11: pii: eaav5908

THE PATIENT COHORT

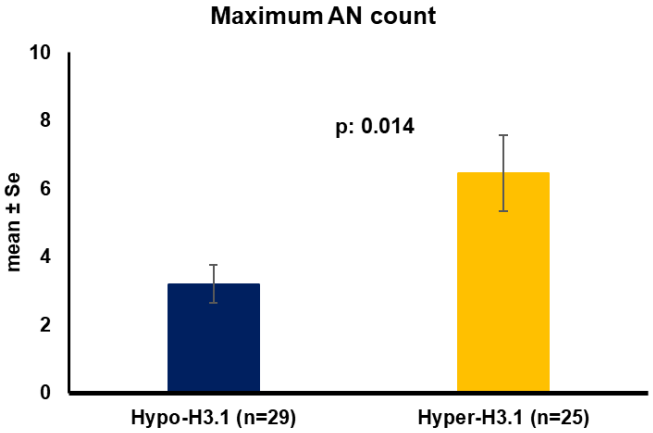
(Theohari et al. *medRxiv* https://doi.org/10.64898/2026.01.13.26343988)

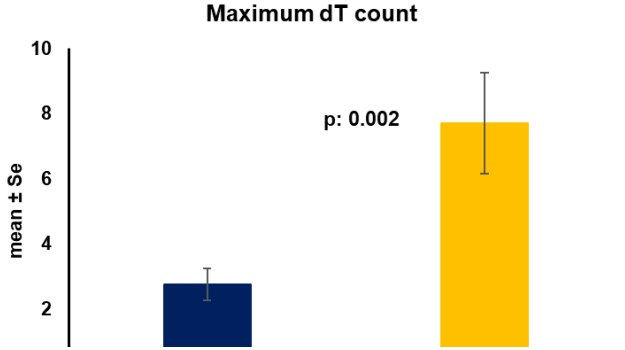
	Patients with single measurements (N=93)	Patients with serial measurements (N=54)	p-value
Age (years), mean (SD)	40.0 (11.8)	34.8 (12.2)	0.053
Age at HS onset (years), mean (SD)	28.5 (12.5)	26.9 (12.4)	0.563
Male/Female, n (%)	19 (48.7)/20 (51.3)	30 (55.6)/24 (44.4)	0.535
BMI, kg/m^2, mean (SD)	29.5 (7.3)	30.1 (5.7)	0.709
Smoking, n (%)	23 (59.0)	38 (70.4%)	0.276
IHS4 score, mean (SE)	17.5 (3.5)	23.5 (3.6)	0.255
IHS4 classification, n (%)			
Moderate	17 (47.2)	17 (34.0)	0.266
Severe	19 (52.8)	33 (66.0)	

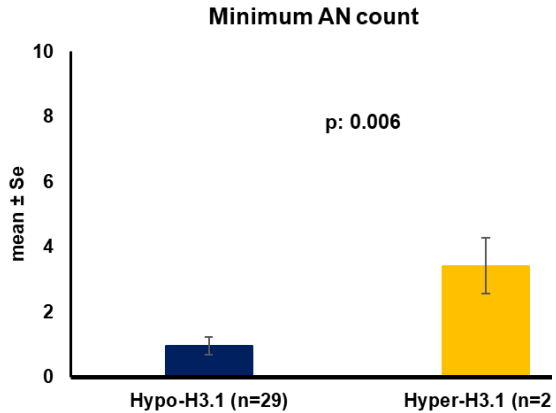
BMI: body mass index
IHS4: international HS 4 score
SD: standard deviation
SE: standard error

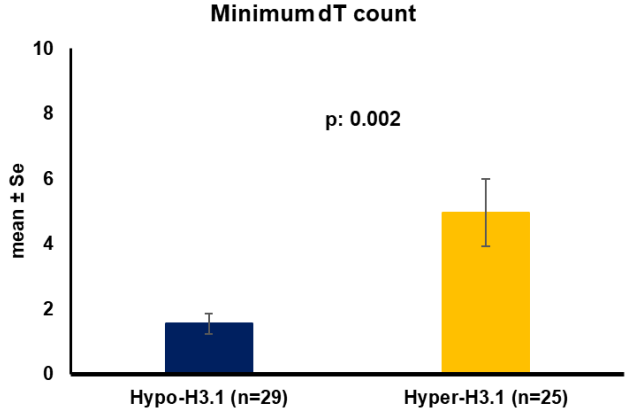
CLASSIFICATION BY H3.1= DEGREE OF INFLAMMATION AND dT FORMATION

(Theohari et al. *medRxiv* https://doi.org/10.64898/2026.01.13.26343988)





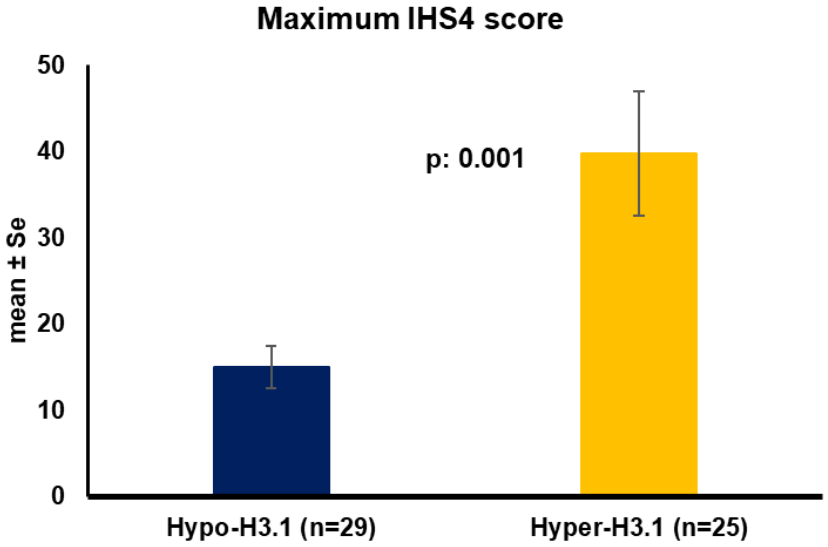


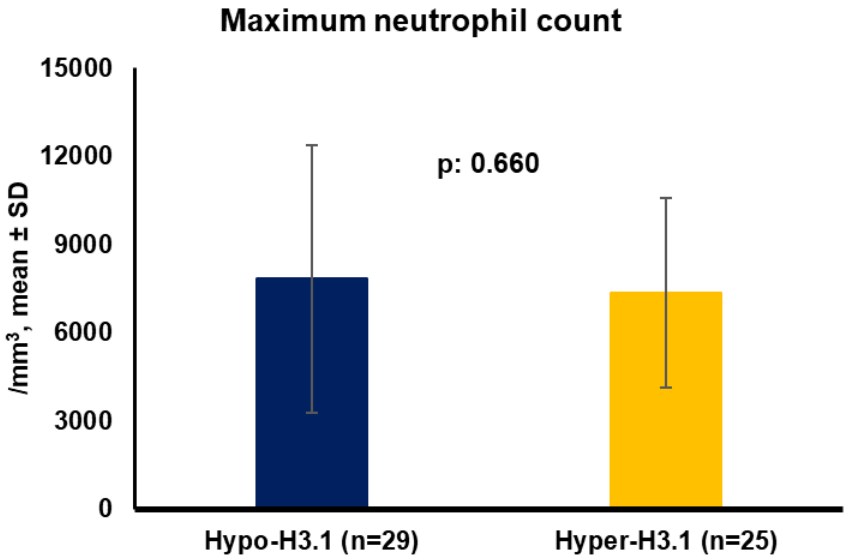


AN: inflammatory lesions
dT: draining tunnels
SE: standard error

THE CLASSIFIER IS INDEPENDENT FROM THE NEUTROPHIL CELL COUNT

(Theohari et al. *medRxiv* https://doi.org/10.64898/2026.01.13.26343988)

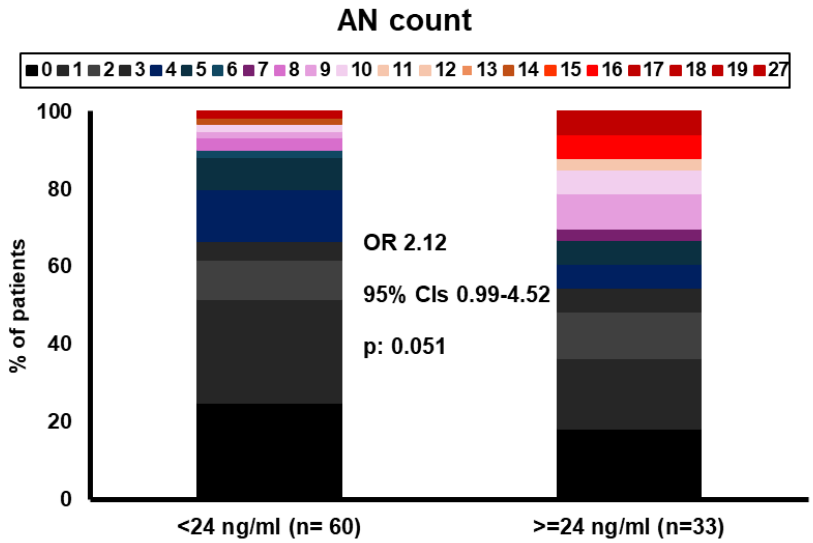


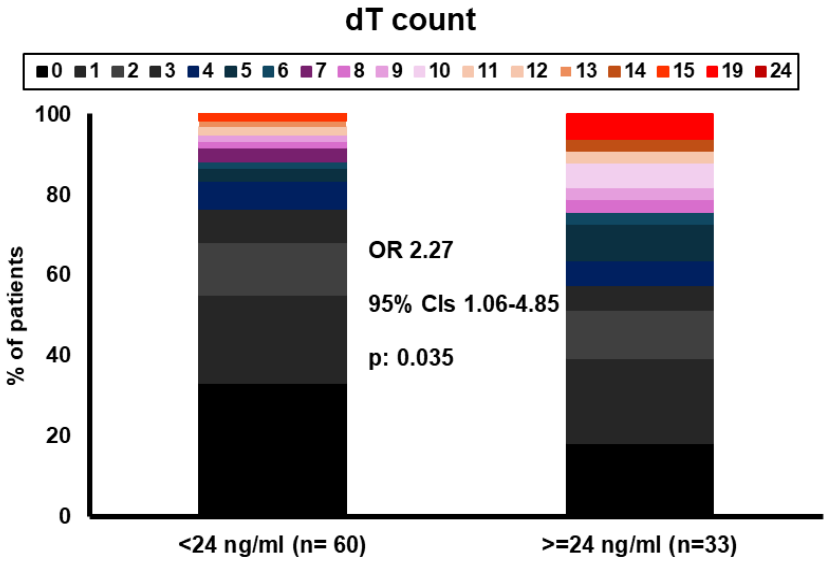


IHS4: international HS 4 score
SE: standard error

ONLY ONE MEASUREMENT IS ENOUGH TO CLASSIFY

(Theohari et al. *medRxiv* https://doi.org/10.64898/2026.01.13.26343988)





AN: inflammatory lesions
CI: confidence interval
dT: draining tunnels
n: number of patients
OR: odds ratio

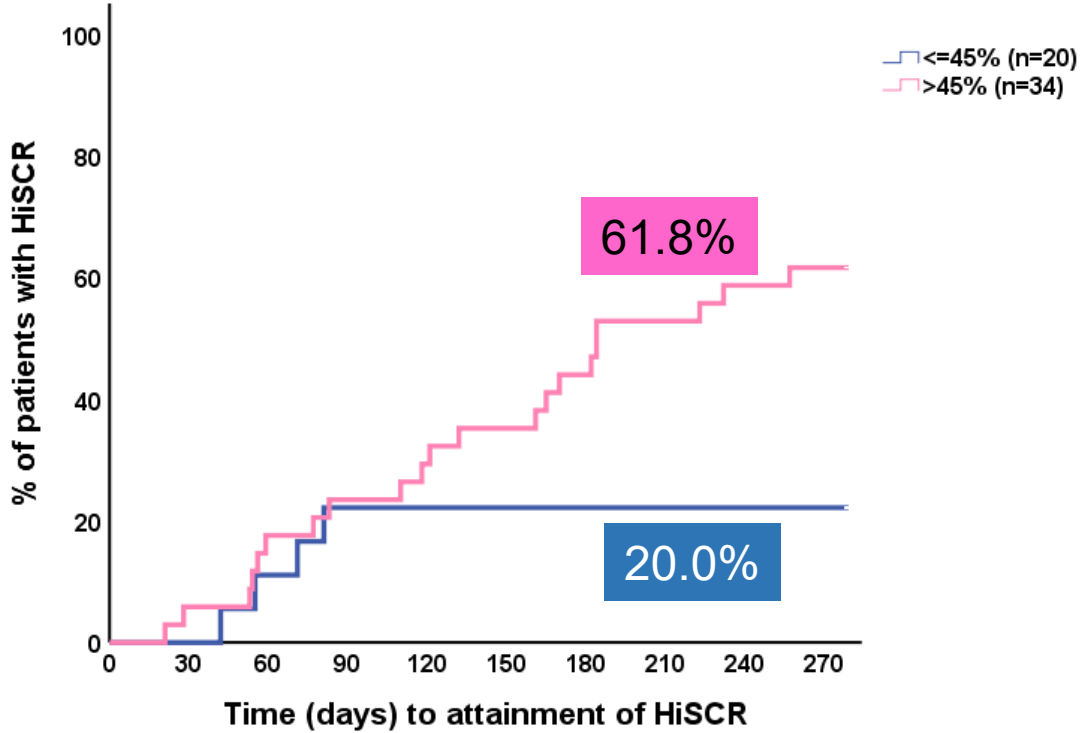
>45% DECREASE OF BLOOD H3.1 FROM BASELINE PREDICTS HiSCR

(Theohari et al. *medRxiv* https://doi.org/10.64898/2026.01.13.26343988)

HR: 3.33

95% CIs 1.14 to 9.72

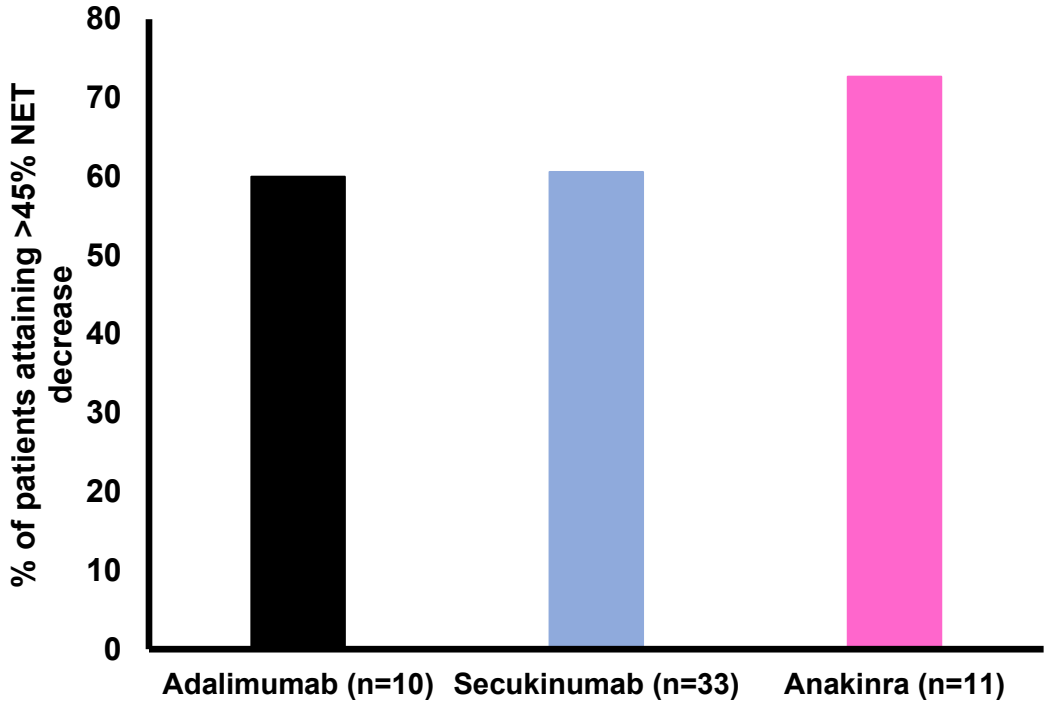
p: 0.028



CI: confidence interval
HiSCR: HS clinical response score
HR: hazard ratio
n: number of patients

ATTAINMENT OF >45% DECREASE OF NETs IS SIMILAR BETWEEN BIOLOGICALS

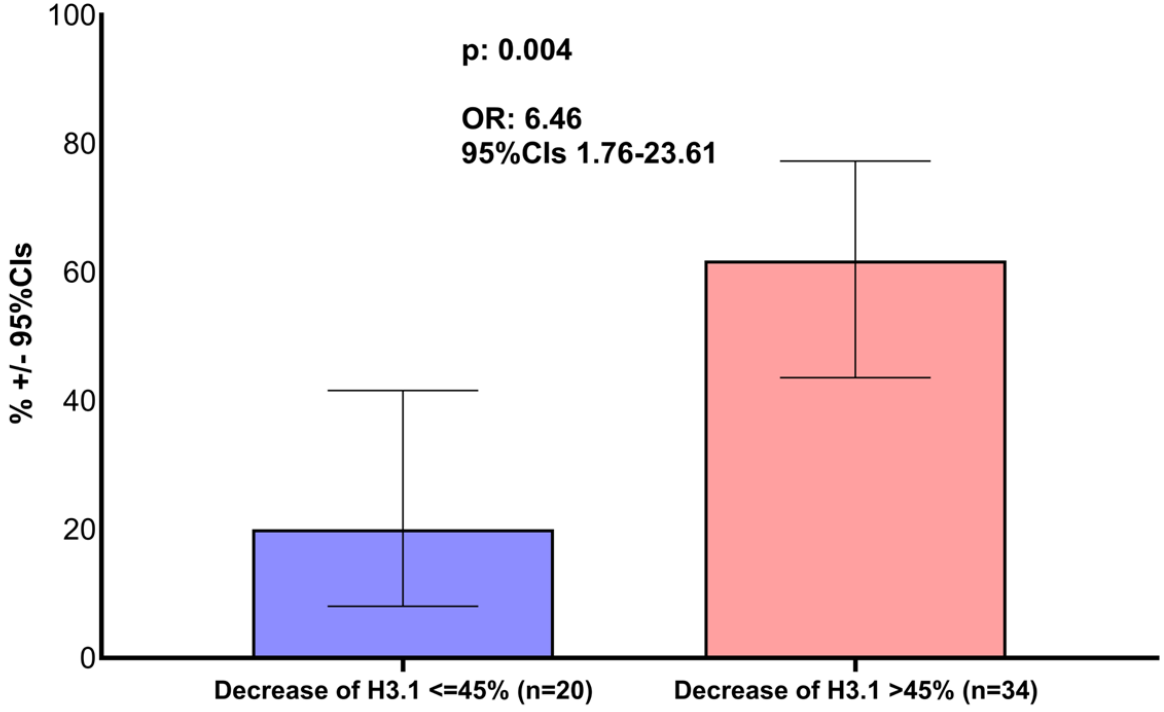
(Theohari et al. *medRxiv* https://doi.org/10.64898/2026.01.13.26343988)



n: number of patients
NET: neutrophil extracellular traps

>45% DECREASE OF BLOOD H3.1 PREDICTS IHS4-55 RESPONSE

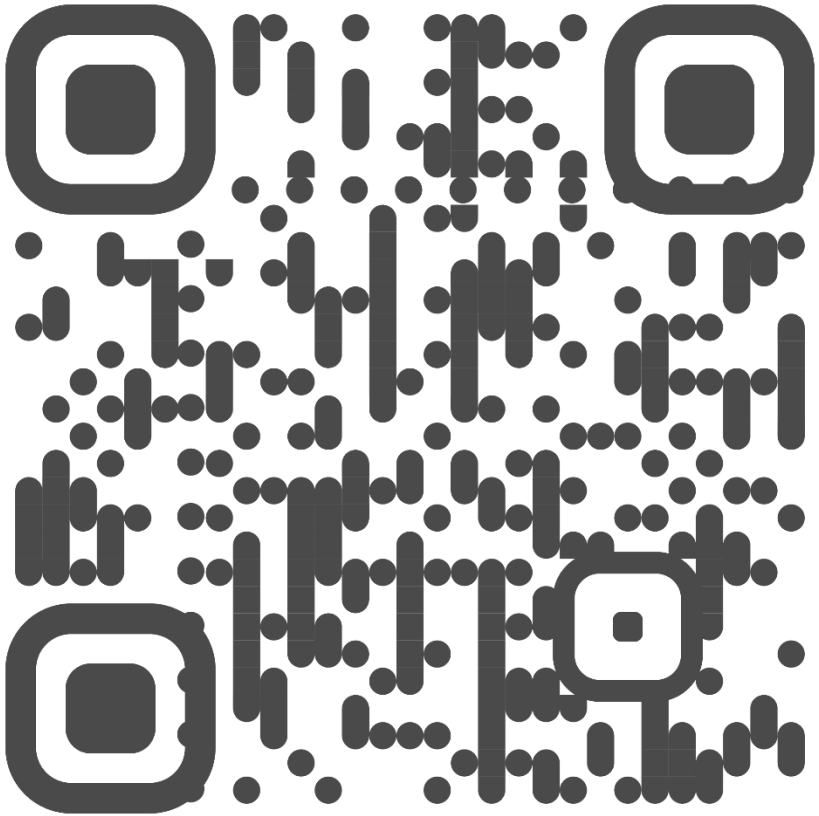
(Theohari et al. *medRxiv* https://doi.org/10.64898/2026.01.13.26343988)



CI: confidence interval
IHS4: international HS 4 score
n: number of patients
OR: odds ratio

PLASMA H3.1-NUCLEOSOMES TO CLASSIFY SEVERITY AND SURROGATE RESPONSE TO TREATMENT IN HIDRADENITIS SUPPURATIVA: A COHORT STUDY

Theohari et al. *medRxiv*
https://doi.org/10.64898/2026.01.13.26343988



How to measure Nu.Q® H3.1 biomarker

Automated solution

AVAILABLE NOW

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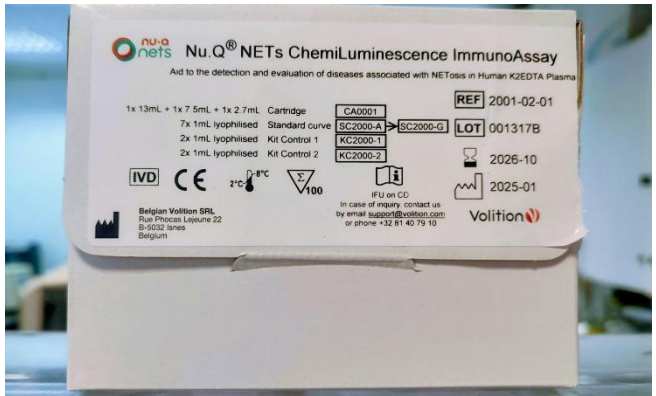

Point-of-Care solution

UNDER DEVELOPMENT

CONCLUSIONS & CONSIDERATIONS

Conclusions

- Blood H3.1 ≥24ng/ml classifier of HS
- Indicates higher degree of inflammation and dT formation
- >45% decreases predict HiSCR responses

Considerations for precision immunotherapy

- Use H3.1 ≥24ng/ml classifier to select patients for treatment?
- Can >45% decrease used to decide on duration of treatment?

dT: draining tunnes
HiSCR: HS clinical response score

OUR RESEARCH GROUP

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