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HELLENIC INSTITUTE FOR THE STUDY OF SEPSIS

CHANGE OF GENOMIC EXPRESSION TO PREDICT OUTCOME

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CONFLICT OF INTEREST DISCLOSURE

- Honoraria (paid to the University of Athens) from AbbVie USA, Biotest AG Germany, Brahms ThermoFisher GmbH Germany and The Medicines Company USA
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WHAT DOES GENOMIC ANALYSIS OFFER?

- Overall understanding of the pathophysiology of the host through pathway analysis
- Association between predominance or attenuation of a pathway and final outcome
- Association between change of pathway expression and carriage of gene SNPs

THE BEST EXAMPLE: GAinS STUDY

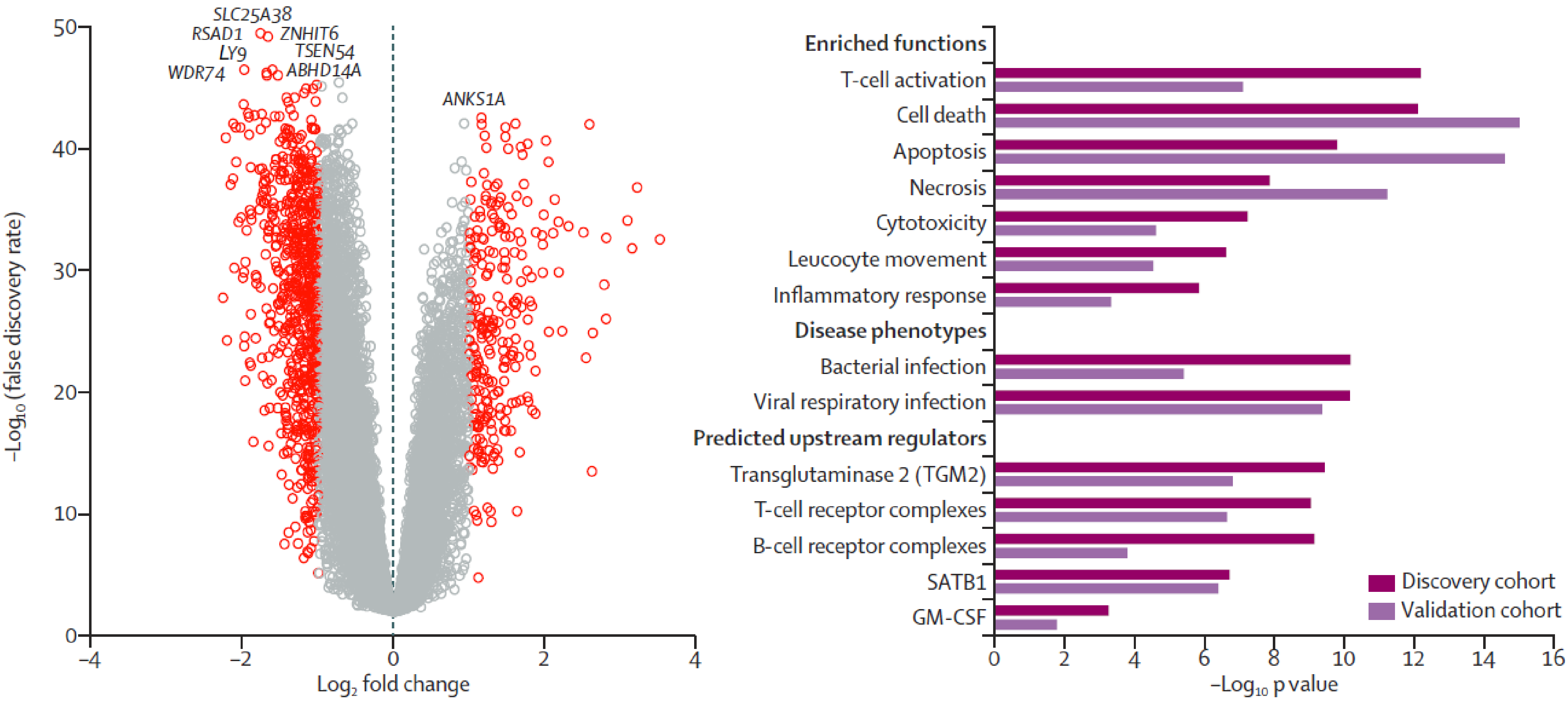
(Davenport EE, et al. *Lancet Resp Med* 2016; 4: 259)

- 26,185 gene probes
- 644,390 SNPs vs 17,437 probes
- Association with 393 probes from LPS-tolerated monocytes

- UK Genomic Advances in Sepsis
- Collaboration of 29 ICUs
- Total blood leukocyte profiling
- Community-acquired pneumonia
- Sampling immediately after ICU admission

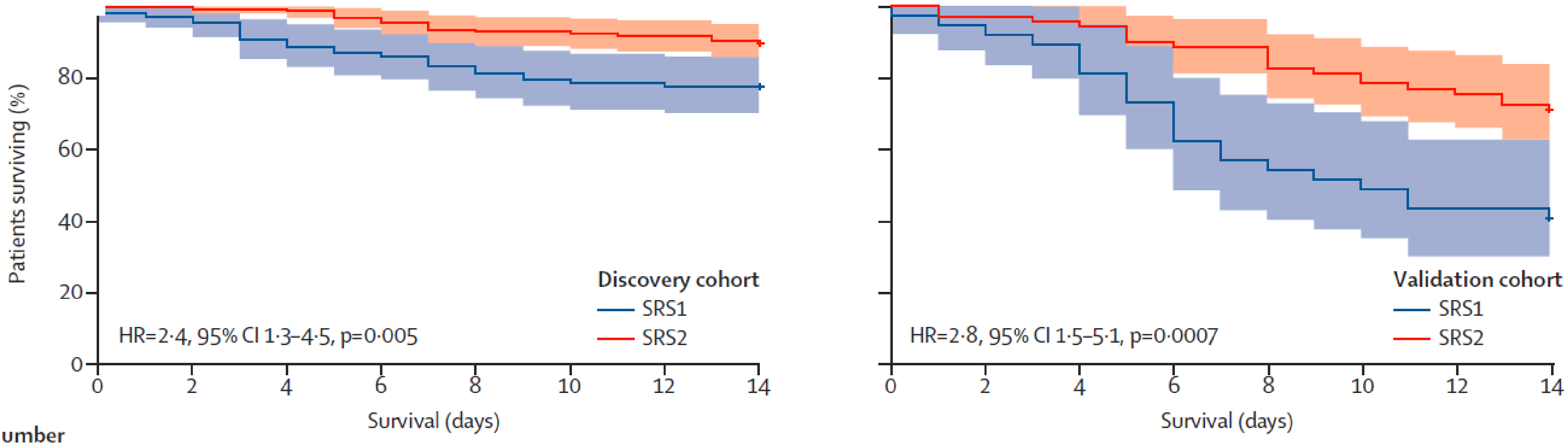
	Discovery cohort	**Validation cohort**
Patients	265	106
Male gender	145 (55%)	79 (75%)
APACHE II	18	23
14-day mortality	15%	40%

3,080 DIFFERENTIALLY EXPRESSED GENES



2,260 DOWN-REGULATED GENES: SEPSIS RESPONSE SIGNATURE (SRS)1

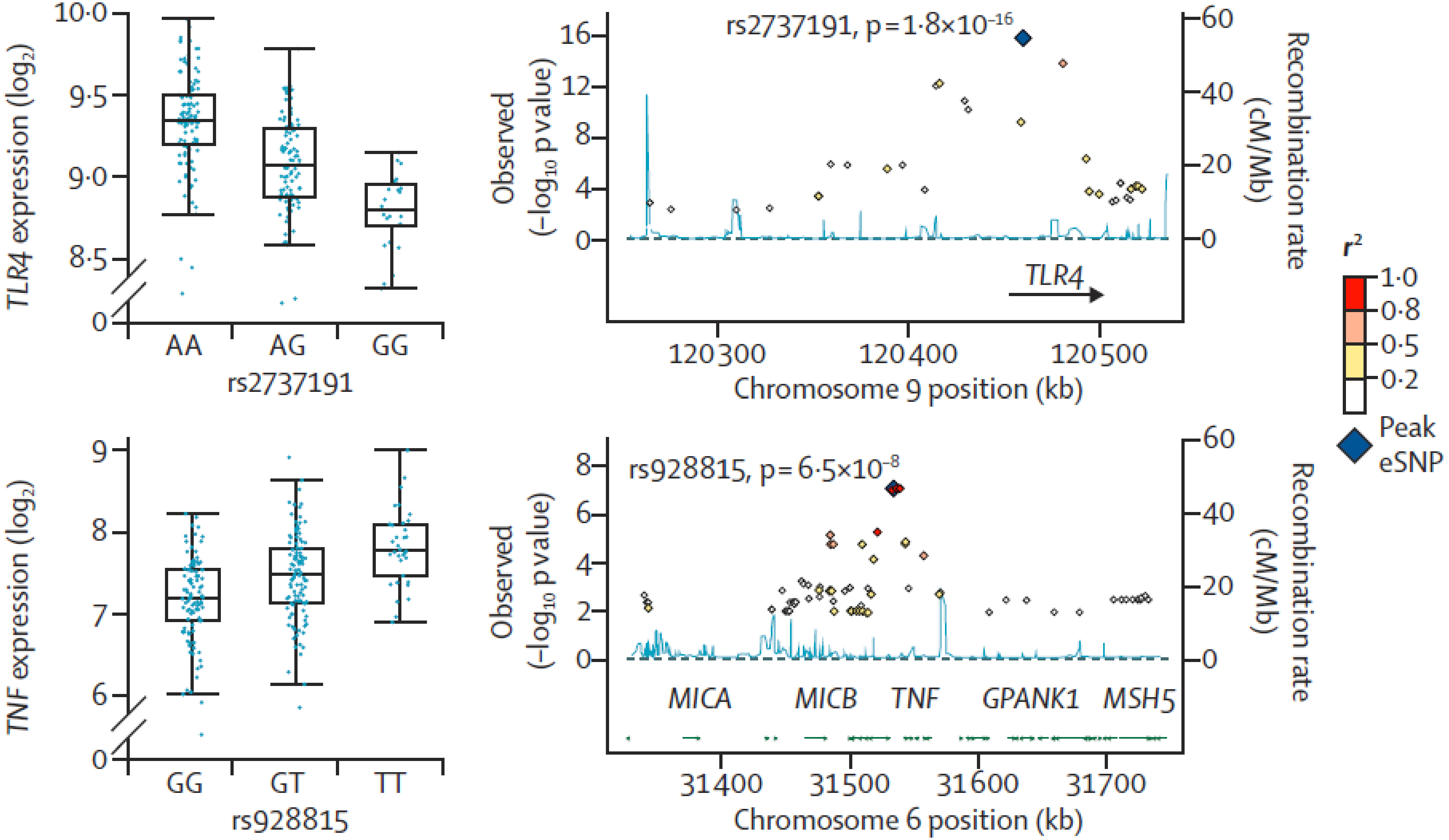
SRS1: *DYRK2, CCNB1IP1, TDRD9, ZAP70, ARL14EP, MDC1, ADGRE3*



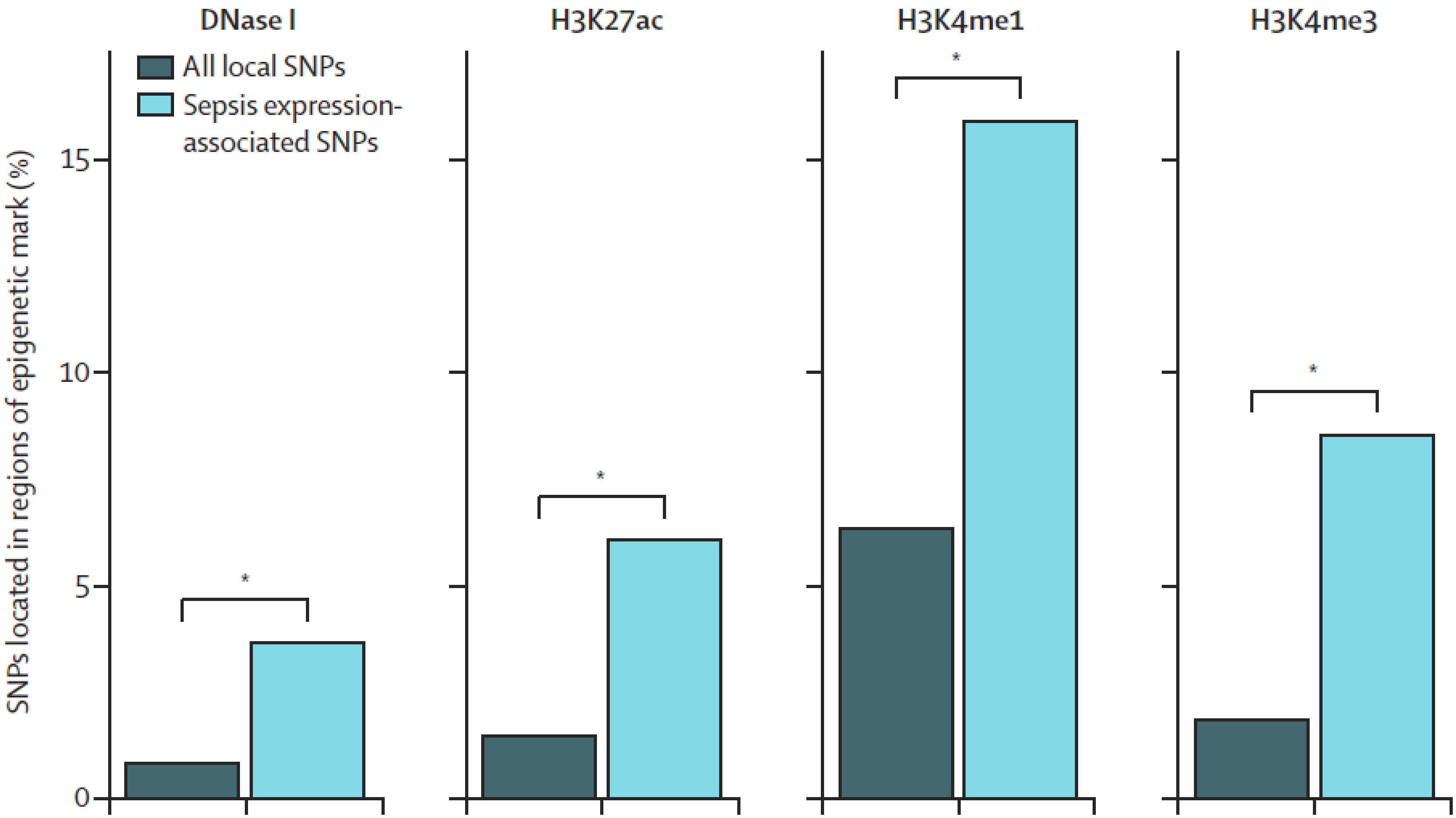
Number at risk																
SRS1	106	103	96	93	88	85	84	84	36	34	30	23	20	18	16	15
SRS2	157	156	155	150	146	145	144	141	69	67	65	61	57	54	52	49

TNF, IL-6, IL-1β were not changed….

EXPRESSION QUANTITATIVE TRAIT LOCI
TNF- TLR4 EXPRESSION IS IMPORTANT



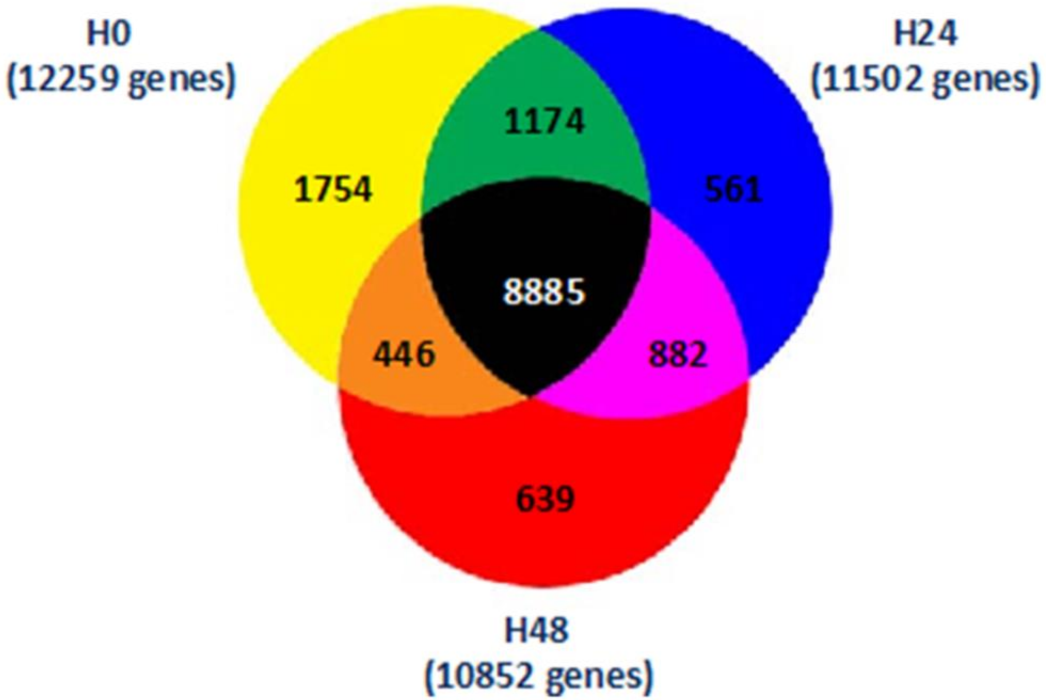
qQTL AND EPIGENETIC SNPS



OVER TIME CHANGE OF GENE EXPRESSION

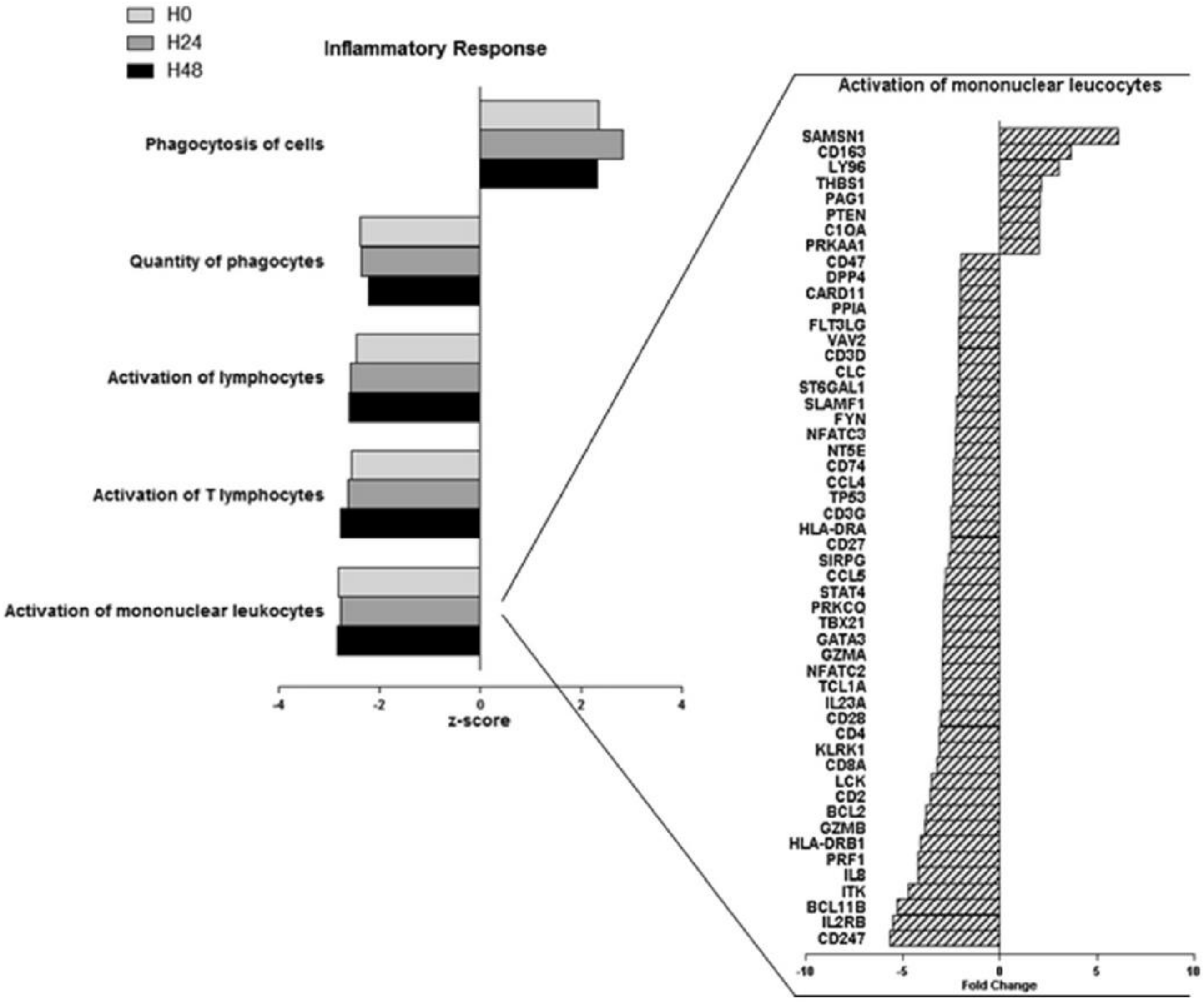
(Cazalis A, et al. *Intensive Care Med Exper* 2014; 2: 20)

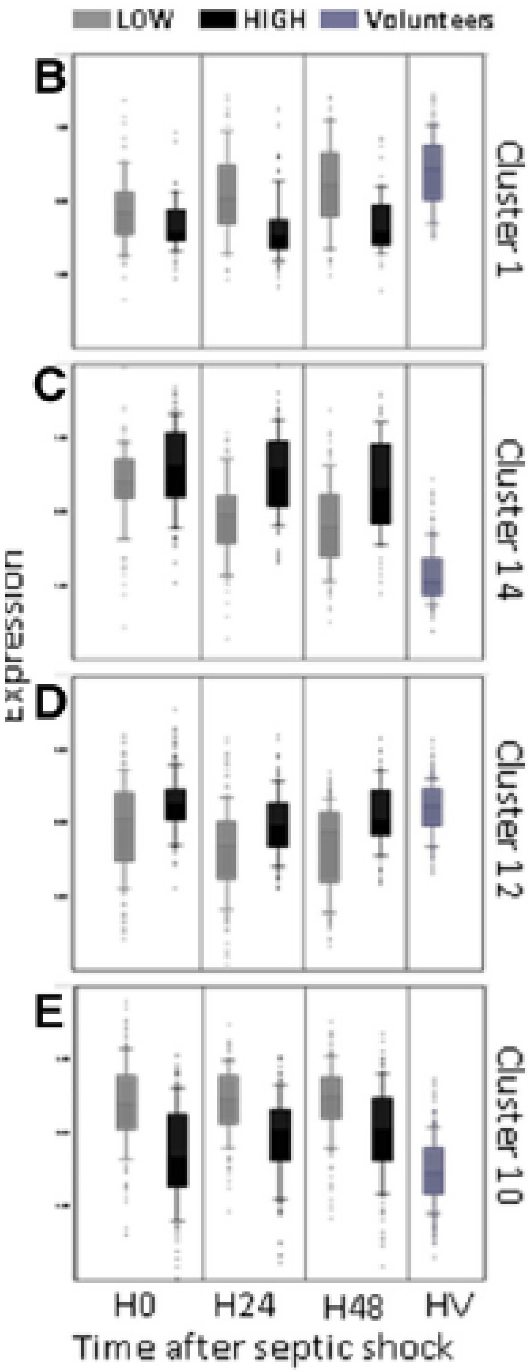
- 28 patients with septic shock
- Sampling <12 hrs from vasopressors
- Total whole blood profiling
- Repeat sampling after 24 and 48 hours



ASSOCIATION WITH IMMUNE FUNCTION

(Cazalis A, et al. *Intensive Care Med Exper* 2014; 2: 20)





Down-regulated pathways

Up-regulated pathways

Down-regulated pathways ONLY in SAPSII low group

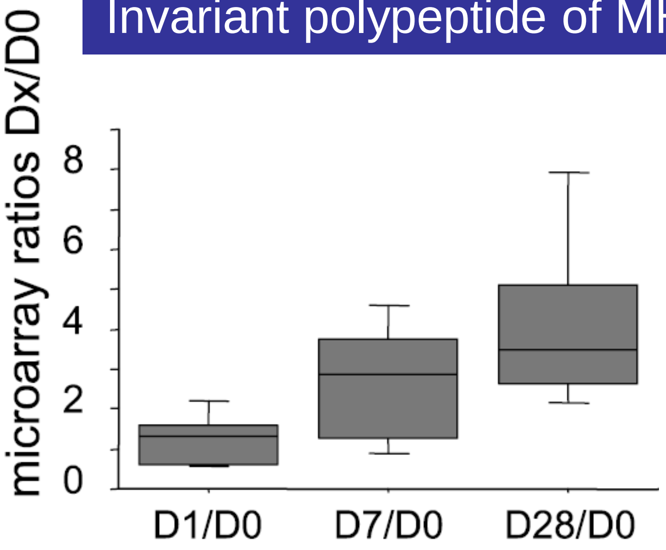
Up-regulated pathways ONLY in SAPSII low group

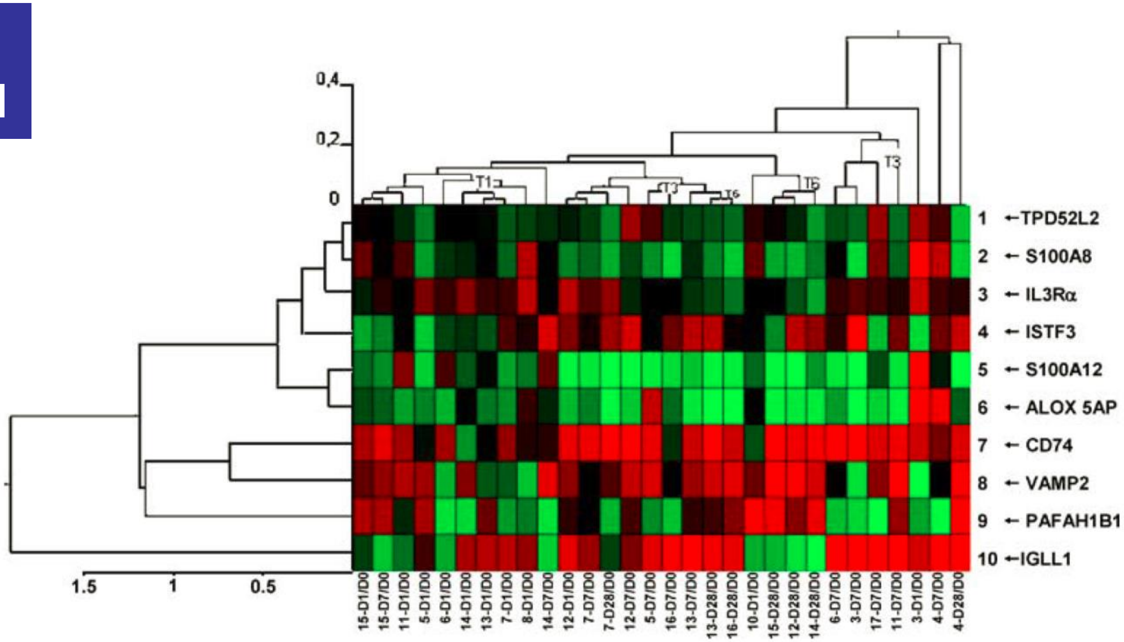
OVER-TIME CHANGE AND OUTCOME

(Payen D, et al. *Intensive Care Med* 2008; 34: 1371)

- 17 patients with septic shock
- Total mononuclear cell profiling
- Repeat sampling after 1, 7 and 28 days

CD74
Invariant polypeptide of MHC-II





A PHASE II STUDY

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Research Paper

A Transcriptomic Biomarker to Quantify Systemic Inflammation in Sepsis — A Prospective Multicenter Phase II Diagnostic Study

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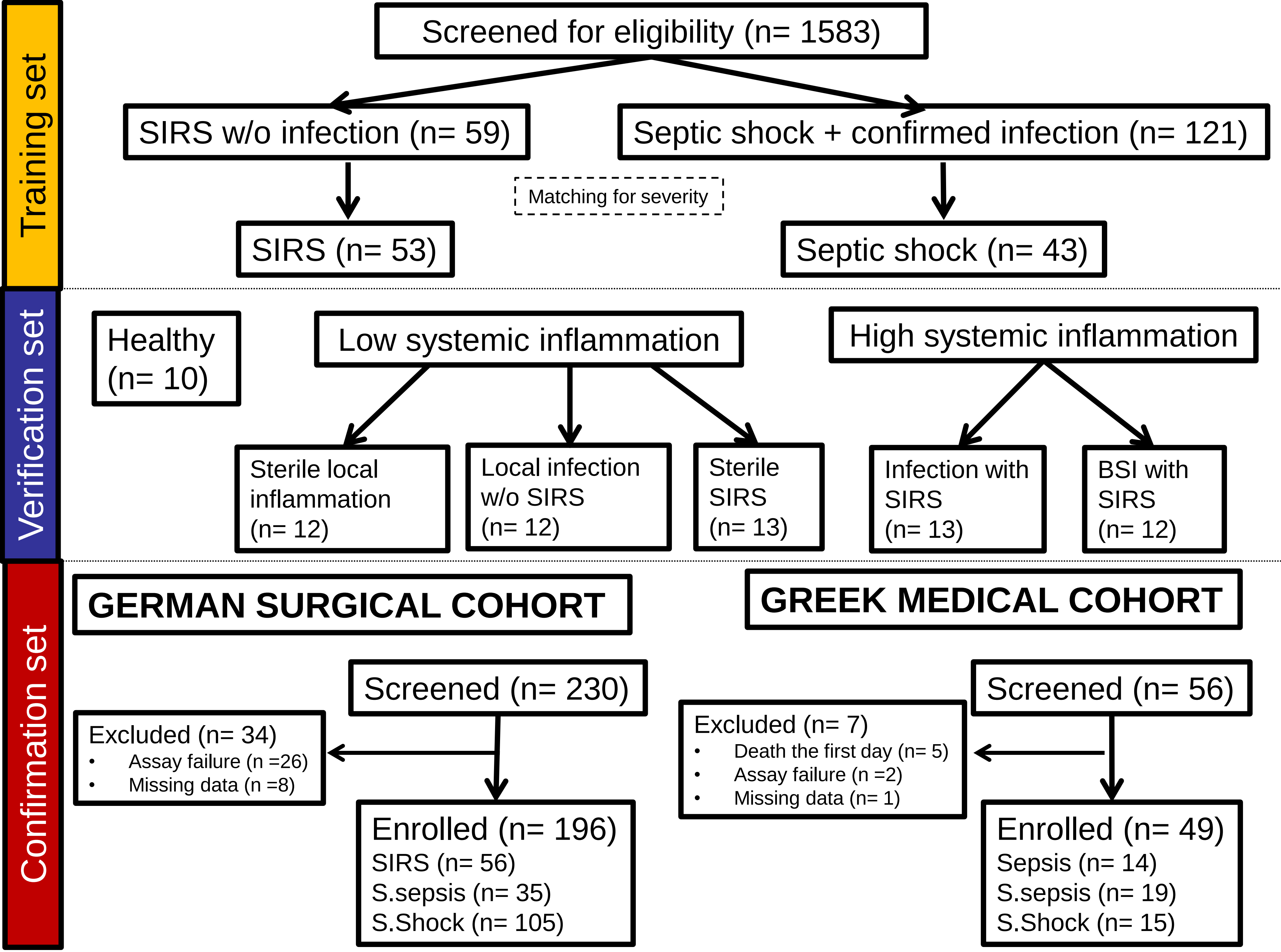
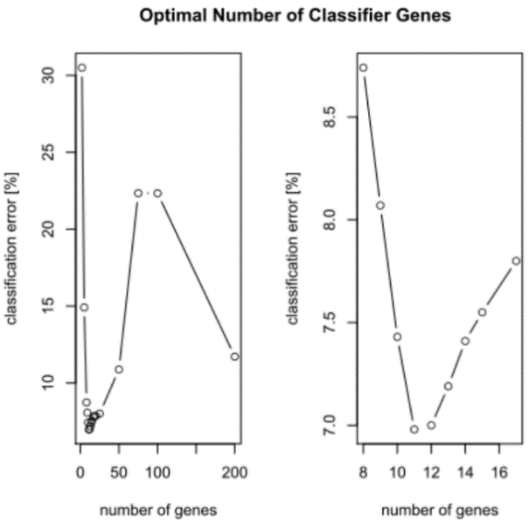
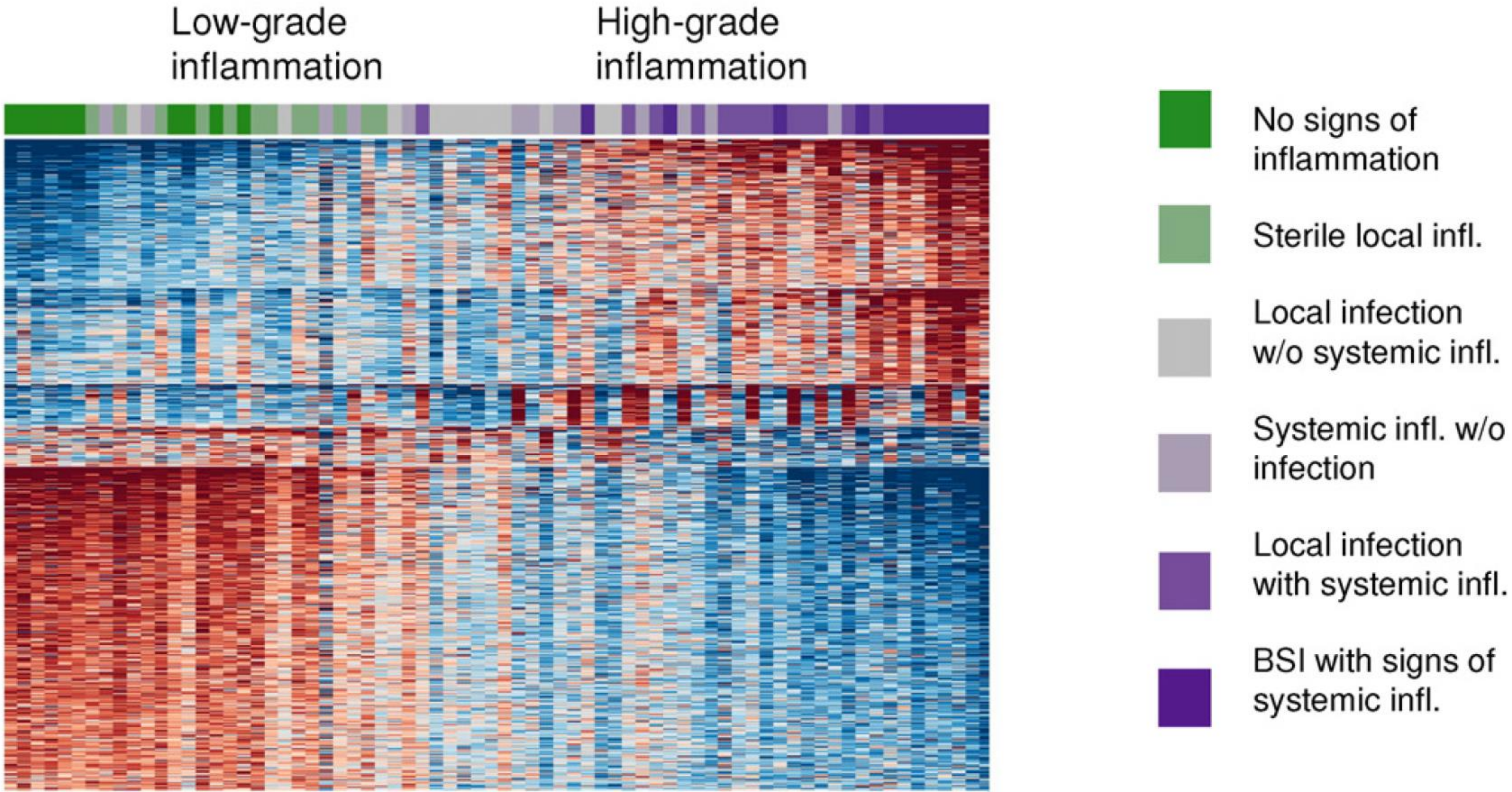

Training set
Screened for eligibility (n= 1583)
SIRS w/o infection (n= 59)
Septic shock + confirmed infection (n= 121)
Matching for severity
SIRS (n= 53)
Septic shock (n= 43)
Verification set
Healthy (n= 10)
Low systemic inflammation
High systemic inflammation
Sterile local inflammation (n= 12)
Local infection w/o SIRS (n= 12)
Sterile SIRS (n= 13)
Infection with SIRS (n= 13)
BSI with SIRS (n= 12)
Confirmation set
GERMAN SURGICAL COHORT
GREEK MEDICAL COHORT
Screened (n= 230)
Excluded (n= 34)
Assay failure (n =26)
Missing data (n =8)
Enrolled (n= 196)
SIRS (n= 56)
S.sepsis (n= 35)
S.Shock (n= 105)
Screened (n= 56)
Excluded (n= 7)
Death the first day (n= 5)
Assay failure (n =2)
Missing data (n= 1)
Enrolled (n= 49)
Sepsis (n= 14)
S.sepsis (n= 19)
S.Shock (n= 15)

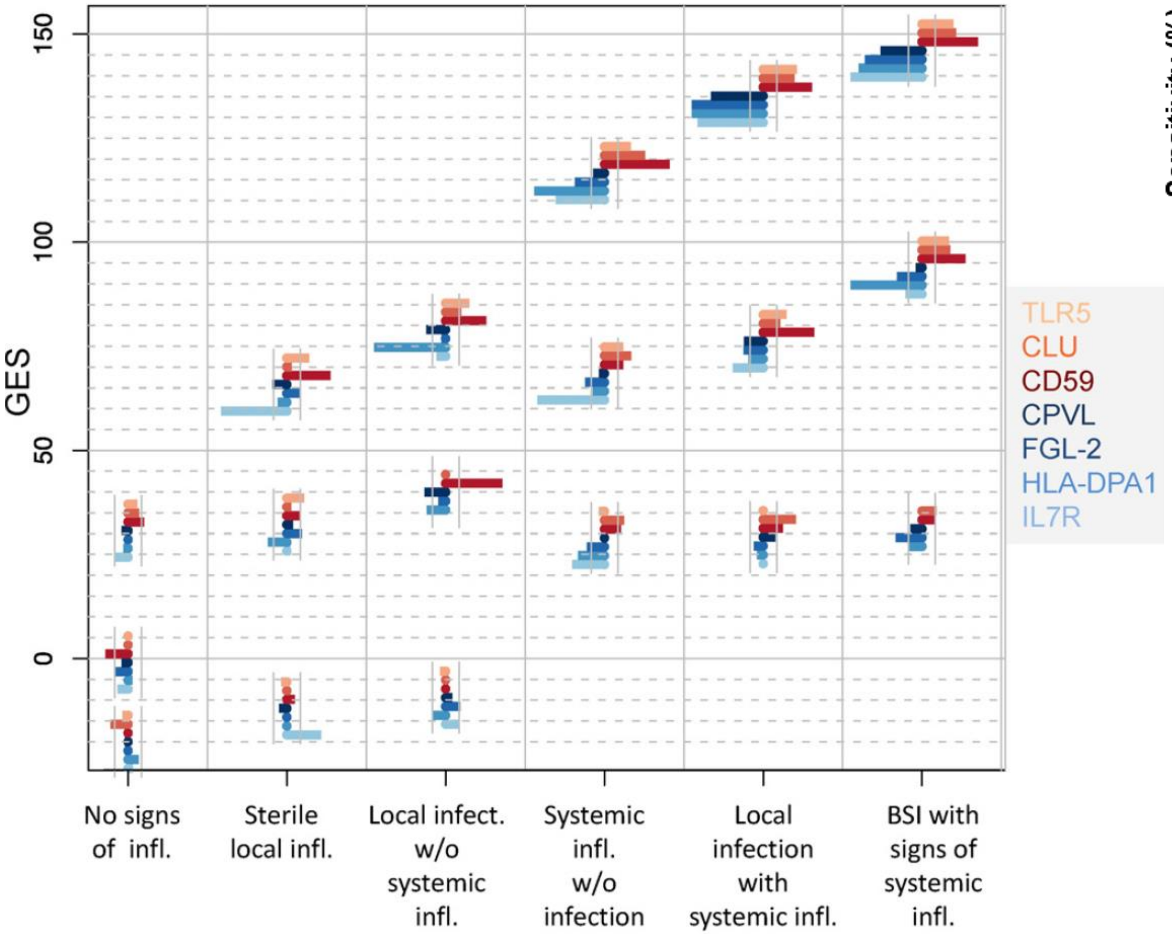
TRAINING SET



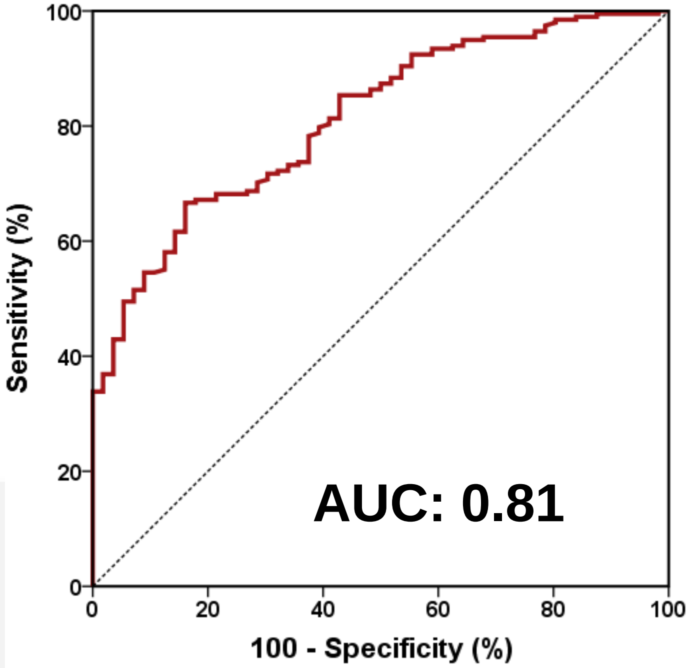


THE GENOMIC SCORE

TRAINING SET



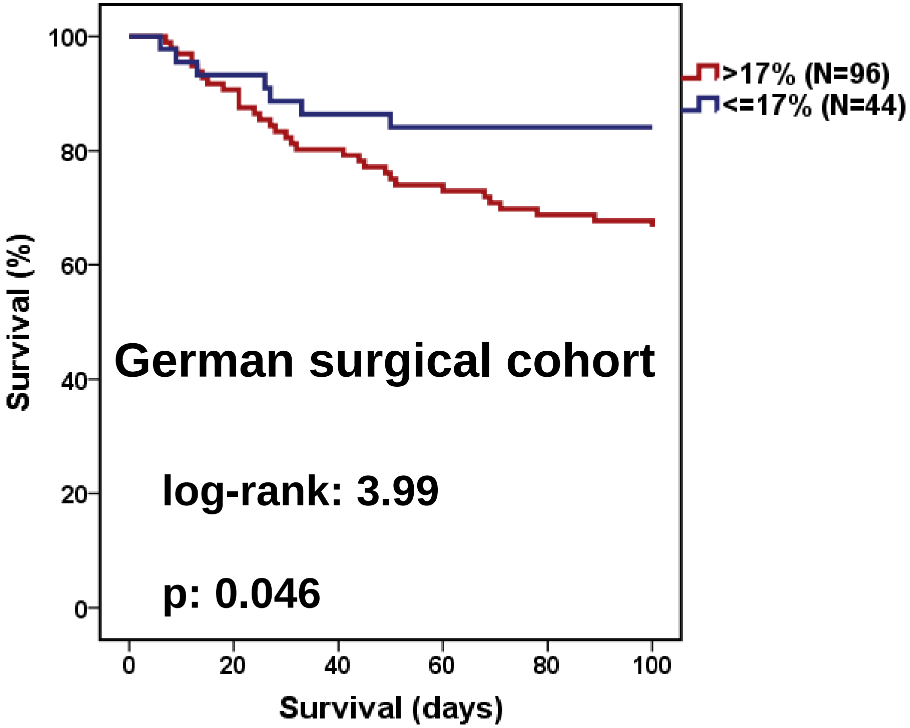
CONFIRMATION SET
Diagnosis of infection

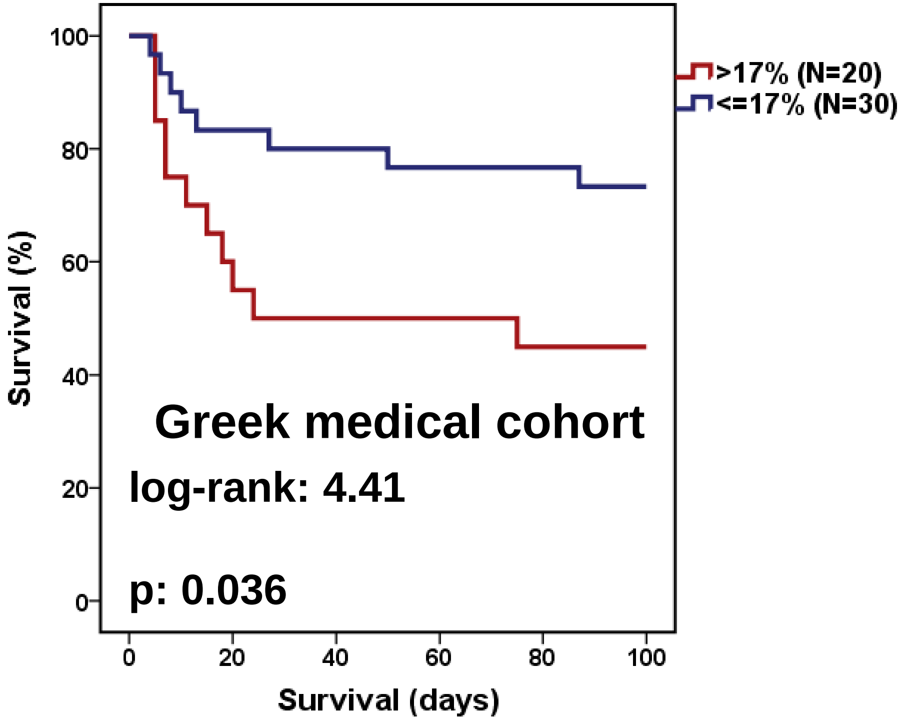


GES ≥55

- Sensitivity: 80%
- PPV: 87%

CHANGE OF THE DOWN SCORE ON DAY 3 AND FINAL OUTCOME





	OR*	95%CIs	p
APACHE II	-		
S.sepsis/ shock	7.92	1.80-34.77	0.006
<17% decrease	0.40	0.17-0.93	0.032

*adjusted

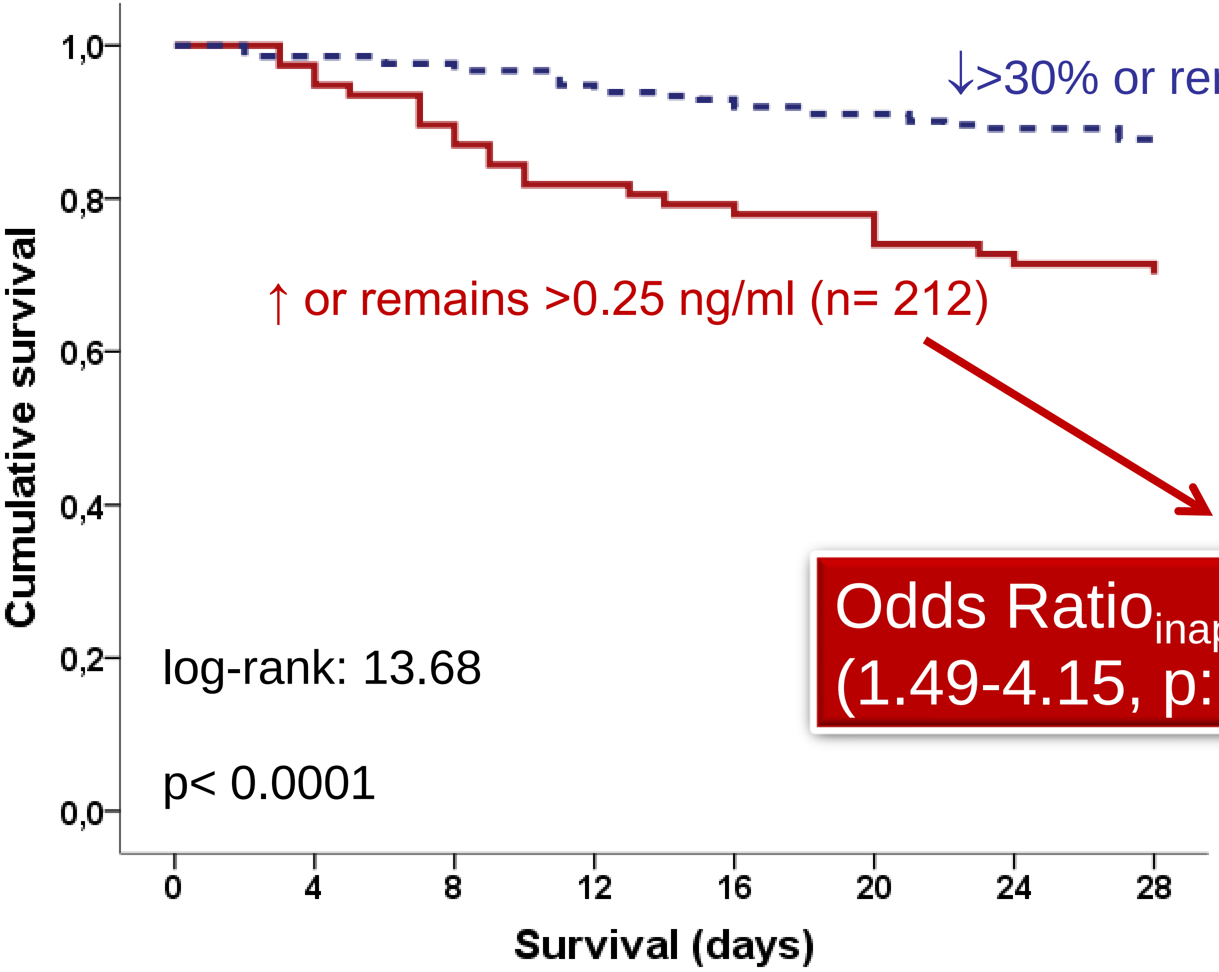
SOME RANDOM AND….

…PROVOCATIVE THOUGHTS

CHANGES DAY 1 TO DAY 3

(Georgopoulou AP, et al. *J Crit Care* 2011; 26: 331.e1)

289 patients, (33.4%) with bacteremia



log-rank: 13.68

p< 0.0001

Odds Ratio$_{\text{inappropriate antimicrobials}}$: 2.52 (1.49-4.15, p: 0.003)

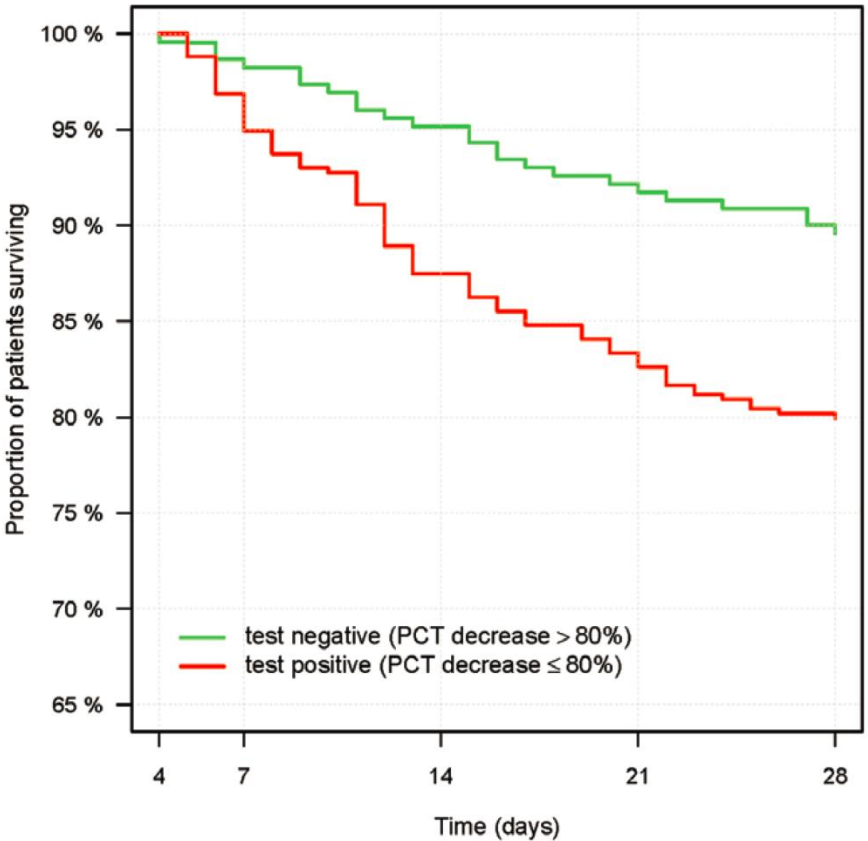
THE MOSES TRIAL

(Schuetz P, et al. *Crit Care Med* 2017; 45: 781)

- PCT measurements
- <12 h from start of severe sepsis/shock
- Daily for 5 days

Variable	Multivariate HR	p-value
≤80% PCT decrease	1.97	0.009
APACHE II	1.17	0.49
Appropriate antibiotics	1.36	0.23

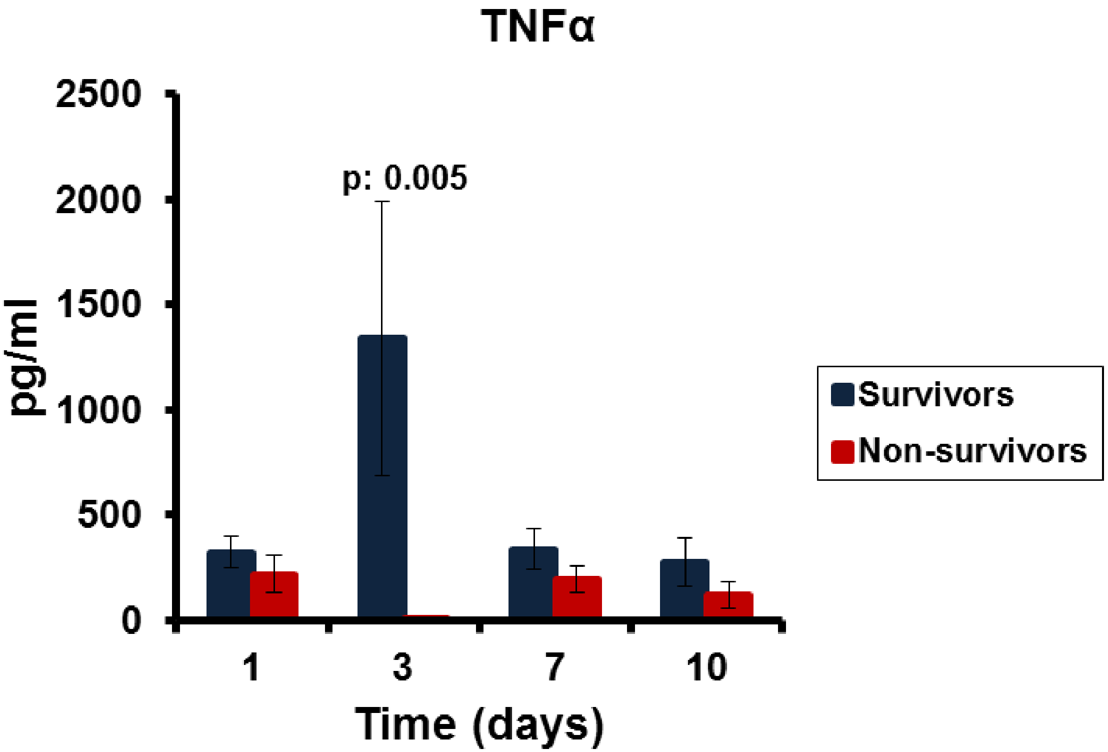
PCT decrease (n=646)



OVER-TIME CHANGE OF TNFα-STIMULATION

(Antonakos N, et al. *Critical Care* 2017; 24: 48)

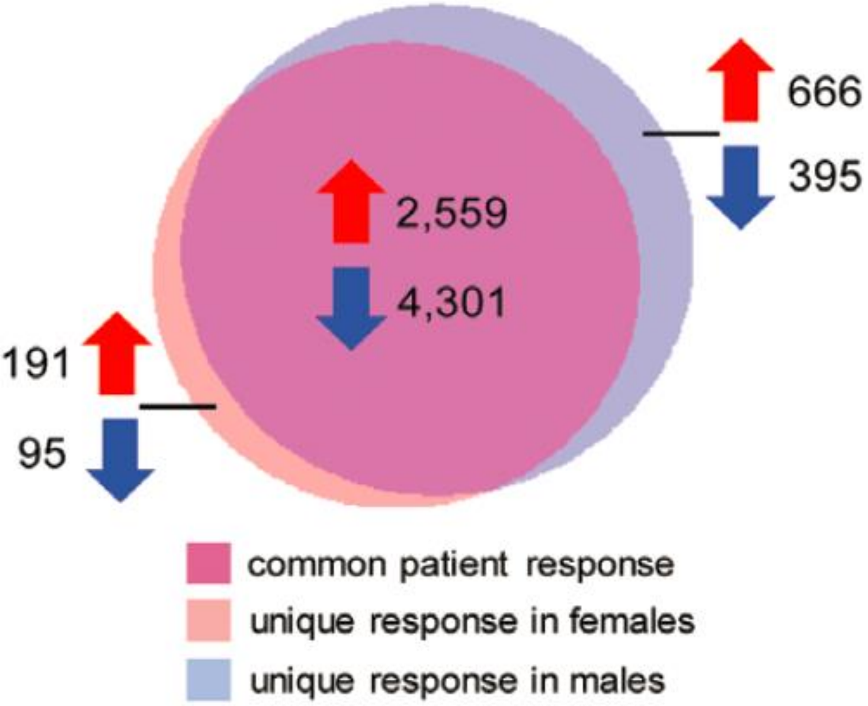
- 95 patients with septic shock
- Isolation and ex-vivo stimulation of PBMCs
- Repeat after 3, 7 and 10 hours

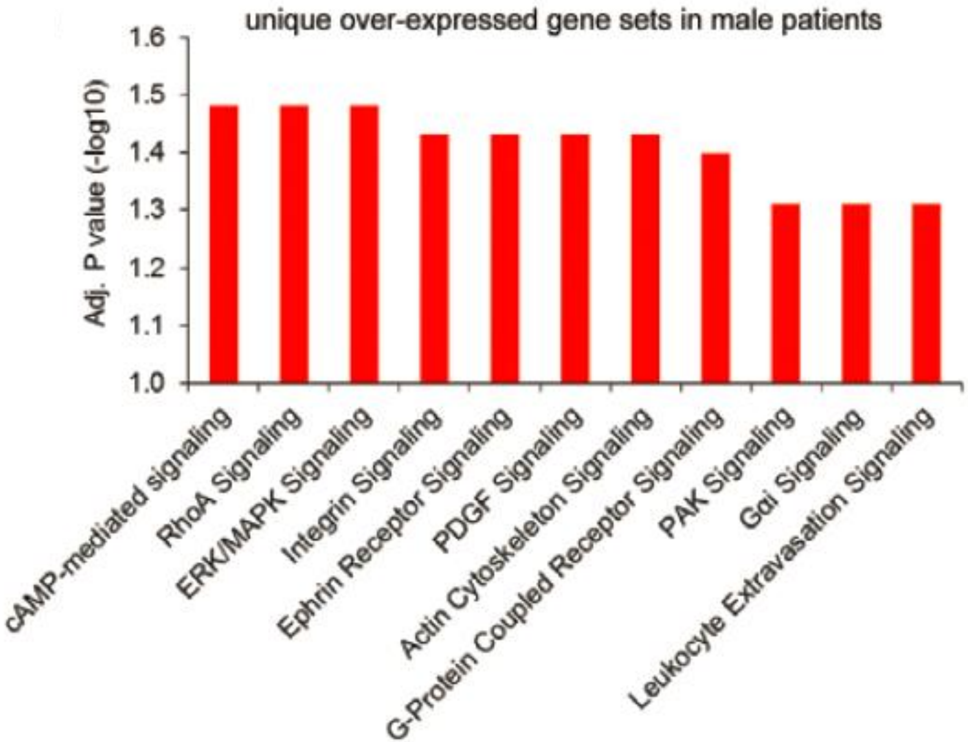


THE EFFECT OF GENDER ON LEYKOCYTE GENE EXPRESSION IN SEPSIS

(van Vught LA, et al. *Critical Care Med* 2017; E-pub)

>80% similar gene expression but…





CONCLUSIONS

- Transcriptomics allow understand the modulated pathway in sepsis
- Study of the impact of individuals gene SNPs

- Association of down-regulation of innate and adaptive immune function pathways with severity
- Reversal of gene expressions associated with impaired immune function the first 72 hours is linked with favorable outcome
- However…..

- This information is also provided by other tests
- Cost? Simplicity?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