A vedolizumab specific four-gene colonic signature accurately predicting future endoscopic remission in patients with inflammatory bowel disease

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Disclosures

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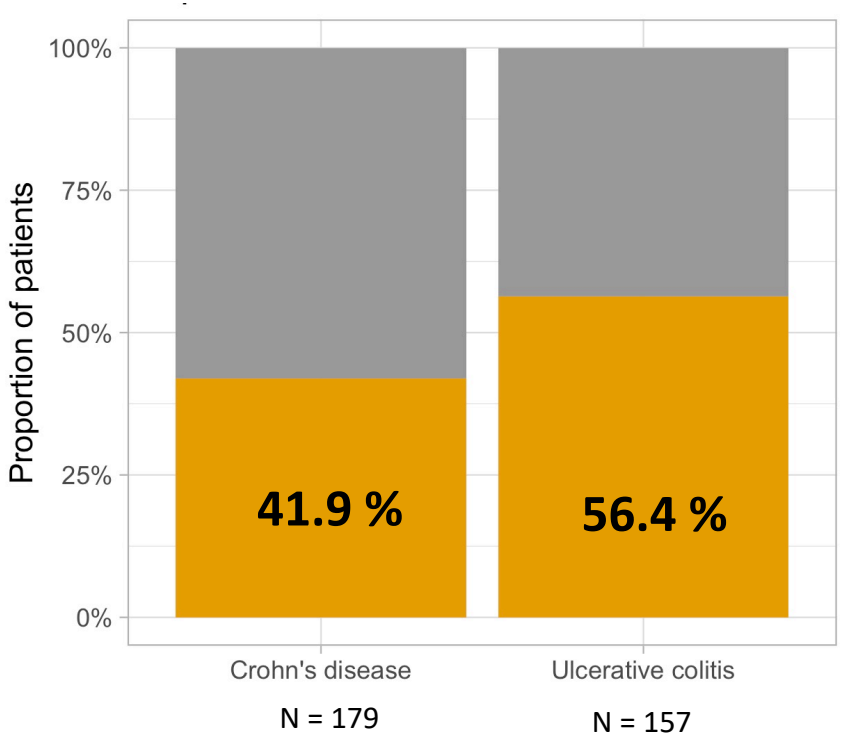
Introduction

- **Vedolizumab**, targeting the α4β7 integrin, has proven **efficacy** in both **Crohn's disease** and **ulcerative colitis** during the GEMINI phase III program[1,2]

- **Real-life endoscopic remission** data are **encouraging**, though we still **face** a **therapeutic gap**[3]

- With the increased therapeutic armamentarium, **predictive biomarkers** are urgently **awaited**.



UC= Mayo endoscopic subscore 0-1

CD = absence of ulcerations

1. Feagan B et al. *NEJM.* 2013.
2. Sandborn WJ et al. *NEJM*. 2013.
3. Verstockt B et al. *14th Congress of ECCO*. 2019.

Aims

To identify **baseline transcriptomic** profiles **predicting future endoscopic remission** in **inflamed colonic biopsies** of IBD patients initiating **vedolizumab**

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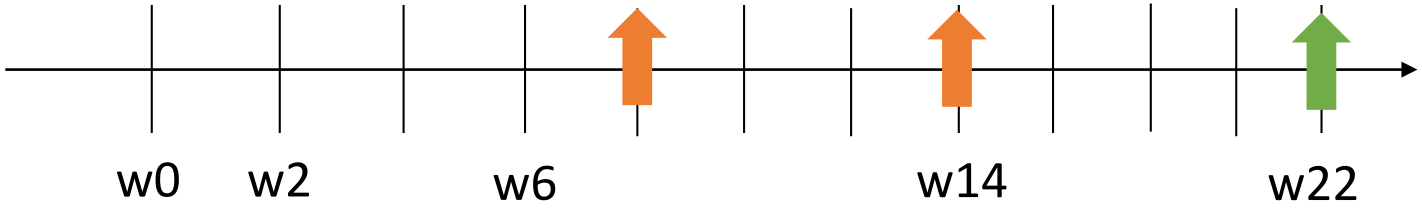
Methods

Inflamed colonic **biopsies** → Total **RNA** → RNA Sequencing Illumina HiSeq 4000 NGS

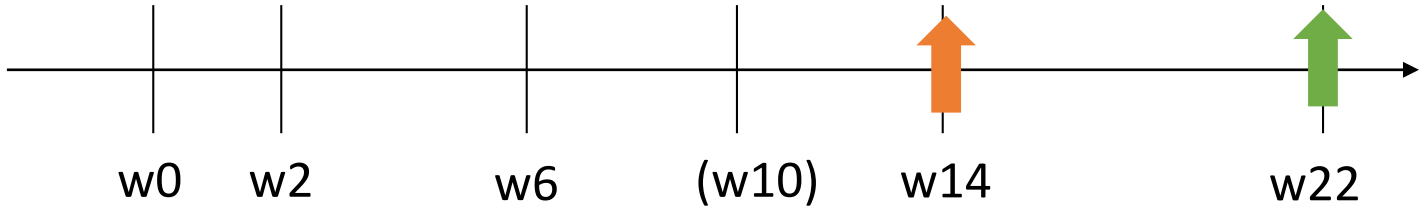
UC : Mayo endoscopic score 0-1

CD: absence of ulcerations

Anti-TNF therapy



Vedolizumab therapy



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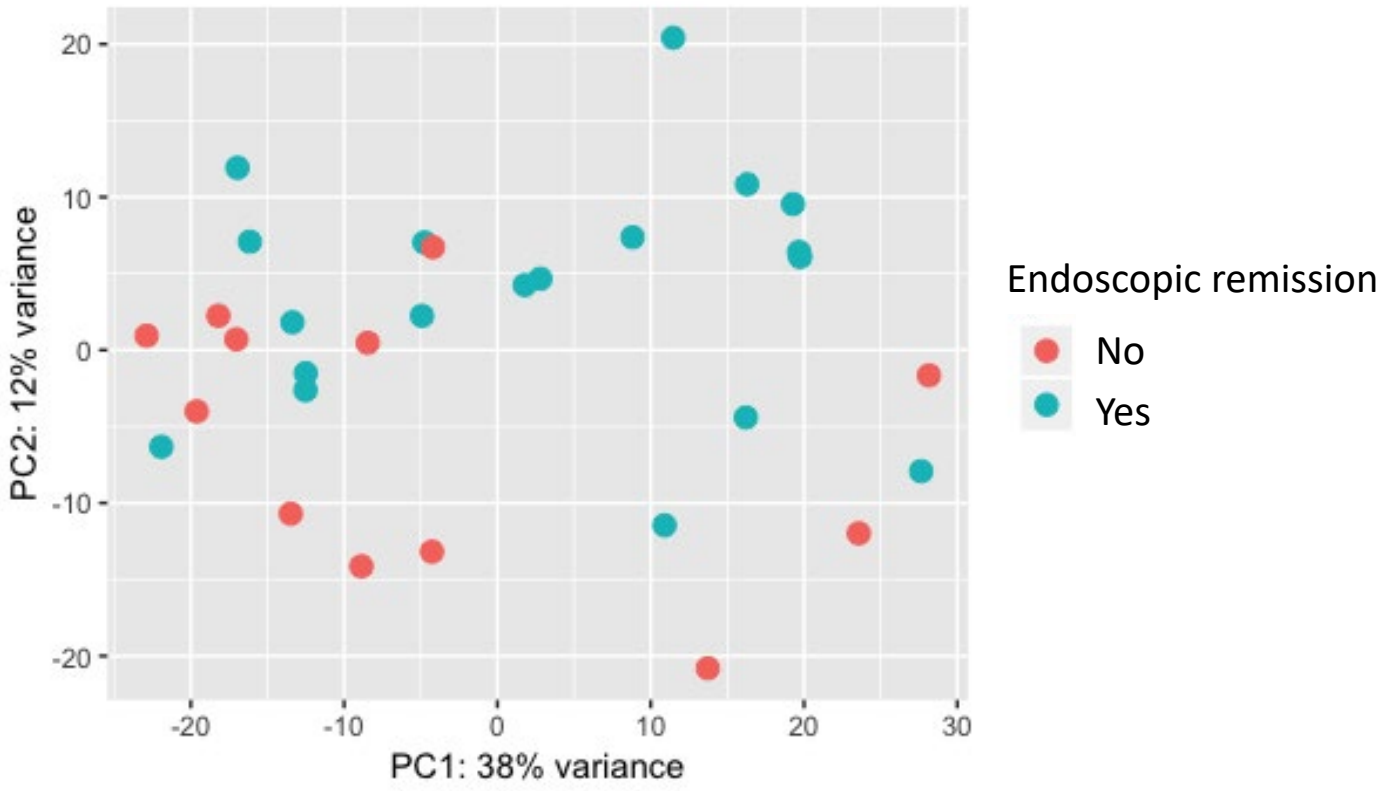
Differential gene expression



	Nominal p-value 0.01	FDR correct p-value < 0.25	FDR correct p-value < 0.10	FDR correct p-value < 0.05
Number of genes differentially expressed	327	44	10	5

Predictive modelling

31 colonic biopsies

20 discovery
9 NH, 11 MH

11 validation
3 NH, 8 MH

44 diff expressed genes
(FDR 0.25)

Random generalized
linear modelling

4 gene signature

Accuracy	80.0%
Sensitivity	81.8%
Specificity	77.8%
PPV	81.8%
NPV	77.8%
LR +	3.7
LR -	0.23

Accuracy	100.0%
Sensitivity	100.0%
Specificity	100.0%
PPV	100.0%
NPV	100.0%
LR +	∞
LR -	0

MH = endoscopic remission
NH = no remission

Predictive modelling – independent validation

RNA-seq validation
n = 16
11 NH, 5 MH

Accuracy	81.3%
Sensitivity	66.7%
Specificity	90.0%
PPV	80.0%
NPV	81.8%
LR +	6.67
LR -	0.37

Microarray validation
n = 13 (MILLENIUM)
10 NH, 3 MH

Accuracy	76.9%
Sensitivity	100.0%
Specificity	70.0%
PPV	50.0%
NPV	100.0%
LR +	3.3
LR -	0

MH = endoscopic remission
NH = no remission

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Predictive modelling – a vedolizumab specific signal

RNA-seq anti-TNF cohort
n = 24
16 NH, 8 MH

Accuracy	58.3%
Sensitivity	75.0%
Specificity	50.0%
PPV	42.9%
NPV	80.0%
LR +	1.5
LR -	0.5

MH = endoscopic remission
NH = no remission

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Conclusions

- We **identified** and **validated** the first **vedolizumab-specific** predictive **4-gene expression signature**
- Allowing **treatment guidance** in **IBD patients** with **colonic involvement**
- Further **validation** in **bigger independent cohorts**

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KU LEUVEN

VVGE Vlaamse Vereniging voor Gastro-Enterologie

erc European Research Council

ECCO European Crohn's and Colitis Organisation

fwo

BIRD BELGIAN INFLAMMATORY BOWEL DISEASE RESEARCH AND DEVELOPMENT

THE LEONA M. AND HARRY B. HELMSLEY CHARITABLE TRUST

Back up

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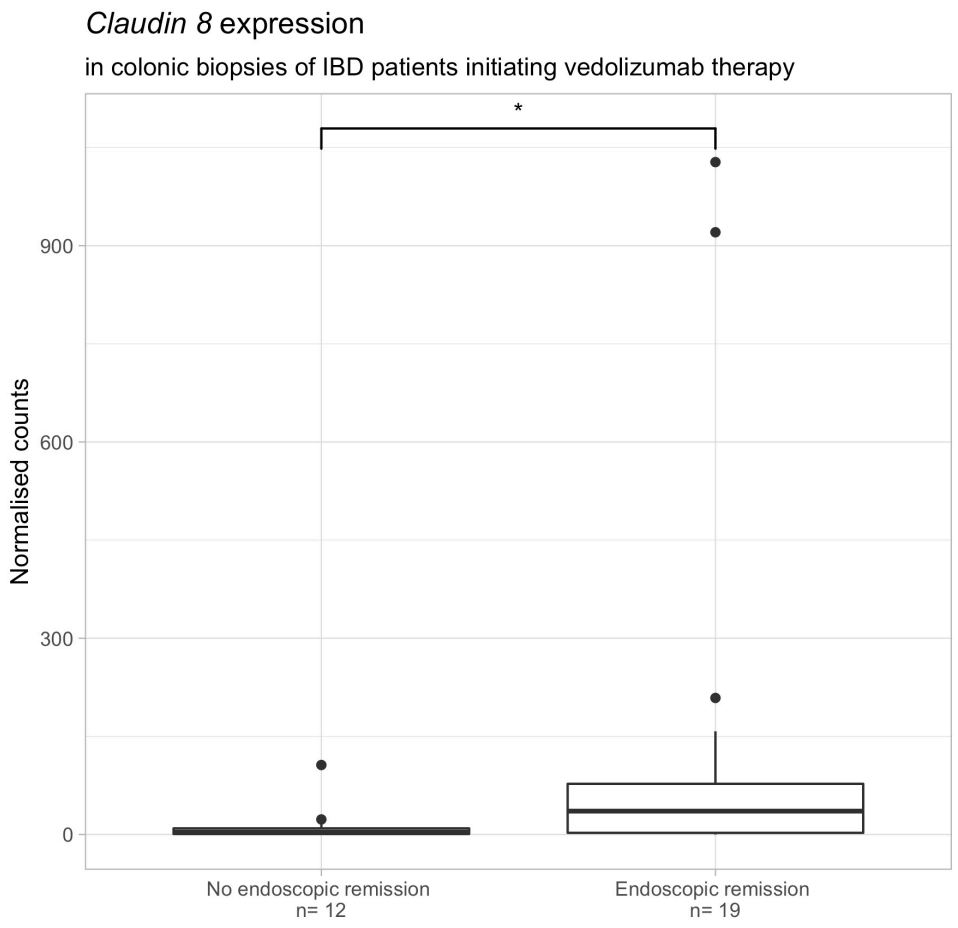
Included patients

	VEDOLIZUMAB (n=31)	ANTI-TNF COHORT (n=24)
Diagnosis, *n*, %		
- **Ulcerative colitis**	20 (64.5)	16 (66.7)
- **Crohn's disease**	11 (35.5)	8 (33.3)
Age, *years*, (median, IQR)	45.3 (29.6 – 56.3)	36.0 (22.0 – 54.9)
Gender, *n women*, %	17 (54.8)	15 (62.5)
Disease duration, *years*, (median, IQR)	8.4 (4.0-15.3)	1.9 (0.5 – 7.0)
Disease location, *n*, %		
- **L1**	0 (0)	0 (0.0)
- **L2**	2 (18.2)	2 (25.0)
- **L3**	9 (81.8)	6 (75.0)
- **L4**	2 (18.2)	1 (12.5)
- **E1**	3 (15.0)	0 (0.0)
- **E2**	10 (50.0)	13 (81.3)
- **E3**	7 (35.0)	3 (18.7)

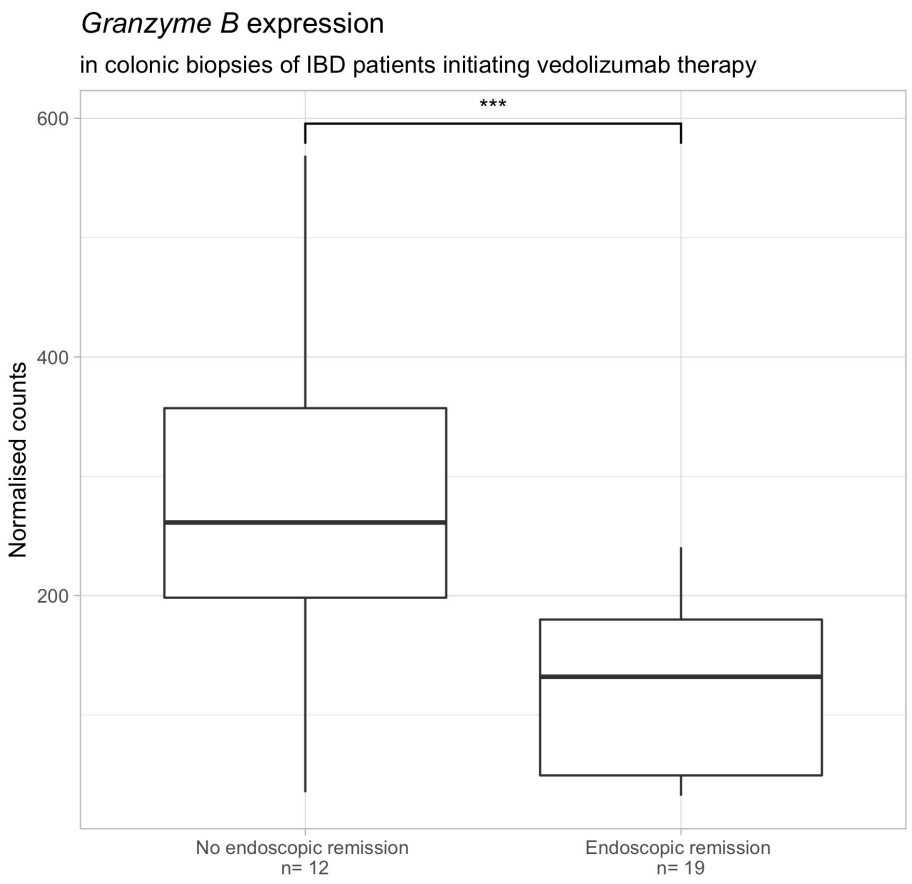
Included patients

Disease behaviour, *n*, %		
- **B1**	6 (54.5)	4 (50.0)
- **B2**	3 (27.3)	3 (37.5)
- **B3**	2 (18.2)	1 (12.5)
- **Perianal**	5 (45.5)	2 (45.5)
Steroid use during induction, *n*, %		
- **Topical**	10 (32.3)	5 (16.1)
- **Systemic**	8 (25.8)	7 (22.6)
Previous anti-TNF exposure, *n*, %		
- **Naïve**	10 (32.3)	NA
- **exposed**	21 (67.7)	
C-reactive protein, *mg/L*, (median, IQR)	2.0 (0.9 – 6.7)	6.3 (1.8 – 17.0)

Differential gene expression – some top hit examples



Nominal p-value 5.0×10^{-6}
FDR correct p-value 0.02



Nominal p-value 1.0×10^{-4}
FDR correct p-value 0.12

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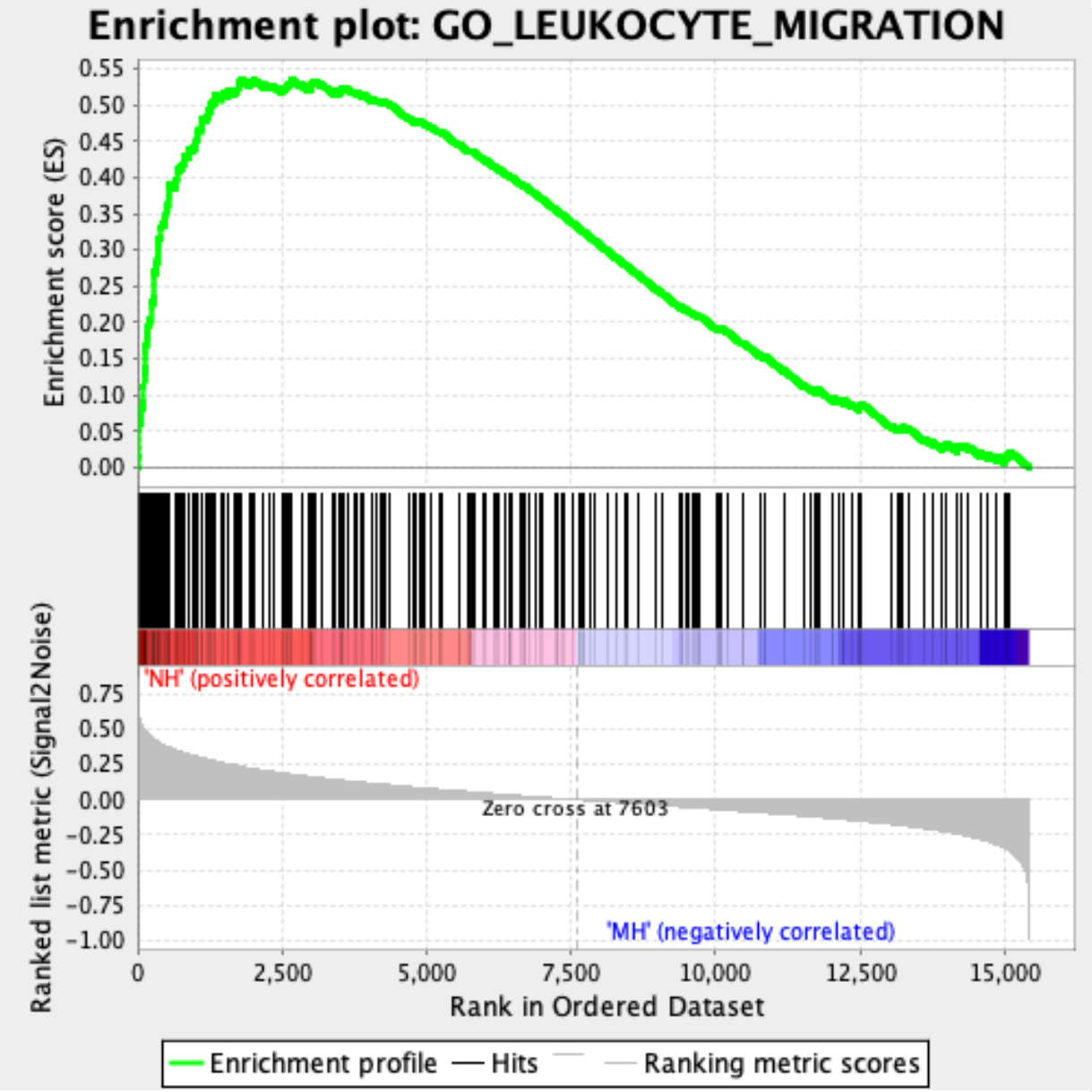
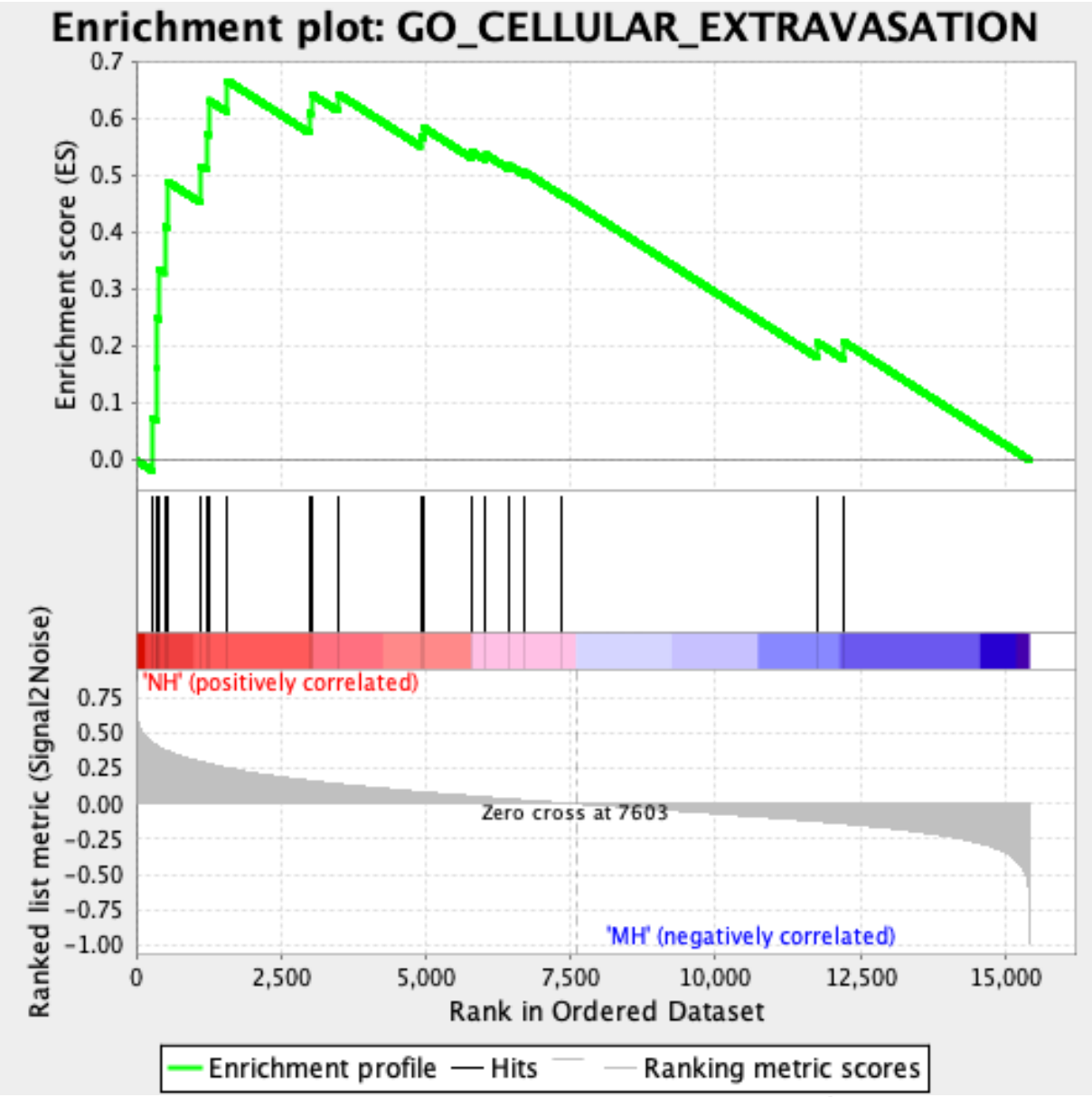

Enrichment plot: GO_LEUKOCYTE_MIGRATION
Enrichment score (ES)
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
'NH' (positively correlated)
Ranked list metric (Signal2Noise)
0.75
0.50
0.25
0.00
-0.25
-0.50
-0.75
-1.00
Zero cross at 7603
'MH' (negatively correlated)
0
2,500
5,000
7,500
10,000
12,500
15,000
Rank in Ordered Dataset
Enrichment profile
Hits
Ranking metric scores


Enrichment plot: GO_CELLULAR_EXTRAVASATION
Enrichment score (ES)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
'NH' (positively correlated)
Ranked list metric (Signal2Noise)
0.75
0.50
0.25
0.00
-0.25
-0.50
-0.75
-1.00
Zero cross at 7603
'MH' (negatively correlated)
0
2,500
5,000
7,500
10,000
12,500
15,000
Rank in Ordered Dataset
Enrichment profile
Hits
Ranking metric scores