Molecular Surrogates of Histologic Activity in Crohn's Disease

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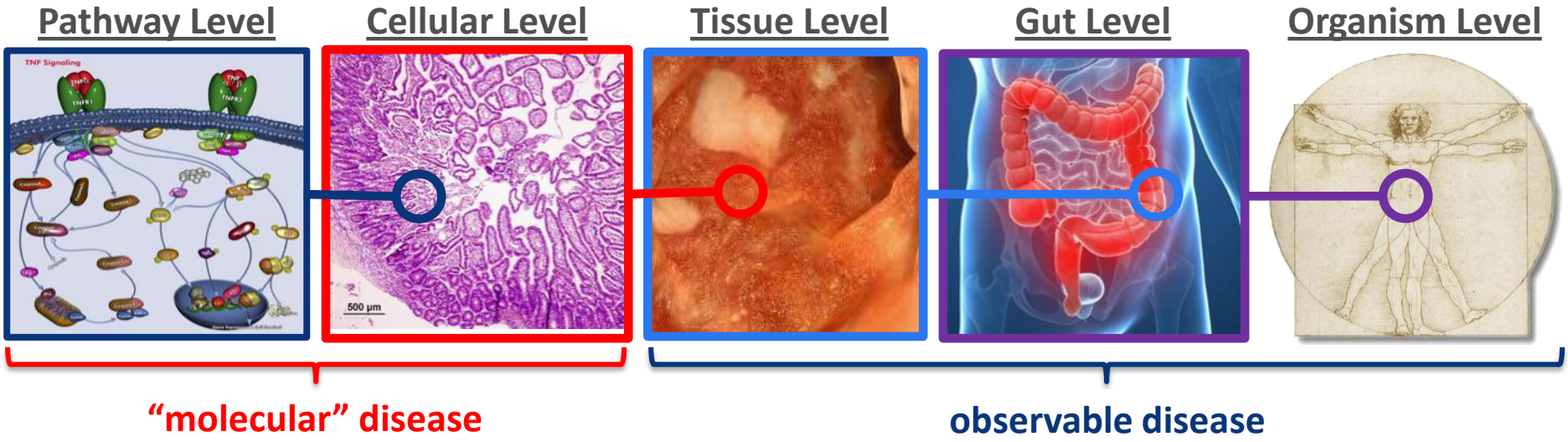
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- Frédéric Baribaud is a current employee and share holders of Janssen R&D a pharmaceutical companies of Johnson & Johnson.

Significant Opportunity for Disease Severity Biomarkers in Inflammatory Bowel Disease (IBD)

- Objective markers of disease severity in IBD that support clinical decision-making are still needed
- IBD clinical endpoints, especially in Crohn's Disease (CD), are variable, driving increases in trial size, cost and timelines
- CD endpoints are being re-evaluated but there has been little progress in integrating biomarkers
- **Goal: Identify biomarkers that can support clinical endpoints with molecular data that relate to resolution of molecular disease**

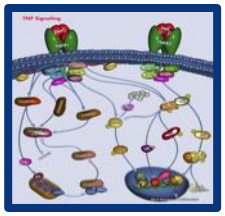
Vision: Leverage Janssen's "Multi-scale" Understanding of Disease



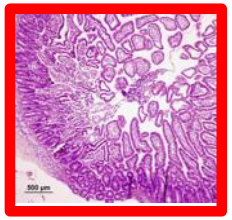
- IBD is driven by molecular processes
  - Confers risk of developing disease
  - Highly dysregulated in disease
  - Molecular perturbations (drugs) capable of inducing clinical remission

- **Yet, molecular markers are not central to decision-making**

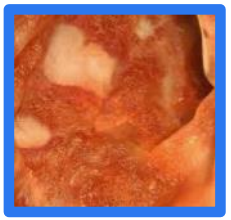
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- Proteomics
- Transcriptomics



- Flow cytometry



- Histology

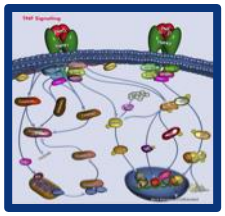


- Endoscopy

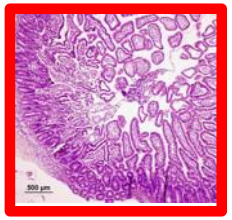


- PROs
- Symptoms

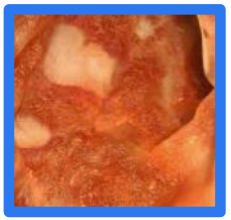
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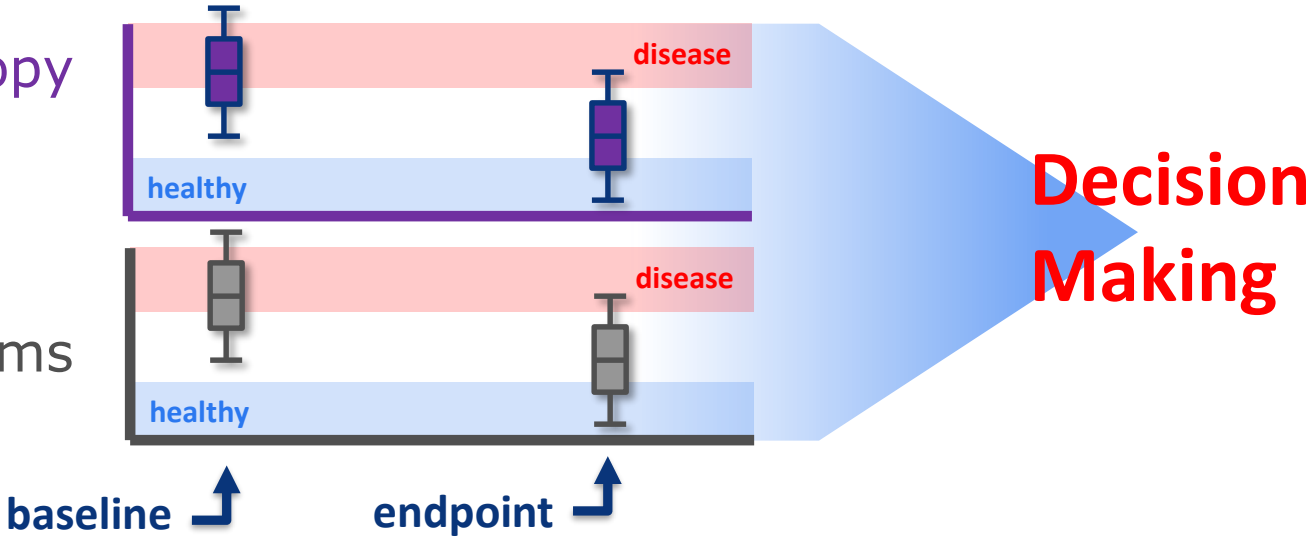
- Histology



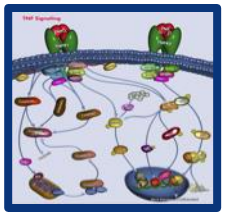
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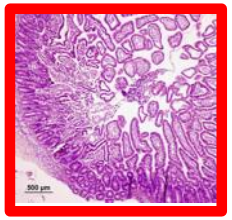
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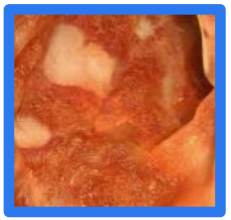
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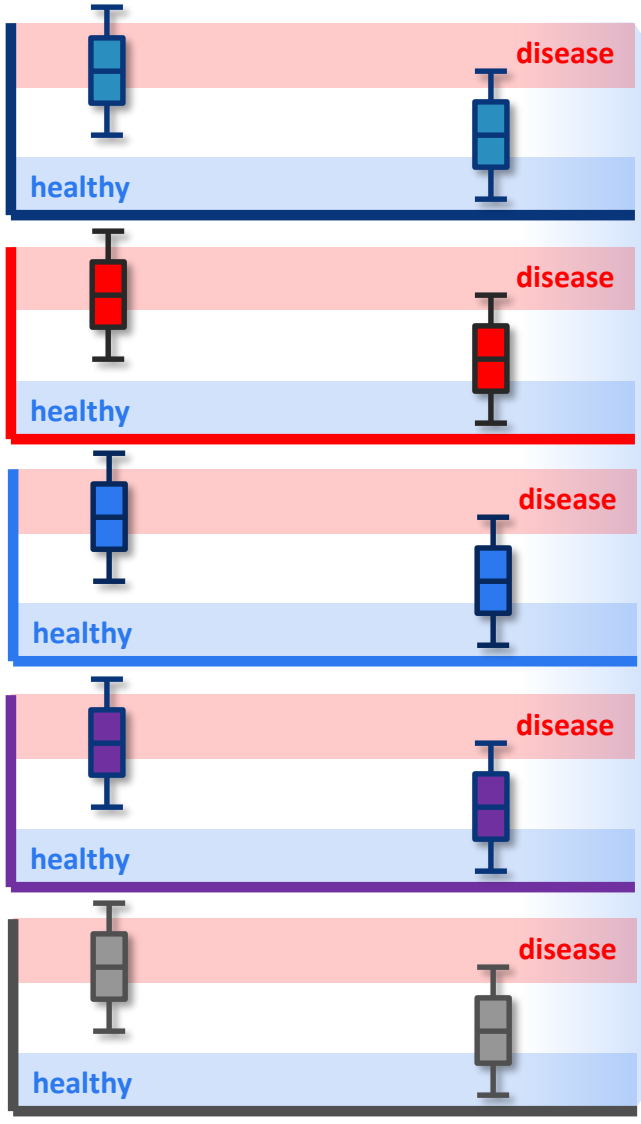
- Histology



- Endoscopy



- PROs
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Decision Making

Our Strategy

- Generate candidate scores with two approaches
  - Machine Learning and “Unsupervised”

- Assess scores based on a range of considerations
  - Performance
  - Feasibility of implementation
  - Biological plausibility
  - Stability

Two Computational Approaches: Machine Learning

- "Choose biomarkers that correlate with a clinical measure"
  - Anchor biomarker discovery on a clinical endpoint
  - Use machine learning to generate a biomarker score that correlates with that endpoint
  - Biomarker score is your molecular endpoint

  - **Pros**: can assess quality of the score with clinical correlation

  - **Cons**: if clinical assessment is noisy this will not work well

Two Computational Approaches: "Unsupervised"

- "All biomarkers that are different in IBD compared to normal are important"
  - Biomarker discovery is not anchored on a clinical score ("unsupervised")
  - Identify all markers that are different from normal
  - Define a biomarker score that quantifies how far each patient is from normal
  - Biomarker score is your molecular endpoint

  - **Pros**: not directly hampered by noisy clinical endpoint

  - **Cons**: difficult to interpret results if there is only weak clinical association found

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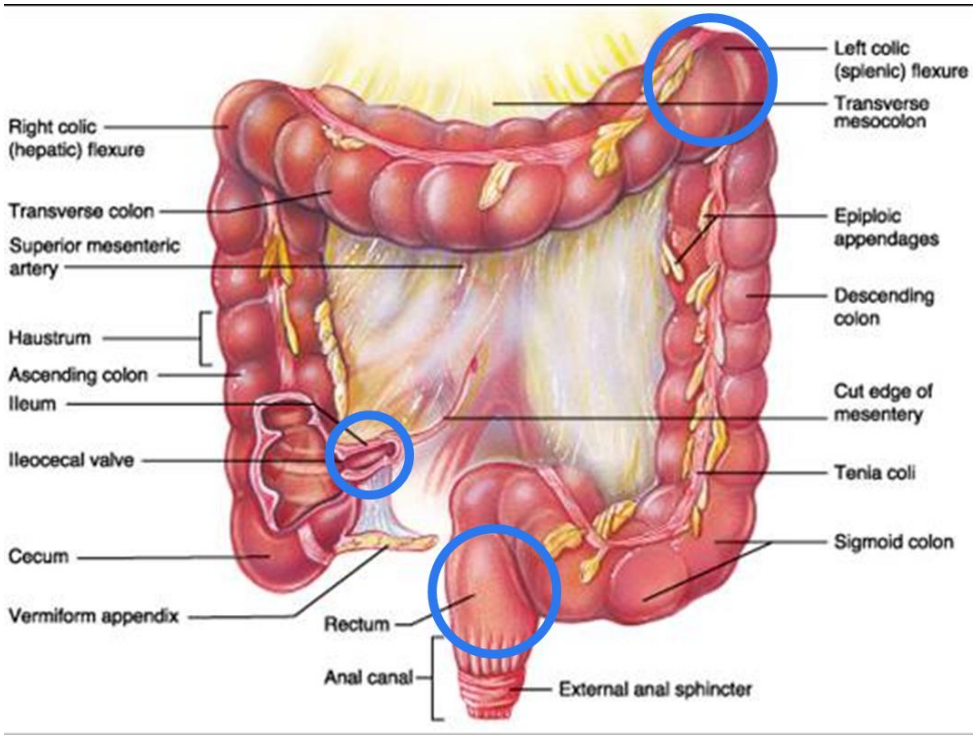
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Prioritization: Begin in the Gut, Focus on CD

- Assumption: IBD disease is driven by the gut, thus, gut inflammation markers capture the disease state
- Choose a clinical endpoint: histology scores
- Choose biomarker data: biopsy transcriptomics
- Choose a machine learning algorithm:
  - PLS = partial least square and RF = random forest
- Choose a strategy for discovery and validation: each time point and biopsy location is a separate validation cohort

Biopsy Transcriptomic Data

- Cohorts
  - UNITI1 (TNF experienced)
  - UNITI2 (TNF naïve)
- Sample details
  - Week 0 and week 8
  - 3 gut locations
    - rectum, splenic flexure, ileum
- 1 model for rectum/spflex and 1 model for ileum
  - External validation: each remaining visit/tissue provided we separate by location
  - Circumvents multiple samples per subject complication



Model Outcomes

Rectum/splex model

- 16 probes
- 5 external validation groups, 2 separate trials
- Some overfitting but still very performant across groups

Utility	Model 1 – rectum/spflex	R^2
training	**spflex wk0 (3001)**	**0.78**
testing	spflex wk8 (3001)	0.32
testing	rectum wk0 (3001)	0.59
testing	rectum wk8 (3001)	0.54
testing	rectum wk0 (3002)	0.35
testing	rectum wk8 (3002)	0.43

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Ileum model

- 14 probes
- 3 external validation datasets, 2 separate trials
- Model nicely stable though slightly less performant compared to spflex/rectum

Utility	Model 2 – ileum	R^2
training	**Ileum wk0 (3001)**	**0.5**
testing	ileum wk8 (3001)	0.45
testing	Ileum wk0 (3002)	0.48
testing	ileum wk8 (3002)	0.39

Conclusion

- In general, both models contained genes related to tissue degradation, barrier function, and immune regulation.
- Both models retained performance in external validation datasets from UNITI-2 but exhibited lower performance.
- Our analysis supports the ability of biopsy transcriptomics combined with machine learning approaches to
  - capture disease-relevant variability in Crohn's disease
  - supports the use of similar approaches to identify additional surrogate markers
- Our pipeline can be applied to other clinical endpoint/biomarker data combinations
  - Specifically, endoscopy where there is more experience (though still limited) with making a clinical response call

Next Steps

- CD Biopsy Score Trained on Endoscopy
  - Goal: Identify biopsy biomarker scores that capture high proportion of endoscopic assessment
- Peripheral Biomarkers as Molecular Endpoints in CD
  - Hypothesis: Peripheral proteins carry information regarding the degree to which the gut is inflamed.
  - Goal: Use computational approaches to identify peripheral proteins that accurately predict disease severity of each individual.

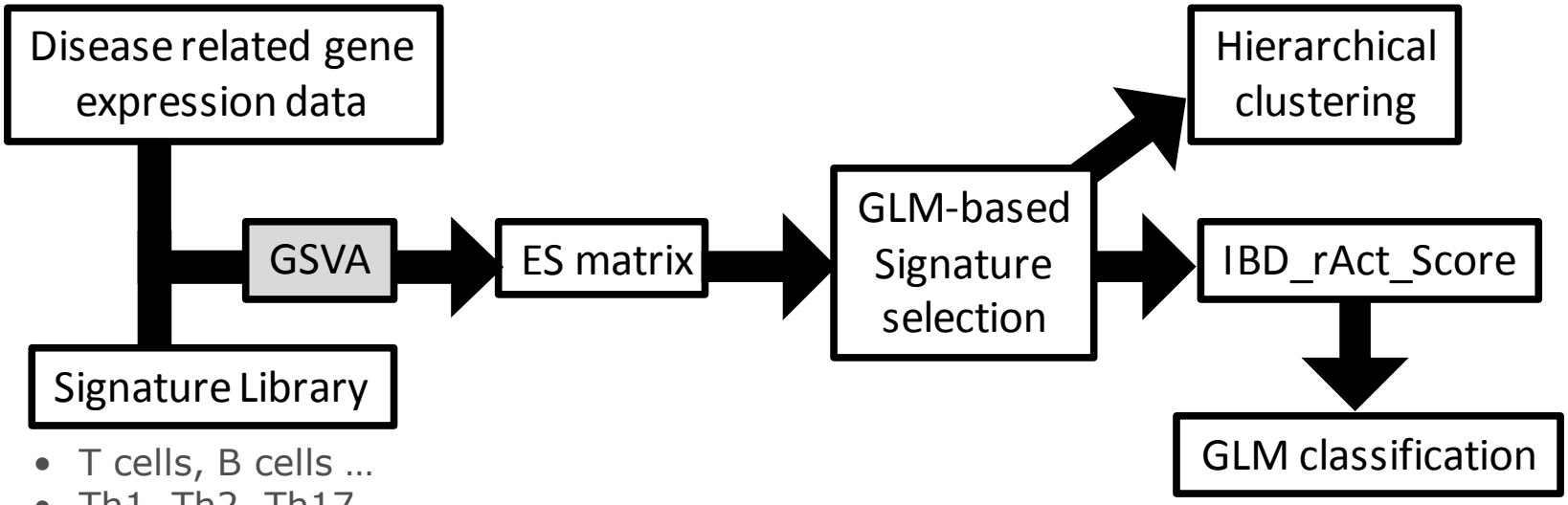
Enabling IBD Interception using a Molecular Activity Score

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The What

- Use extensive molecular data to define IBD molecular severity scores across multiple molecular dimensions
  - Transcriptomics, genetics, microbiome, and proteomics
  - Define a gradient of molecular disease severity from health to severe IBD
- Classify IBD patients into subpopulations that capture differences in disease phenotype and progression
- Contextualize the molecular changes observed in pre-disease cohorts to intercept progression to IBD.

The How

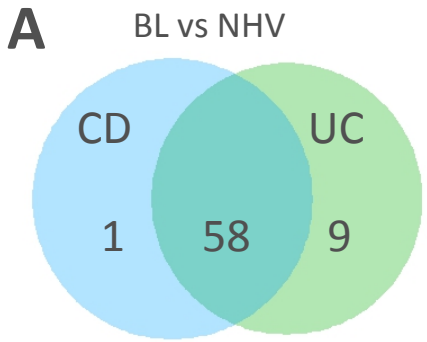


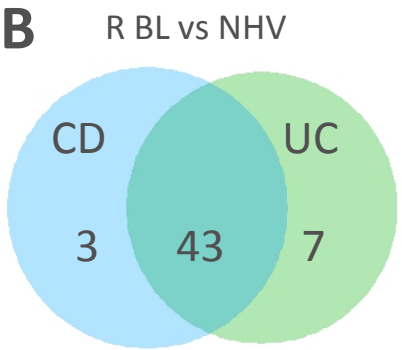
- T cells, B cells …
- Th1, Th2, Th17 …
- Inflammation …

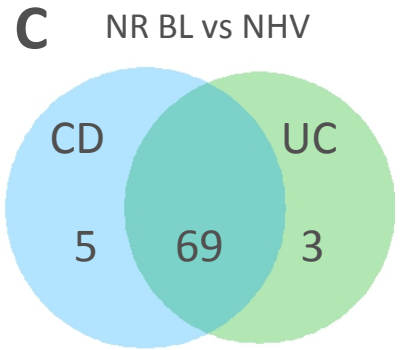
- GSVA = gene set variation analysis
- ES = enrichment score
- GLM = general linear model

Defining deregulated biology in IBD

- (A): many different signatures enriched in both Crohn's disease (CD) and ulcerative colitis (UC)
  - 58/103 (56%)
  - Activated T, B, monocytes, macrophages, DCs etc…
- (B), (C): a striking difference in enrichment when separating at baseline anti-TNF responders (R) from non-responders (NR) is seen: 42% vs 67%





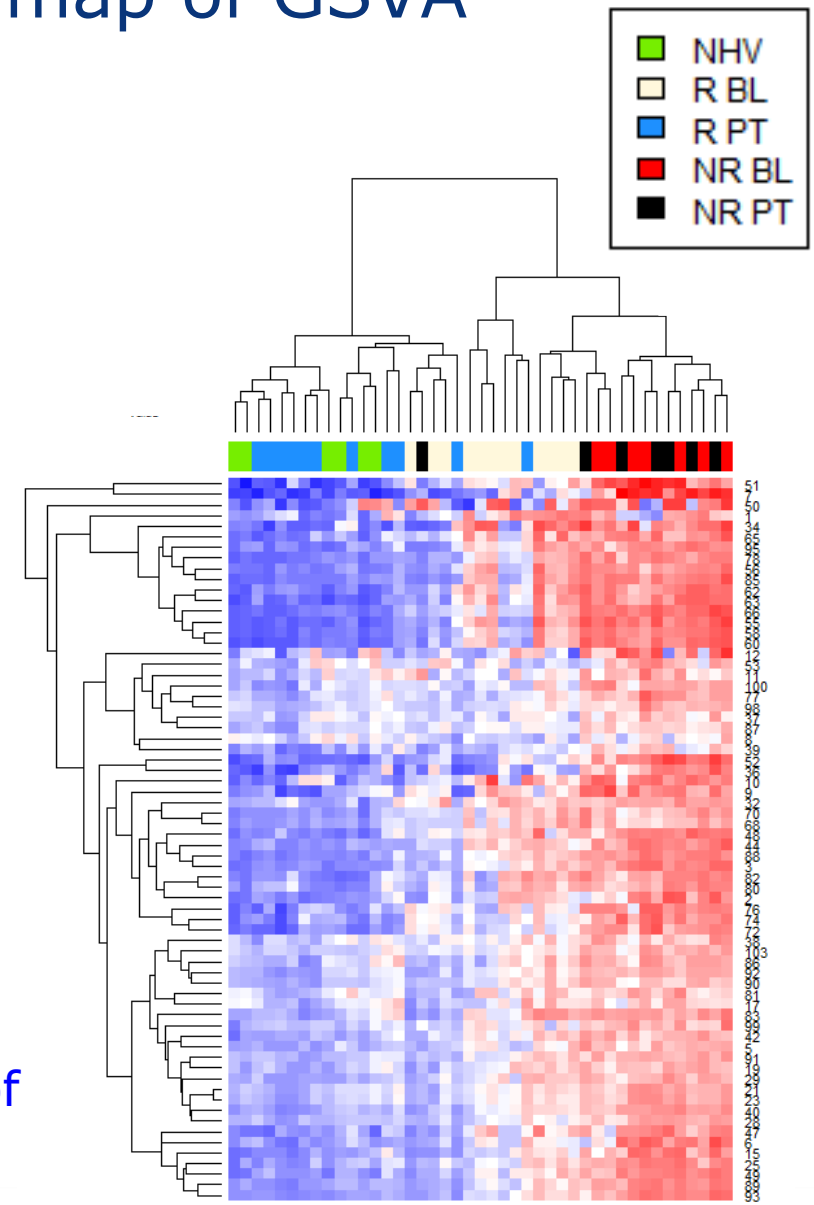


Many various overlapping biologies are deregulated in CD & UC
More deregulations in NR vs R prior to treatment

Hierarchical clustering heat map of GSVA ES of CD samples

- Crohn's disease (CD) participant samples (GSE16879)
- 58 Signatures significantly enriched from comparing post-treatment (PT) vs baseline (BL)

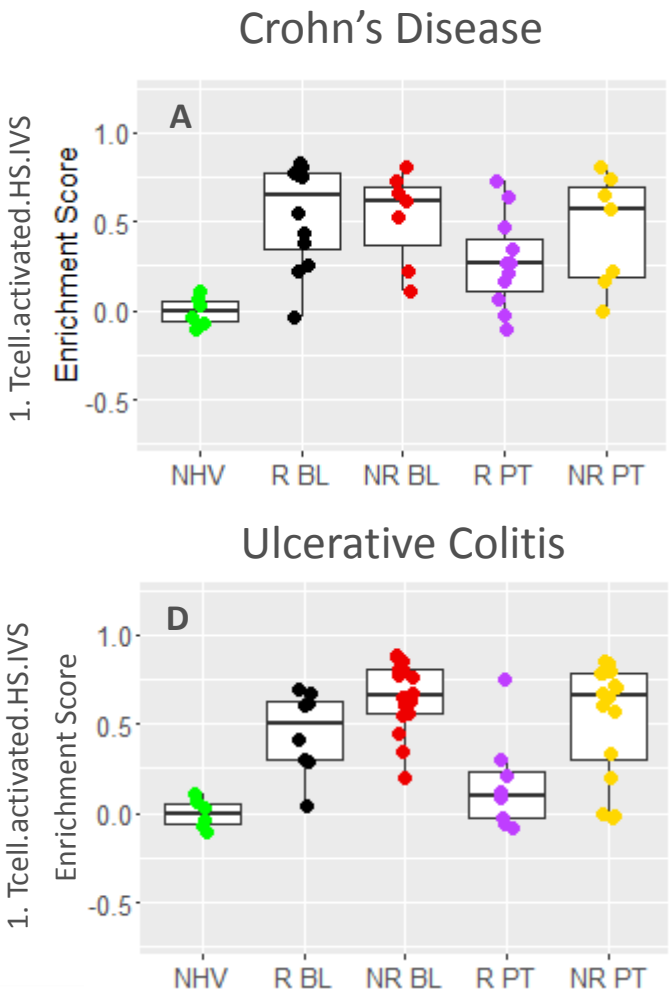
- Clear separation of samples
  - normal healthy volunteers (NHV) from BL
  - Diseased responders (R) from non-responders (NR) @ BL and PT



Enrichment of signatures separates patient samples @ BL & PT as function of response to an anti-TNF

Resembling individual signature enrichment patterns are observed

- Individual signature GSVA ES show a separation of:
  - Disease from NHV
  - BL vs PT in R but not in NR
- GSVA ES pattern are fairly conserved across the UC and CD enriched signatures



Data so far

- System to analyze the enrichment of signatures to find deregulated biology in IBD
- Lots of correlated deregulated biology between CD and UC
- More deregulations in NR than R prior to treatment
- Enrichment of signatures separates patient samples @ BL & PT as function of response to an anti-TNF
  - No apparent dominant disease driving biology
  - A global inflammation axis is present

The Idea

- Combine the GSVA ES to harvest the potential of all deregulations rather than making an uninformed choice of the most important one

Building an IBD activity score (IBD_rActS)

58 signatures

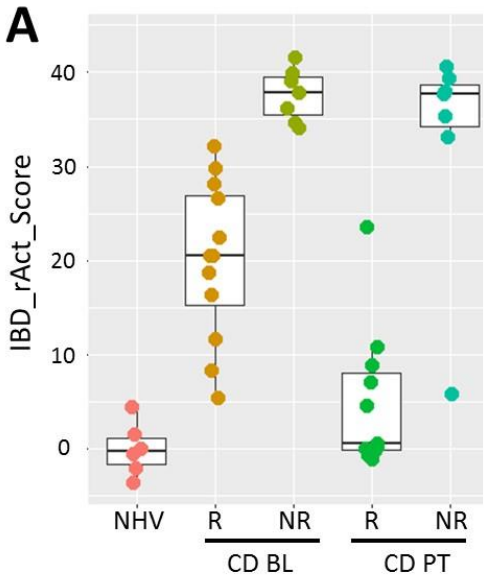
IBD_rAct_Score =

$$\sum_{i=1}^{n} ES(CD\ and\ UC) - \frac{1}{n} * \sum_{i=1}^{n} ES(NHV)$$

Scatter plot display

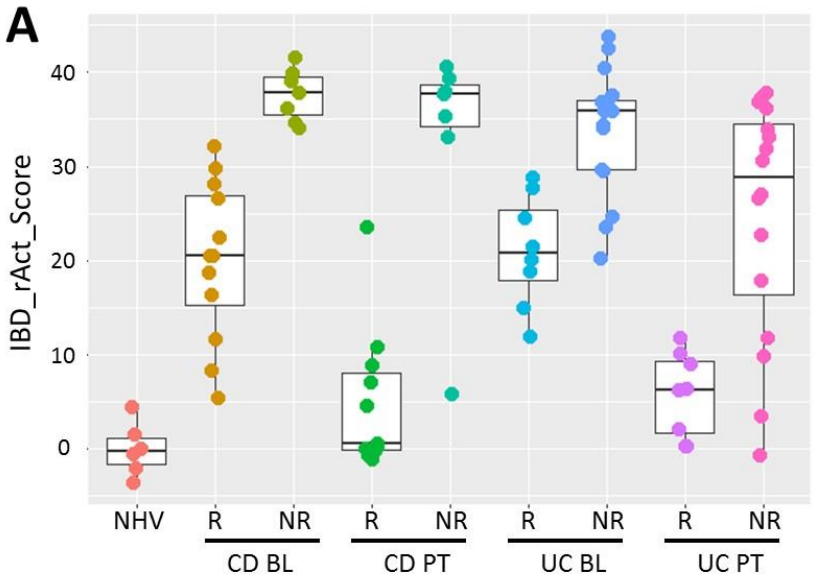
IBD_rActS

- The IBD_rAct_Score results show a very good separation between:
  - NHV and diseased participants
  - Diseased R and NR participant prior to treatment



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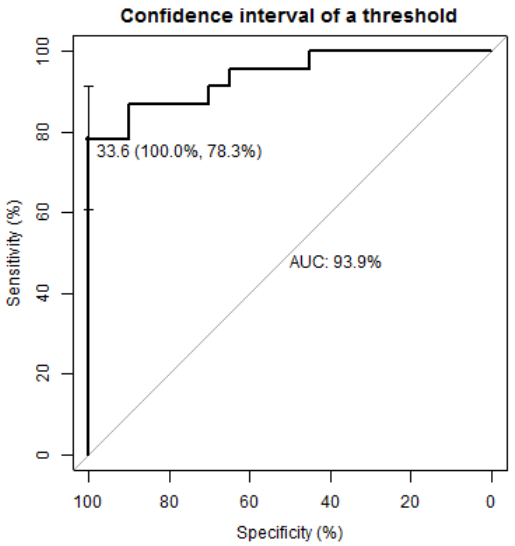
The IBD_rAct_Score across CD and UC separates patient samples @ BL & PT as function of response to an anti-TNF

IBD_rActS

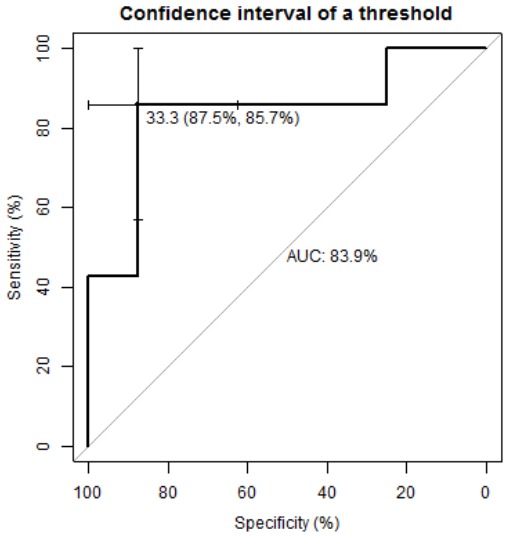
- (B) The IBD_rAct_Score outputs identify clinical responders and non-responders before treatment with 100% specificity and 78.8% sensitivity.
- (C) That finding was confirmed in an independent dataset with 87.5% specificity and 85.7% sensitivity, respectively

The IBD_rAct_Score provides a methodological approach enriching for likely TNF clinical responders and non-responders.

B



C



Conclusions & Next steps

- Our goals are to
  - Develop a personalized medicine approach aligning a therapy with patients most likely to respond: enrichment and prediction
  - Enabling smaller clinical trials to derisk new MOAs aimed to treat IBD
    - Quicker decision making to avoid ineffective treatment for patients
- Our results so far
  - The IBD_rAct_Score provides a methodological approach which maximizes the testing for a new mechanism of action in either CD or UC complementary to an anti-TNF.
- Our next steps
  - Develop similar scores from other 'omics' data sets to examine their complementarity

Acknowledgements

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