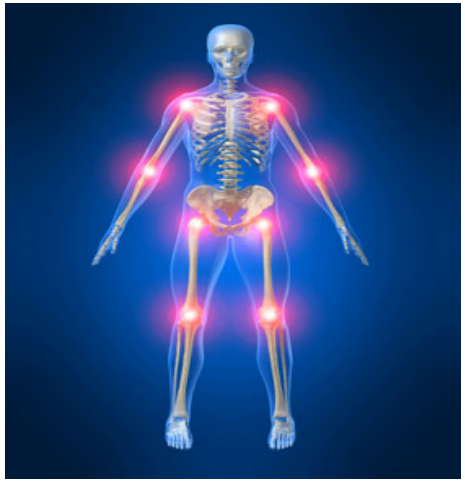
Companion Diagnostics in Autoimmune Disorders: Improving Outcomes Through Personalized Medicine

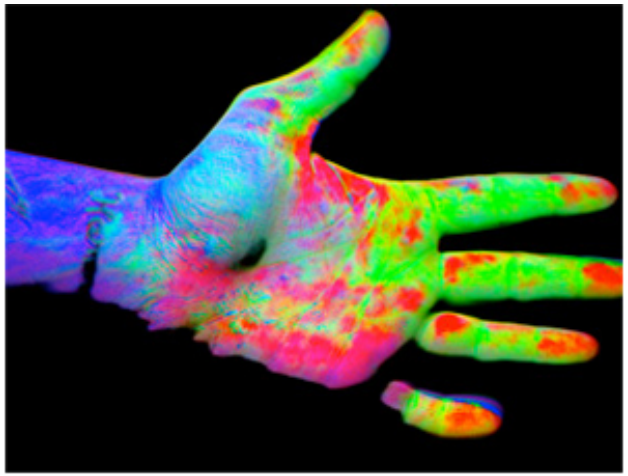
Carrie Brodmerkel, PhD
Immunology Biomarkers
Janssen R&D

Immune-Mediated Diseases



Rheumatoid Arthritis
Lupus

Crohn's Disease
Ulcerative Colitis

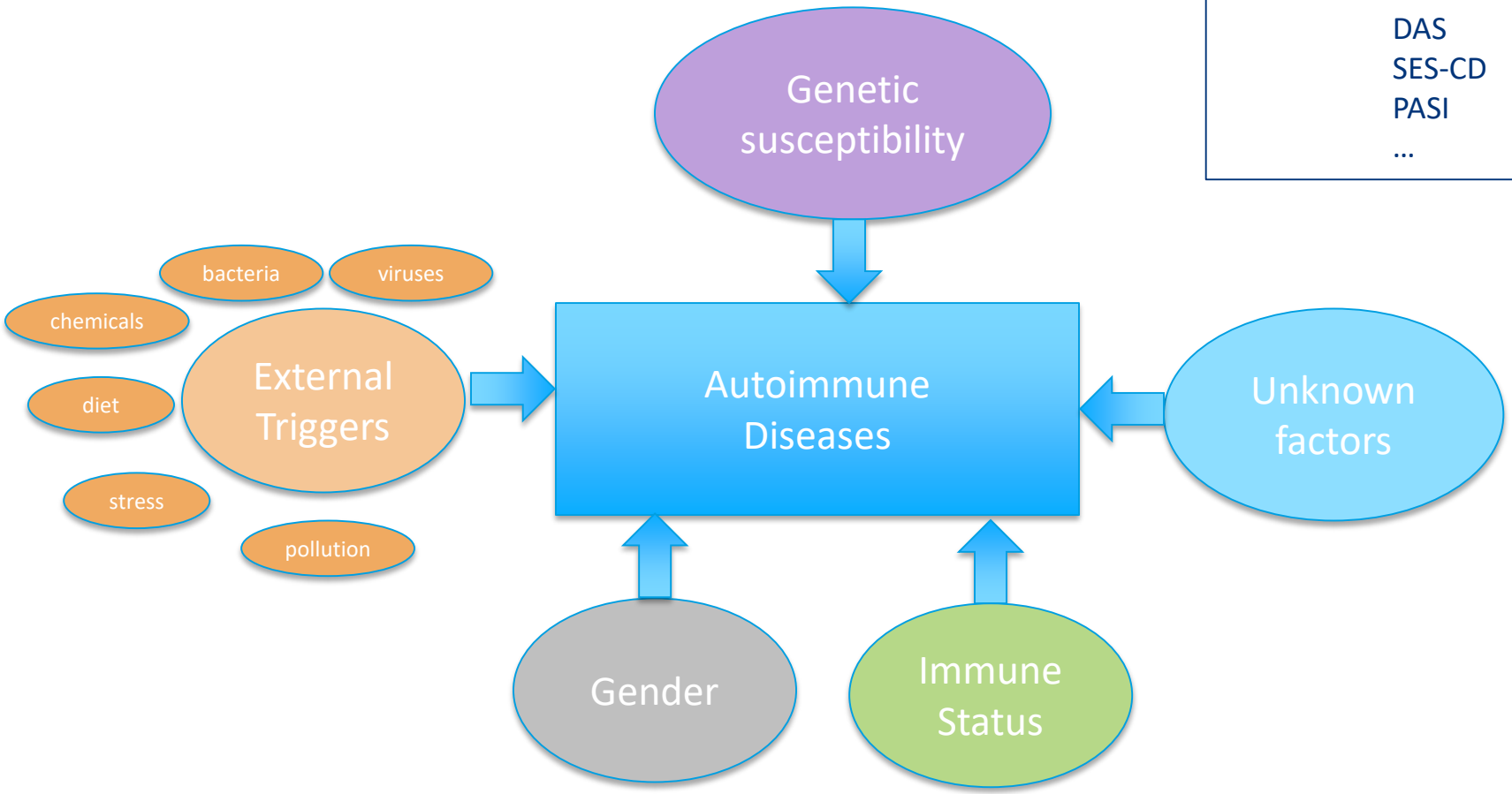


Psoriasis

- Despite advancement of therapeutic options over the past 2 decades, including a range of biologics, only 10-20 percent of patient suffering with known immune inflammatory disorders today are effectively treated

What contributes to the variability in response?

Characteristics
- Waxing and waning
- Complex phenotypes
- Composite Outcome Measures
  - CDAI
  - SLEDAI
  - ACR
  - DAS
  - SES-CD
  - PASI
  - …



Personalized Medicine in Immune Diseases: Promise not achieved

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PLoS one

Journal of Crohn's and Colitis, 2015, 1120–1126
doi:10.1093/ecco-jcc/jjv156
Advance Access publication September 8, 2015
Original Article

OXFORD

JCC

Original Article

A Matrix-based Model Predicts Primary Response to Infliximab in Crohn's Disease

Thomas Billiet,[a] Konstantinos Papamichael,[a] Magali de Bruyn,[a,b] Bram Verstockt,[a] Isabelle Cleynen,[a] Fred Princen,[c] Sharat Singh,[c] Marc Ferrante,[d] Gert Van Assche,[d] Severine Vermeire[d]

Medical Cent
Rheumatolo

RESEARCH ARTICLE Open Access

Pred

Cell Host Microbe. 2017 May 10; 21(5): 603–610.e3. doi:10.1016/j.chom.2017.04.010.

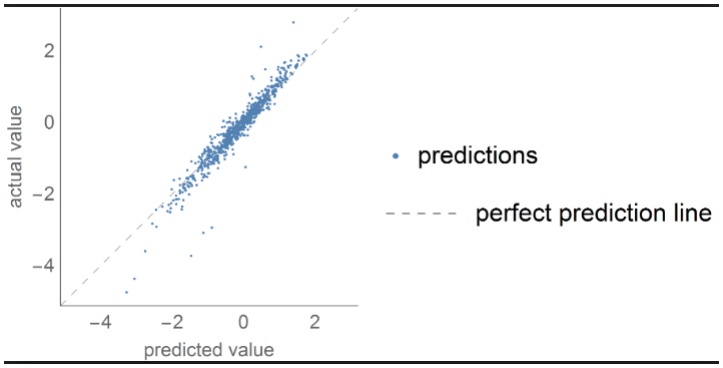
Peripher

Gut microbiome function predicts response to anti-integrin biologic therapy in Inflammatory Bowel diseases

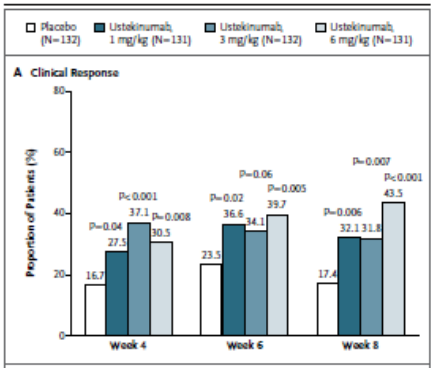
Yoshie S
Shunsuke Fu
Ryutaro M

Ashwin N Ananthakrishnan[*,1,2], Chengwei Luo[*,3], Vijay Yajnik[1,2], Hamed Khalili[1,2], John J Garber[1], Betsy W Stevens[2], Thomas Cleland[1], and Ramnik J Xavier[1,2,3,4]

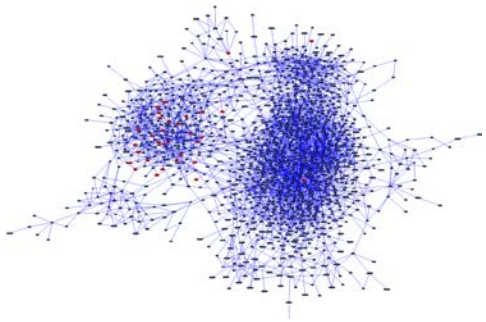
Root cause of failure?



Expectation (PPV>80%)



Phenotype



Disease/Immune Heterogeneity

Expectation vs Perception vs Reality:

- Reality: In IBD for example response rates of 40% even lower for remission rates
- Perception by Individual Physicians: Response Rates of 60-70%
- Expectation of Predictive Test: 80% or better positive prediction

Phenotype Phenotype Phenotype

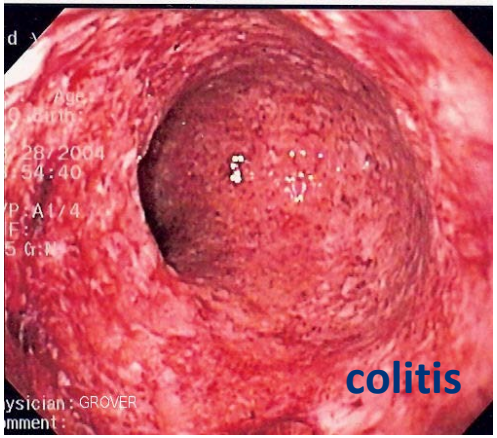
- Registrational endpoints are not adequate measures of response and non-response to allow for molecular prediction… too subjective
- Population results vs individual response

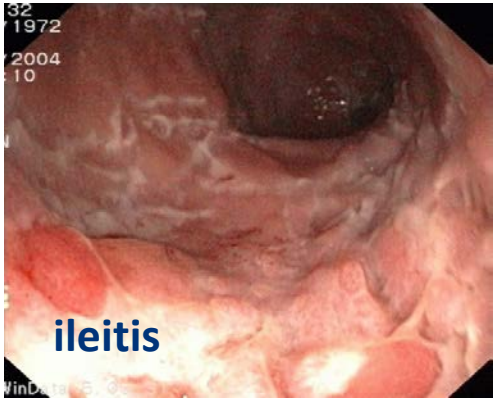
Redefine the disease phenotype and understand the immune heterogeneity

- Clinical Symptoms are not enough: Molecular Phenotype Defines Heterogeneity

Inflammatory Bowel Disease

- Chronic inflammation of the GI tract
  - Abdominal pain, chronic diarrhea, bloody stool, weight loss, perianal disease, extraintestinal manifestations
- Ulcerative colitis
  - Homogenous inflammation in rectum/colon
  - Inflammation confined to the tissue
- Crohn's disease
  - Patchy inflammation throughout GI
  - Systemic inflammation and symptoms
- Etiology unknown but thought to be related to inappropriate inflammatory response to intestinal microbiota
  - Contributing factors: genetic susceptibility, environmental triggers, gut microbiome, immune response





Response Definitions in Ulcerative Colitis

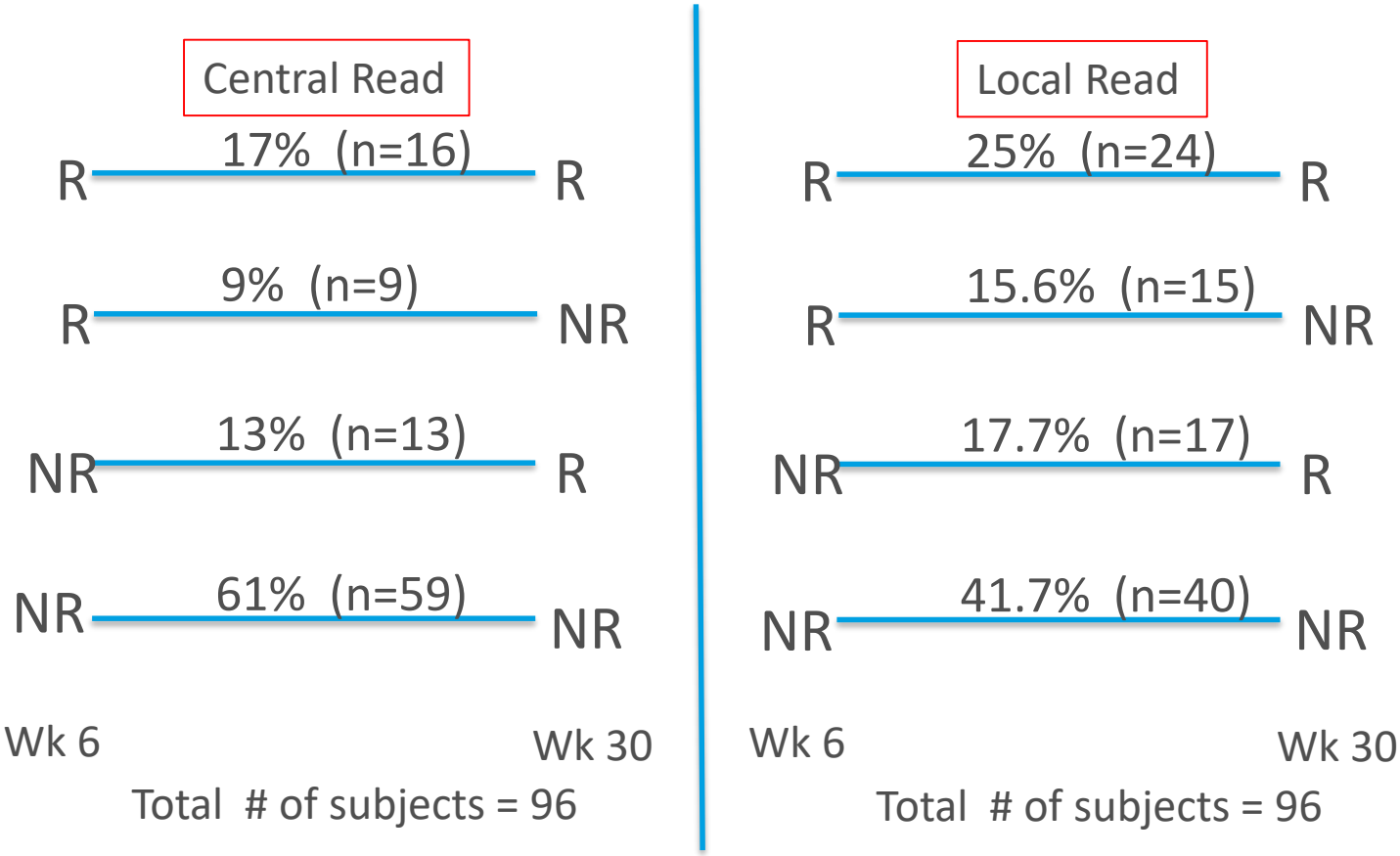
- Clinical response is defined as a decrease from baseline in the Mayo* score by ≥ 30% and ≥ 3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1 (baseline required Mayo of 6 to 12)

- Clinical remission is defined as a Mayo score ≤ 2 points, with no individual subscore > 1.

- Mucosal Healing defined as an endoscopy subscore of 0 or 1 out of a scale of 3 (baseline required endoscopy of ≥2).
  - Standard practice was local endoscopy reader
  - Moving towards standard of central readers

*Mayo – composite index of patient and physician reported measures and endoscopic score

IBD: Is Mucosal Healing a Stable Endpoint?



- Endoscopy scores are highly variable
  - **50% difference** in endoscopy score calls between readers in PROgECT
    -Variability in calls between 1 and 2 significantly **impacts prediction accuracy**

NR = non-response or discontinued

Prediction is possible – Identifying primary non-responders

- Utilized colon tissue biopsies at baseline
- Generated gene expression based signature to predict response to anti-TNF
- Tested in multiple cohorts

Test Population*	AUC	Sensitivity	Specificity	NPV	PPV
ACT I /T37 (N=23)	N/A	0.92	1.00	0.92	1.00
PURSUIT/T17 (N=58)	0.77 [0.75-0.79]	0.90 [0.83-0.96]	0.63 [0.58-0.67]	0.87 [0.81-0.94]	0.68 [0.66-0.70]
PROgECT, central reads (N=97)	0.67 [0.60, 0.74]	1.00 [0.98, 1.00]	0.22 [0.16, 0.29]	1.00 [0.98, 1.00]	0.31 [0.24, 0.39]
Ph. 2 Simponi Japan (N=22)	0.74 [0.57, 0.86]	0.88 [0.74, 0.96]	0.46 [0.30, 0.62]	0.85 [0.70, 0.94]	0.53 [0.37, 0.69]

*13-gene signature applied to all cohorts except for T37 (applied the 109 transcript panel) to predict mucosal healing

Common emerging theme: Prediction of Non-responders (NR)

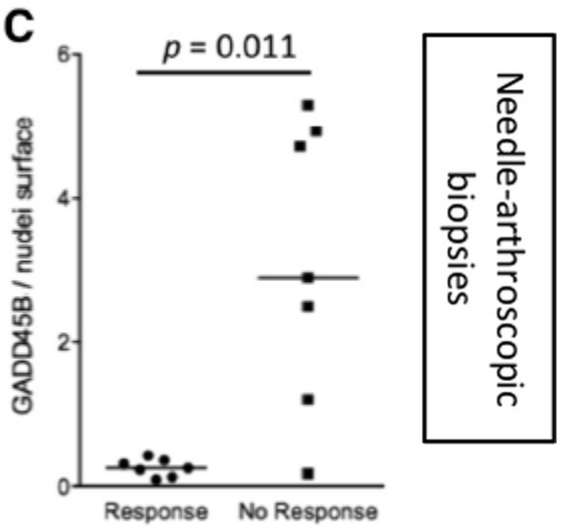
Genetic Markers Predict Primary Nonresponse and Durable Response to Anti–Tumor Necrosis Factor Therapy in Ulcerative Colitis

Kristin E Burke, MD, Hamed Khalili, MD, MPH, John J Garber, MD, Talin Haritunians, PhD, Dermot P B McGovern, MD, PhD, Ramnik J Xavier, MD, PhD, Ashwin N Ananthakrishnan, MD, MPH ✉

Inflammatory Bowel Diseases, Volume 24, Issue 8, 12 July 2018, Pages 1840–1848,

Higher expression of TNFα-induced genes in the synovium of patients with early rheumatoid arthritis correlates with disease activity, and predicts absence of response to first line therapy

Aurélie De Groof[1], Julie Ducreux[1], Frances Humby[2], Adrien Nzeusseu Toukap[1,3], Valérie Badot[4], Costantino Pitzalis[2], Frédéric A. Houssiau[1,3], Patrick Durez[1,3] and Bernard R. Lauwerys[1,3*]



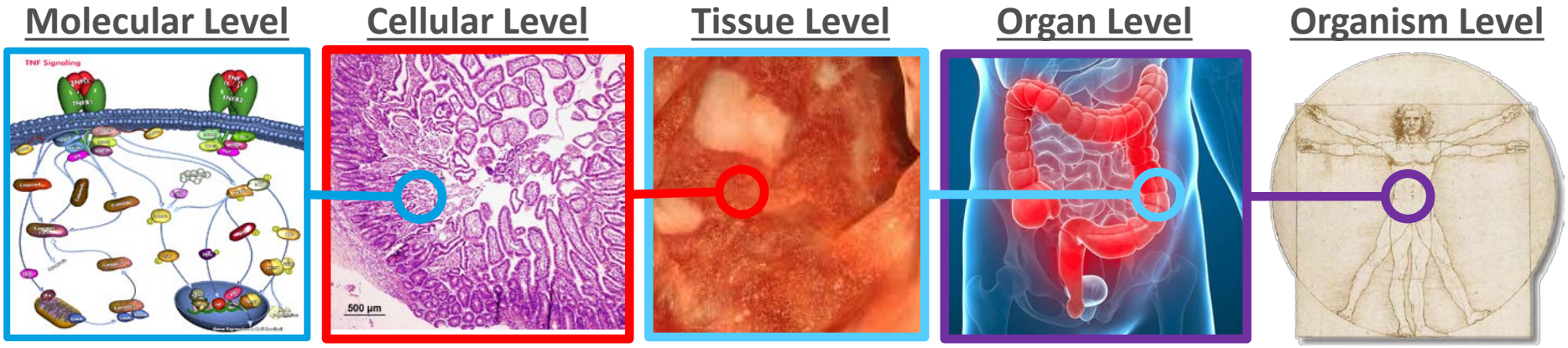
Identifying primary NR is beneficial but likely only accounts for <50% of NR population

Where do go from here?

- Deconvolution of the Non-Responder Population
  - What is the driving biology in this subtype?
  - Does this subtype evolve or it truly a different patient population?
  - What can be done to treat this non-responsive population?
    - Combination therapy?
    - Alternative mechanisms beyond the anti-inflammatory spectrum

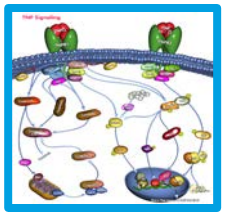
- Reducing subjectivity in outcomes will increase accuracy of prediction…are expectations achievable?
  - Molecular definitions of disease and response may reduce variability
  - Combined clinical and molecular decision making may pave path towards personalized medicine

Where do we go from here…
Immune Diseases Are “Multiscale” Problems

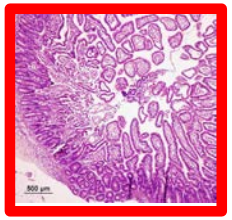


- Immune diseases involve **molecular dysregulation** driving **tissue damage** and **organ dysfunction** leading to **clinical symptoms**
- **Inherent genetic and environmental factors can influence ability to respond**
- Decision-making should include assessment of **multi-scale therapeutic effects**

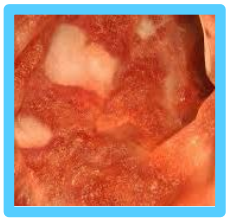
Current use of data for decision making



- Proteomics
- Transcript-omics



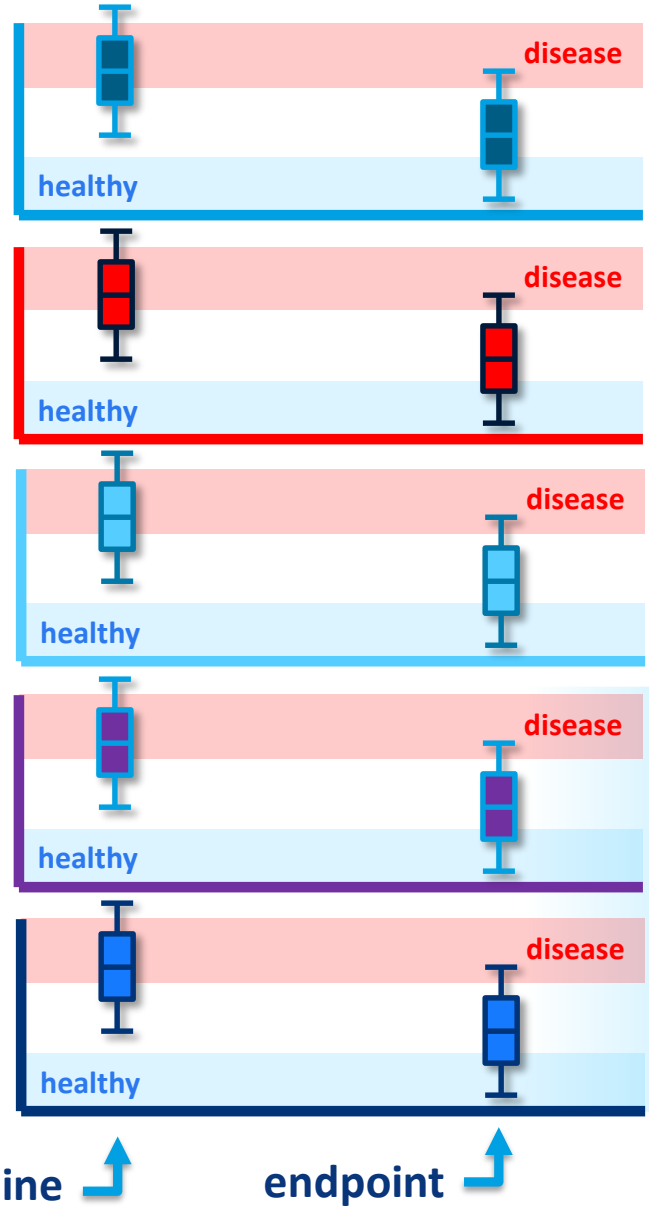
- Flow
- Single cell



- Histology

- Endoscopy

- PROs
- Symptoms



Decision Making

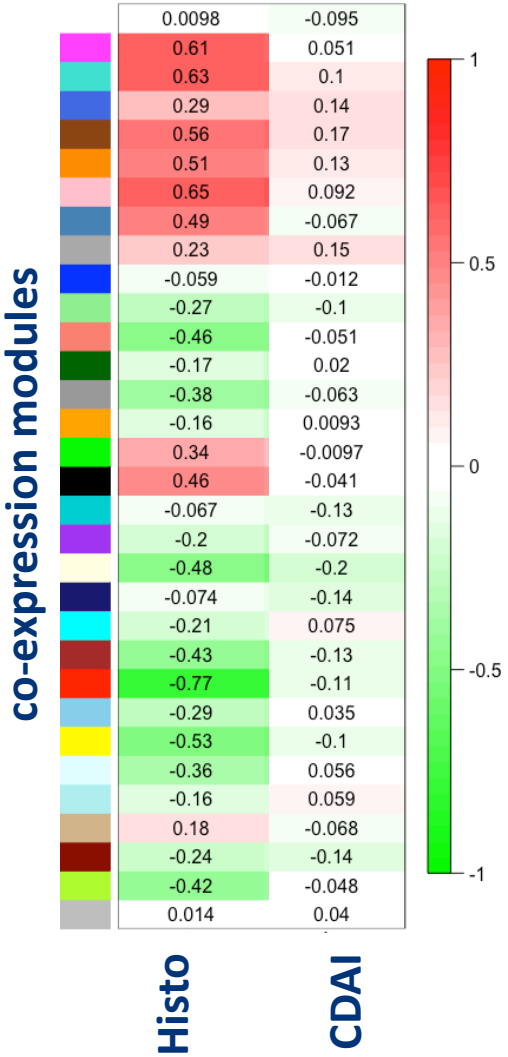
Development of Molecular “Endpoints”

- Utilizing extremes of response (“truth”) to define molecular surrogates to objectively measure response
  - ACR 50 (responder) vs ACR 40 (non-responder) – are these really different? How many times would the assessments reproduce this?
  - <ACR20 response vs >ACR70 response – reproducibly different

- Depending on the disease start at the source of the disease (gut, joint, etc.) and derive molecular endpoints and then move to least invasive method for obtaining the same information
  - e.g. Gut biopsies gene expression ⟹ serum proteins

Example: Tissue gene expression and Clinical Phenotypes in Crohn's Disease

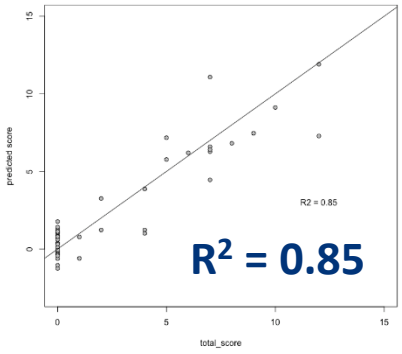
- Co-expression modules (WGCNA) generated
  - Groups of genes that are tightly correlated
  - "Units" of biology from transcriptomics datasets
- Analyzed the association between co-expression modules and clinical parameters
  - Generic way to estimate the strength of association between transcriptomics and metadata
- Results summary
  - Histology: strong
    - Histology scoring: D'Haens et al., Gastroenterology, 1998
  - Endoscopy (not shown): moderate
  - CDAI (registrational endpoint): weak



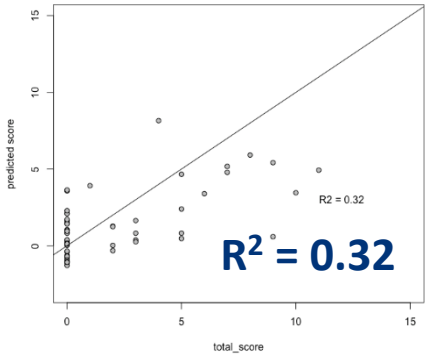
Transcriptomics Data Exhibited Ability to Predict Histology Scores

- Separated data into 1 training set and 3 testing sets
- Train model with multiple machine learning algorithms
  - Including cross validation
- Test on external sets

Training



Testing



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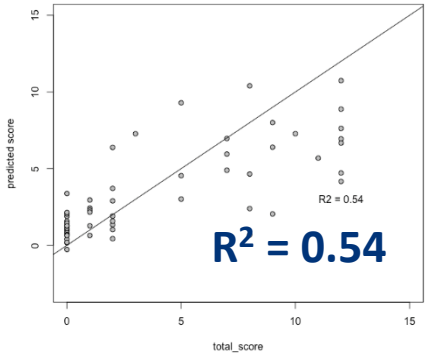

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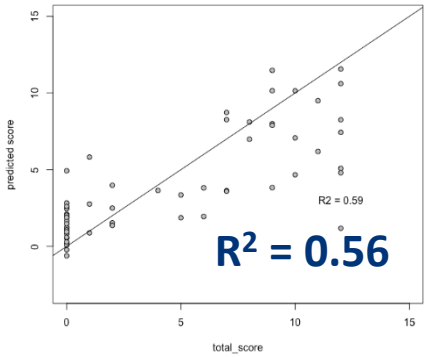
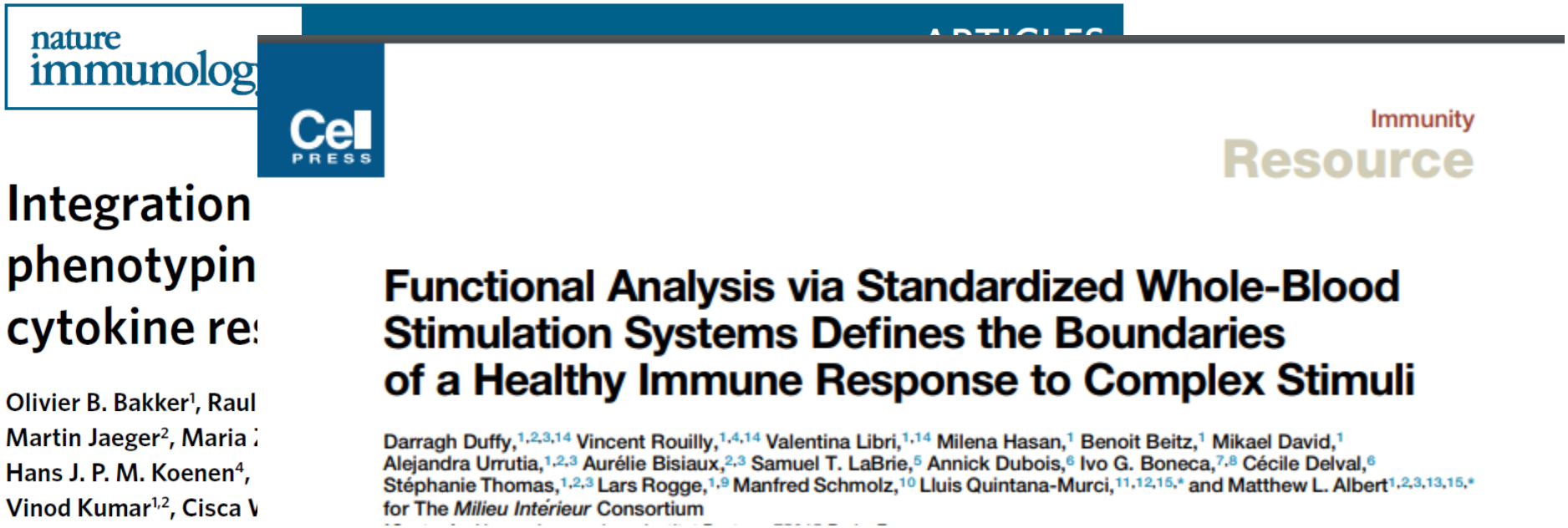


Utility of Molecular Endpoints

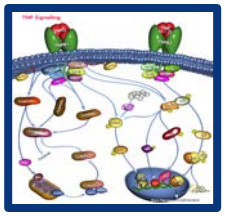
- Supportive decision making in early trials
  - Efficient study designs
- Proving divergence from pbo response allows for opportunity to reduce/eliminate pbo arms in early trials
- Stabilizing response definition can lead to identification of enrichment (population) or predictive markers (individual)

What else can be done to reveal the variability in response to therapies?

- Moving from static assessments to functional assessments of immune “fitness” may illuminate the differences in response not related to alternate disease drivers



Future State : “Multiscale” Approach to Personalized Medicine for Immune Diseases



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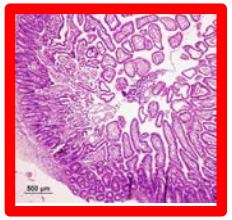
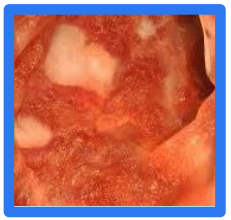


- **Immune perturbation**
- **Flow / Single cell**



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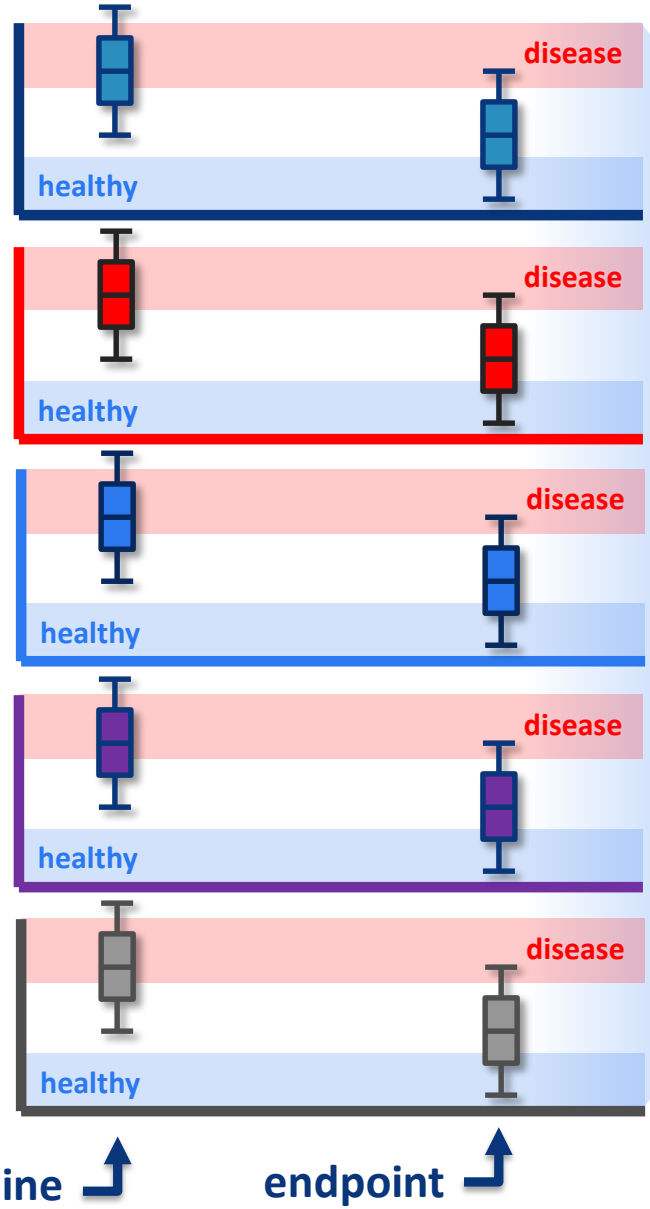

Decision Making

Acknowledgements

- Janssen biomarker team
  - Katherine Li
  - Feifei Yang
  - Fred Baribaud
  - Prerak Desai
  - Josh Friedman
  - Carrie Brodmerkel
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- Clarivate Analytics
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