Personalising IBD Management

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The Francis Crick Institute &
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Disclosure of Conflicts of Interest

I hereby declare the following paid or unpaid consultancies, business interests or sources of honoraria payments for the past three years, and anything else which could potentially be viewed as a conflict of interest:

Scientific consultancy for Abbvie, PredictImmune, C4X Discovery, AgPlus Diagnostics
Research funding from GSK
Patent co-inventor: “Biomarkers for Inflammatory Bowel Disease” smi-3212-15 (2017)

Why do some people think this is unrealistic?

GASTROENTEROLOGY 2006;130:650–656

Predictors of Crohn's Disease

LAURENT BEAUGERIE, PHILIPPE SEKSIK, ISABELLE NION–LARMURIER, JEAN–PIERRE GENDRE, and JACQUES COSNES
Department of Gastroenterology, Saint-Antoine Hospital, and Pierre et Marie Curie University, Paris, France

Clinical Chemistry 59:1
202–204 (2013)

Opinions

Biomarker Failures

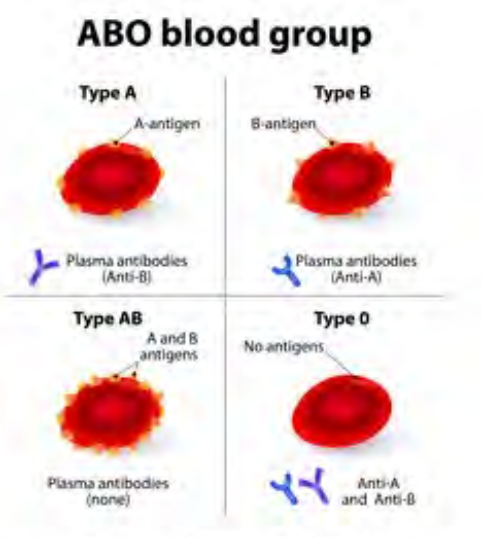
John P.A. Ioannidis[1,2,3*]

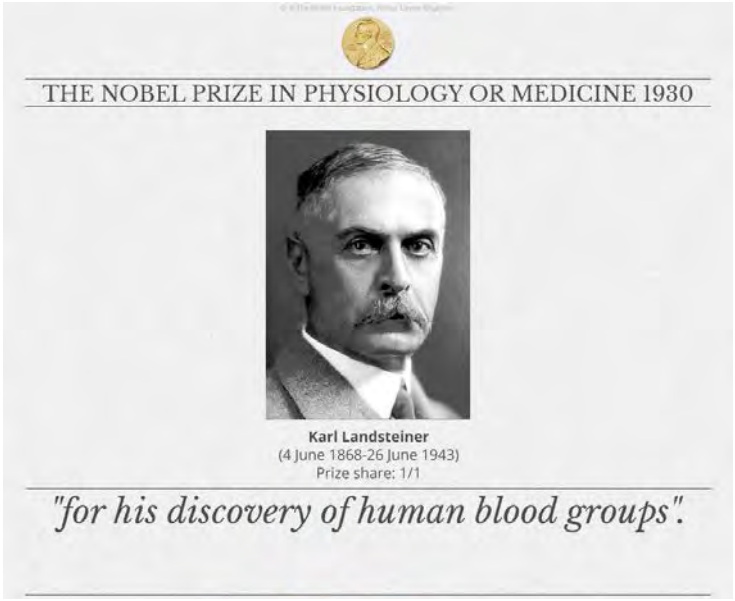
The quest for biomarkers has been a highly prolific, exciting field of research. Despite major promises, however, that biomarkers can improve diagnosis, prognosis, prediction, overall management, and eventually the health outcomes of single people and many different populations, the yield of successful biomarkers with unquestionably favorable health impacts has been extremely limited to date. In fact, biomarker failures are rather the rule.

Is Personalised Medicine even possible?

Karl Landsteiner

1900





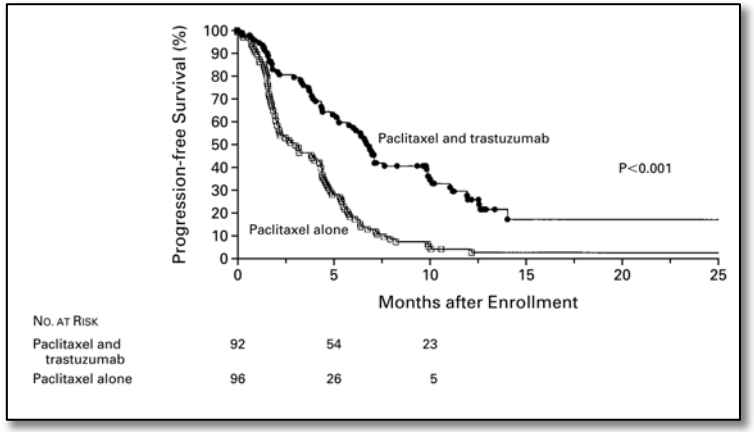
Reuben Ottenberg

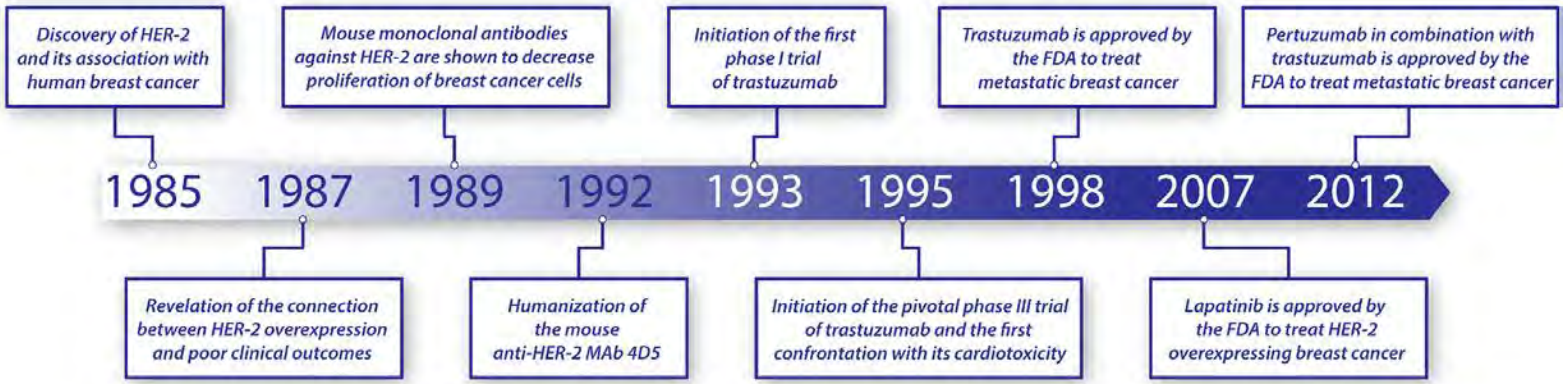
1907

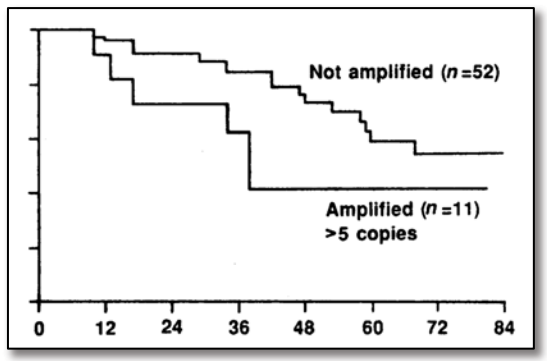
RESEARCH ARTICLE

Tyrosine Kinase Receptor with Extensive Homology to EGF Receptor Shares Chromosomal Location with *neu* Oncogene

Lisa Coussens, Teresa L. Yang-Feng, Yu-Cheng Liao
Ellson Chen, Alane Gray, John McGrath, Peter H. Seeburg
Towia A. Libermann, Joseph Schlessinger, Uta Francke
Arthur Levinson, Axel Ullrich

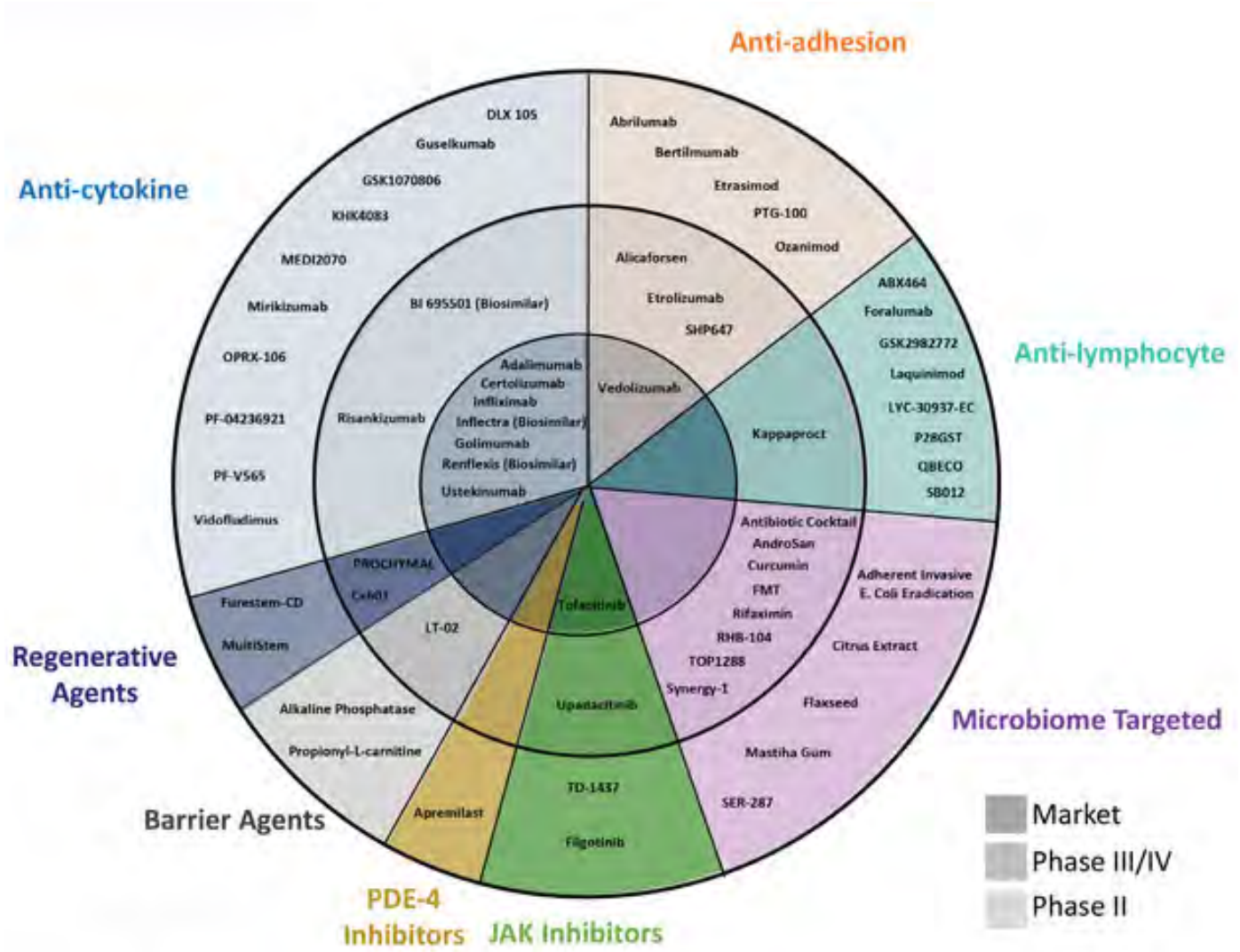


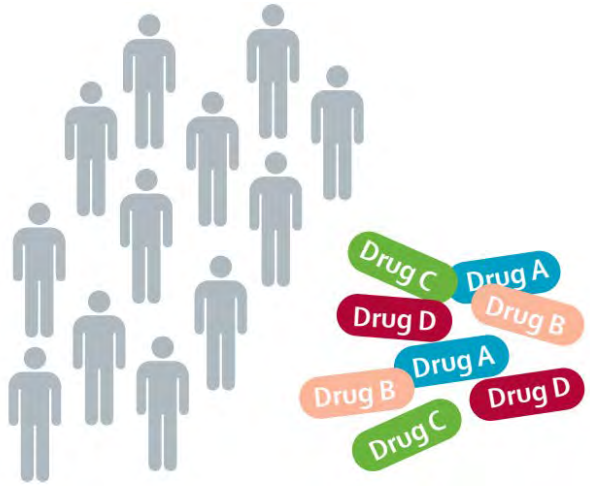




What are the biomarkers we need in IBD?

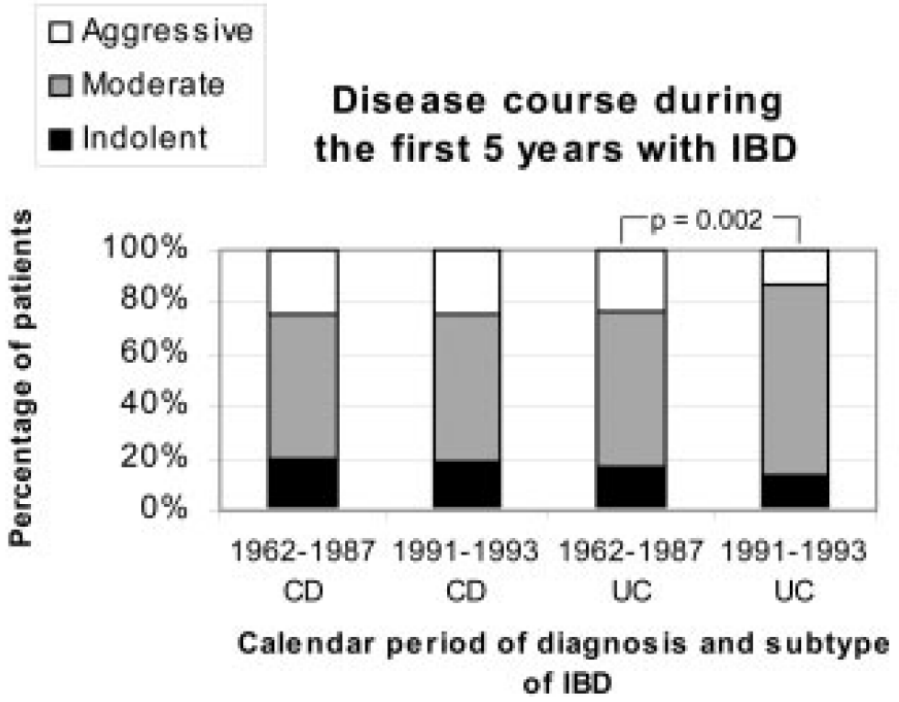
Challenge #1



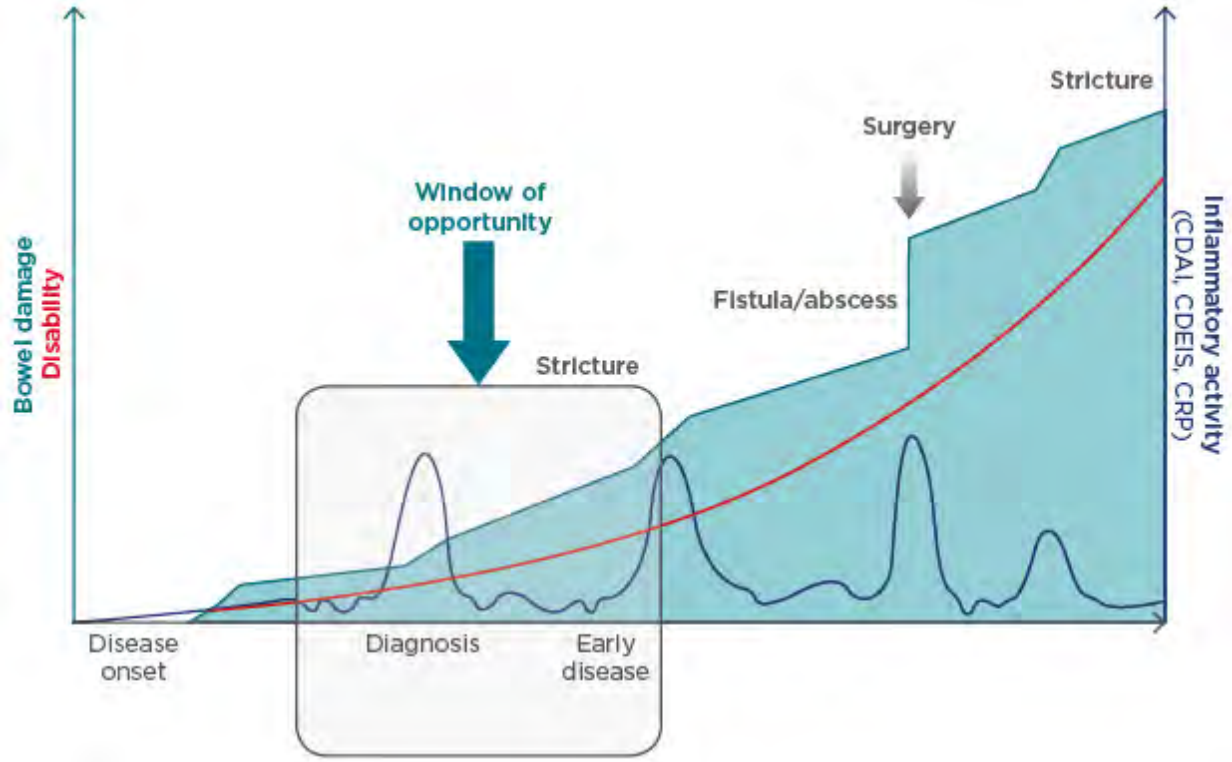


Steiner et al. Prac Gastro 2019
Verstockt, Noor et al. Lancet Gastro Hep 2020

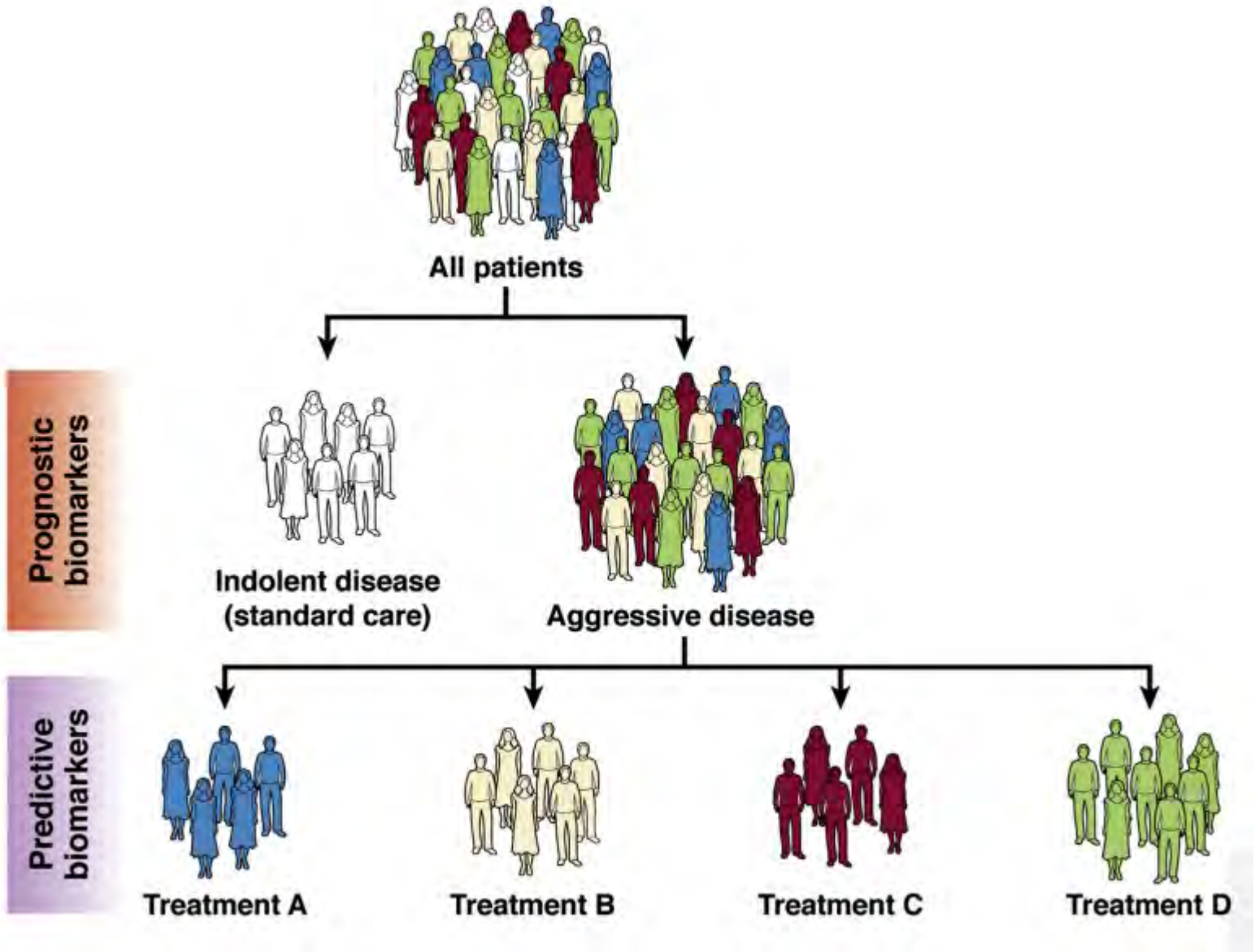
Challenge #2



Jess et al. Inflamm Bowel Dis (2007)

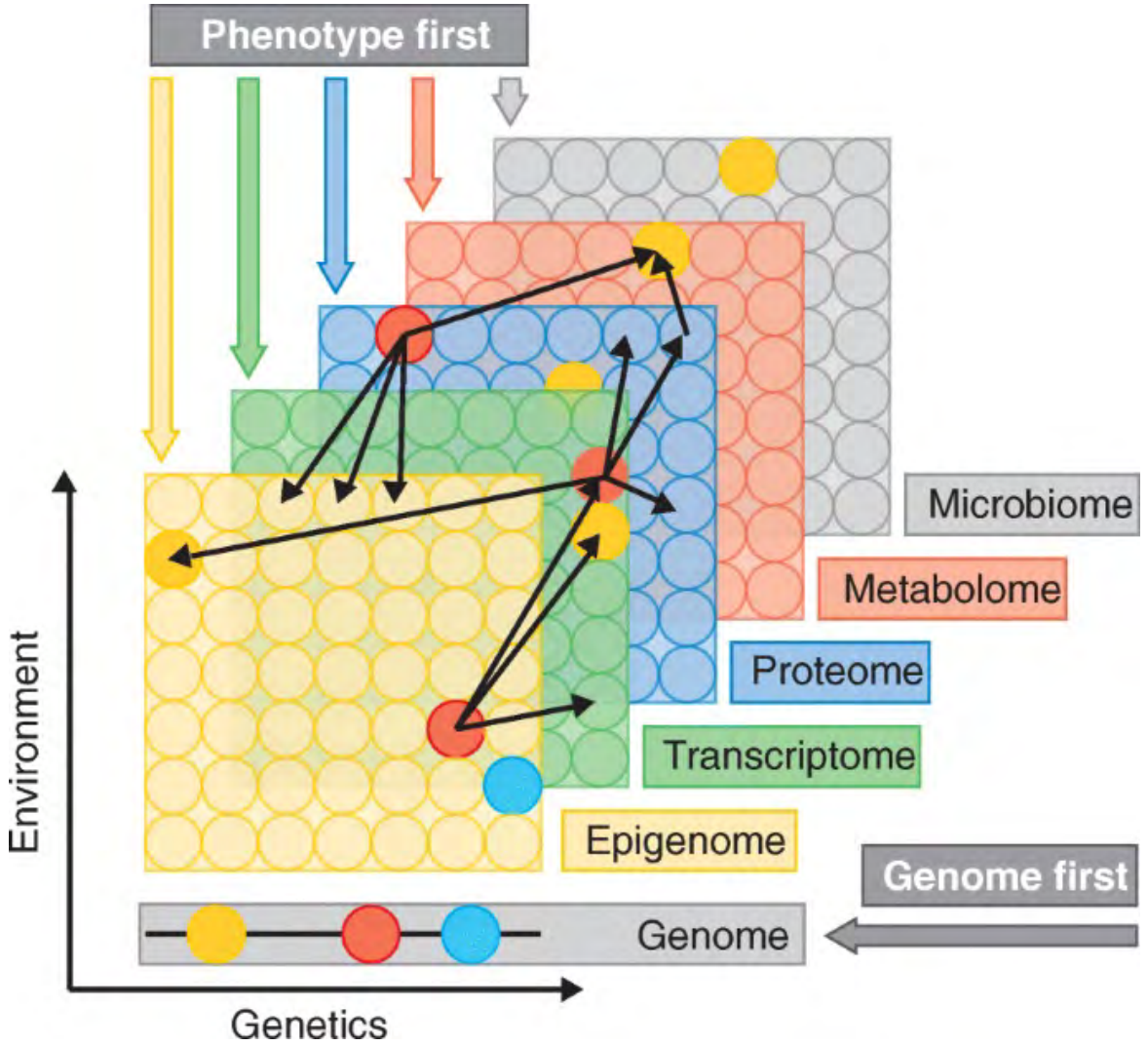


The goal

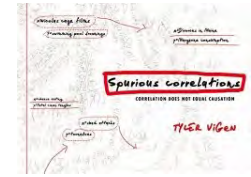


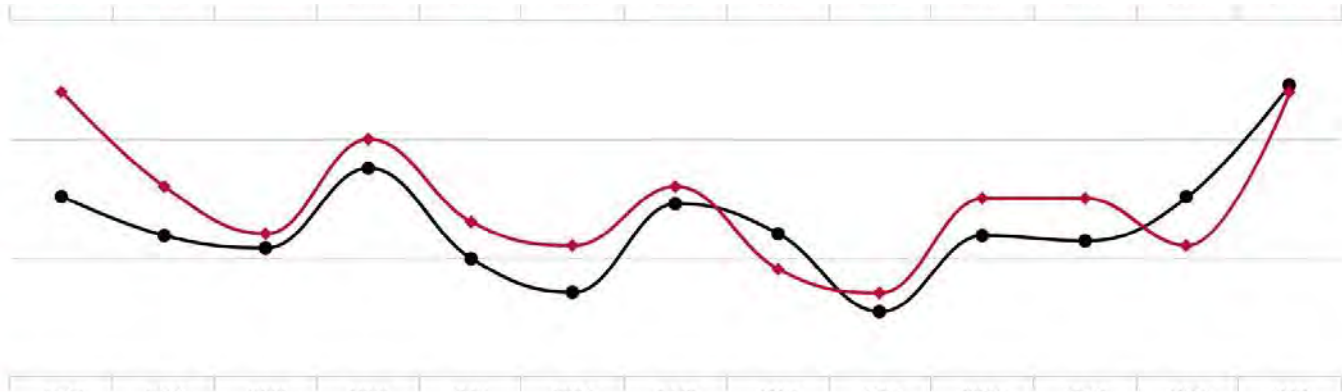
Verstockt et al. Gastroenterology 2022

The –omics revolution

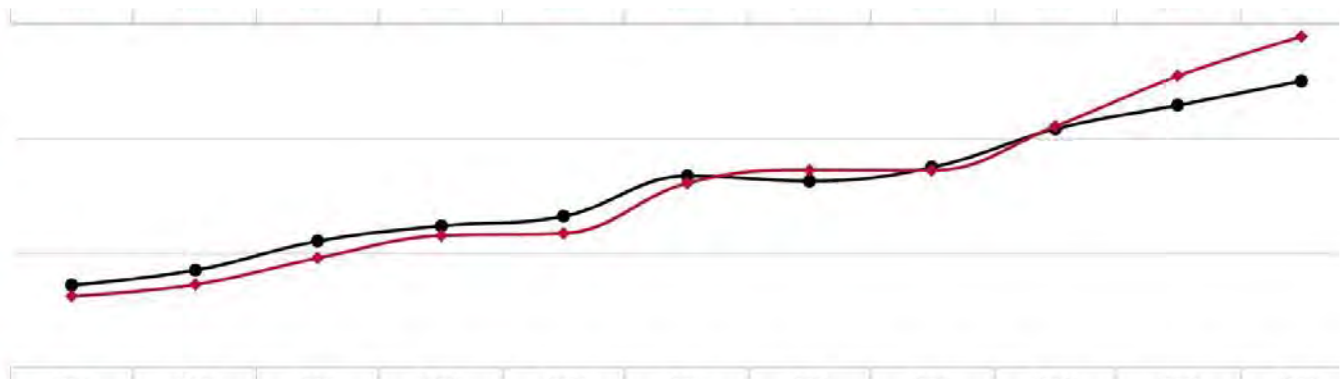


Hasin et al. Genome Biology (2017)





tylervigen.com



tylervigen.com

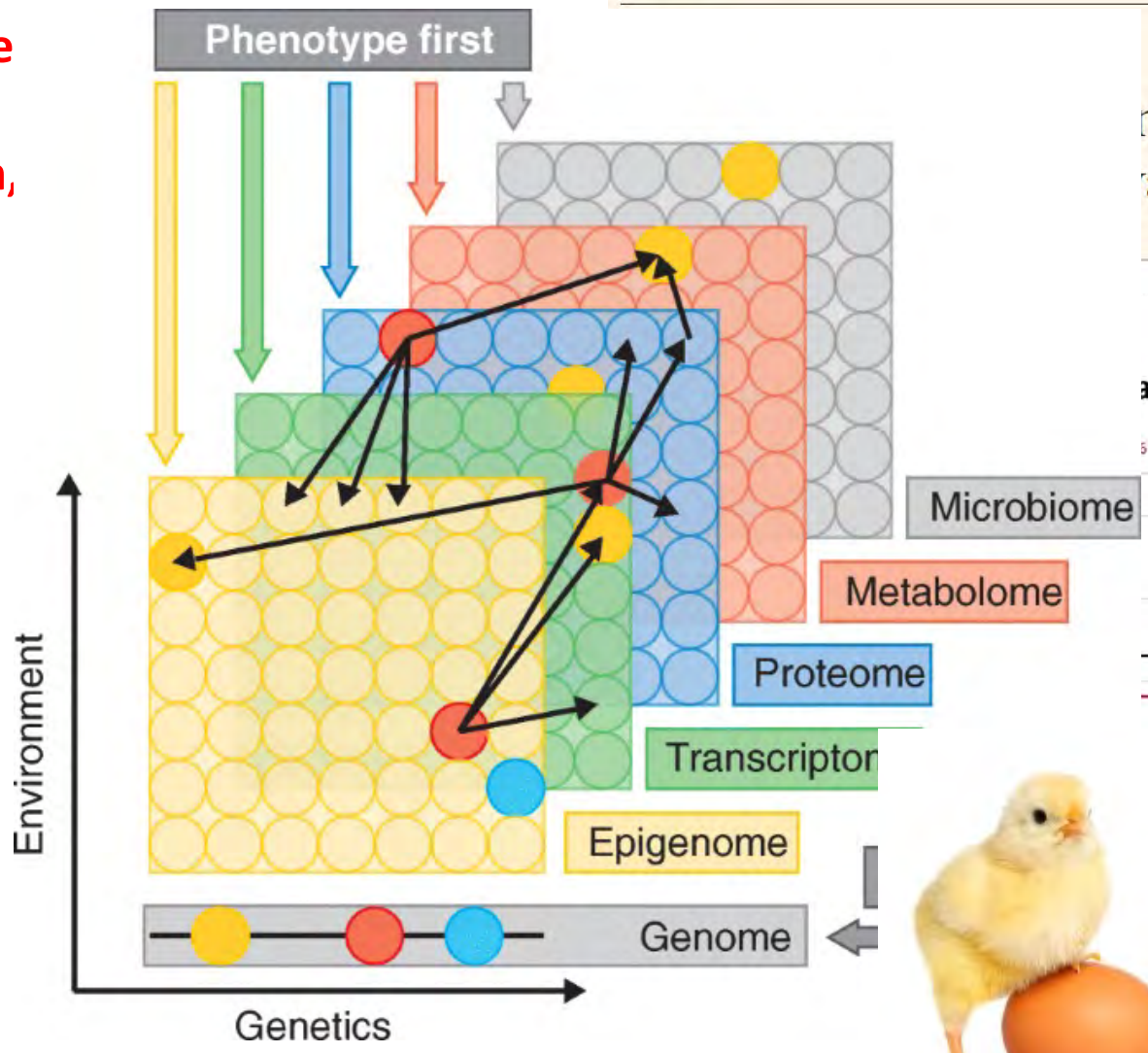
So how do we ensure that our predictive biomarkers will work?

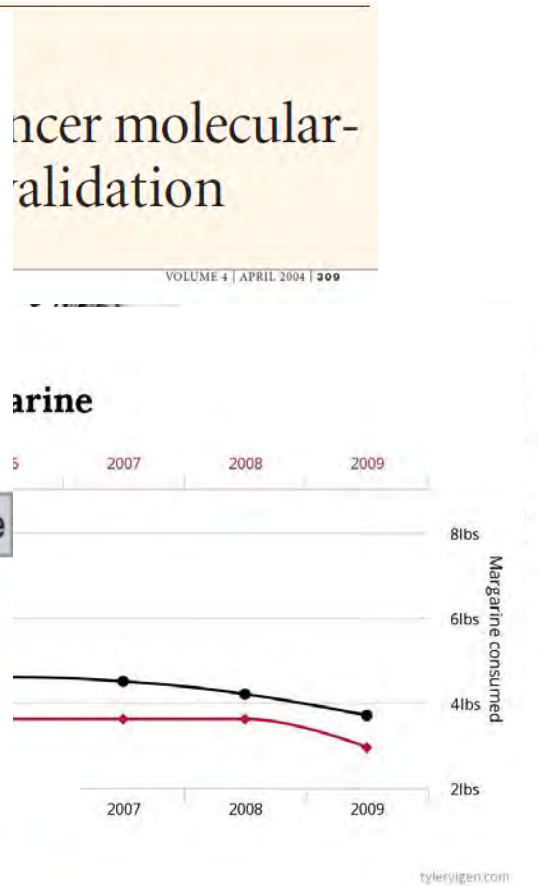
1. Make sure they work to be

2. Study design, study design,

3. Validation…

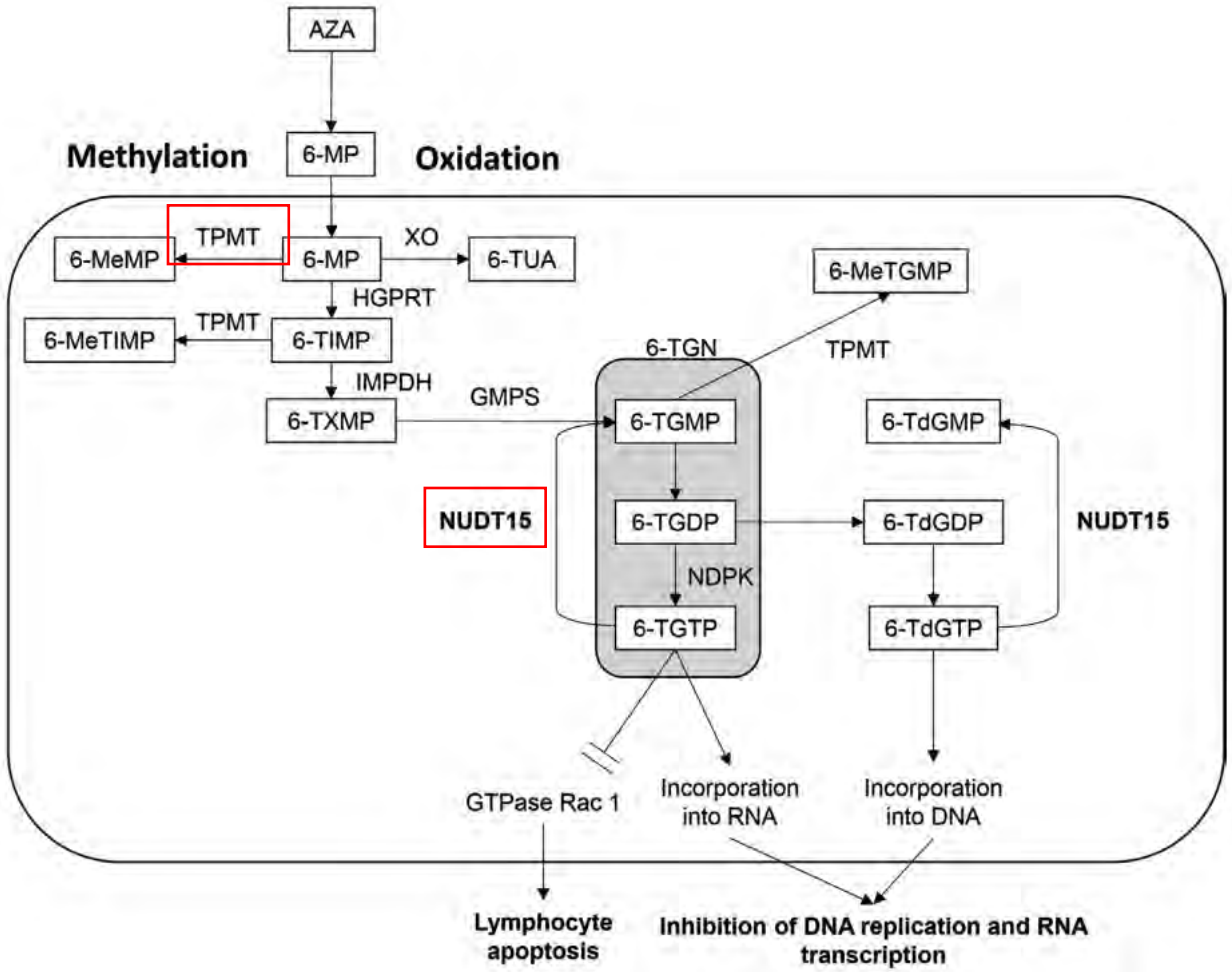
4. Biological plausibility…

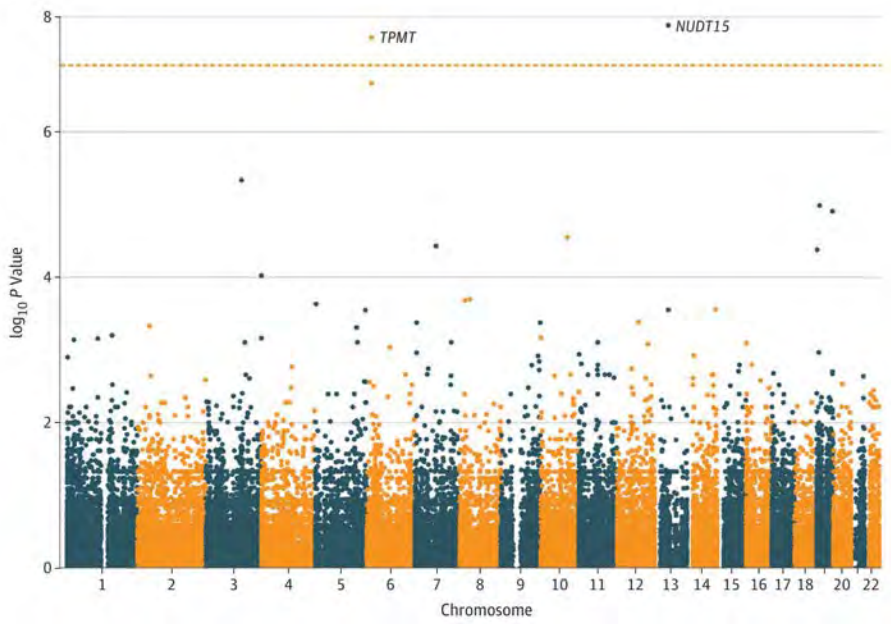




So are there examples of molecular insights leading to predictive biomarkers in IBD?

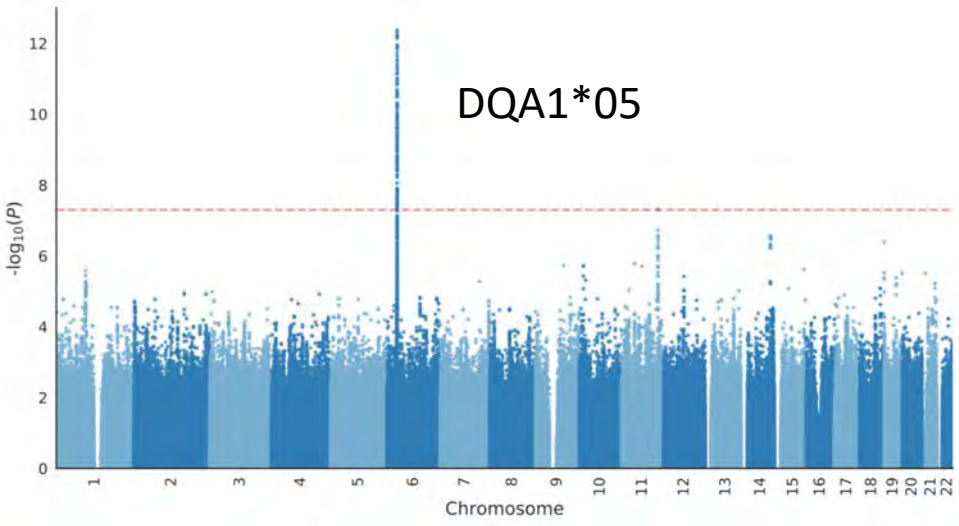
Predictive biomarkers - toxicity



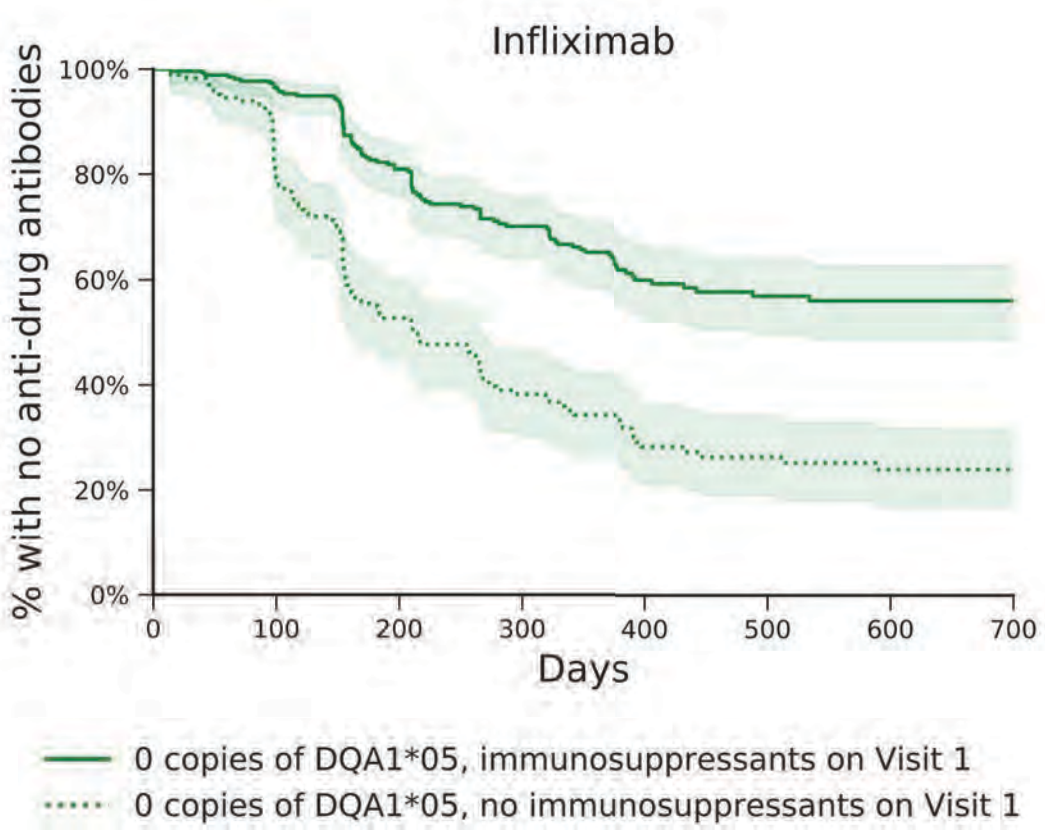


Walker et al. JAMA 2019

Predictive biomarkers - immunogenicity

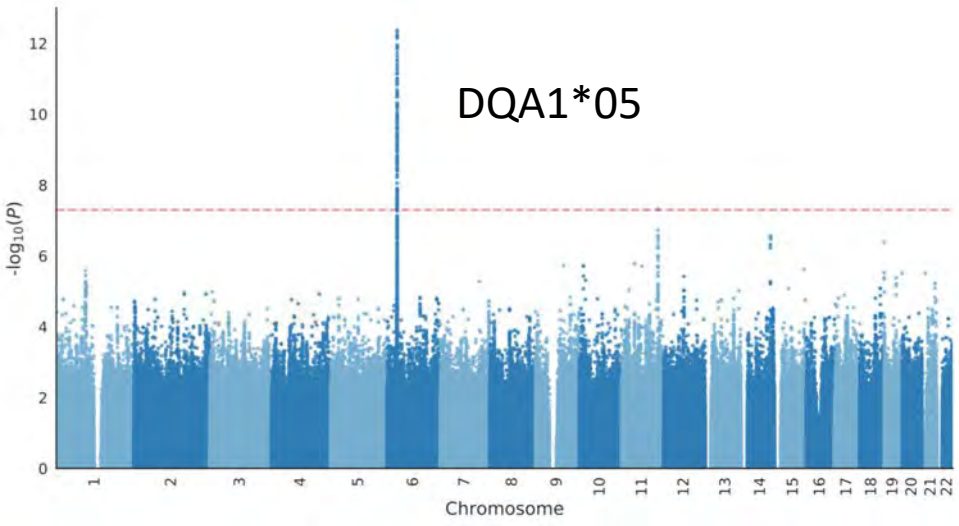


Chr.	Top variant	Minor Allele Frequency	Hazard ratio	P-value	Replication
6	rs2097432	20%	1.68	4.2×10^{-13}	7.84×10^{-4}



Sazonovs et al. Gastro 2020

Predictive biomarkers - immunogenicity



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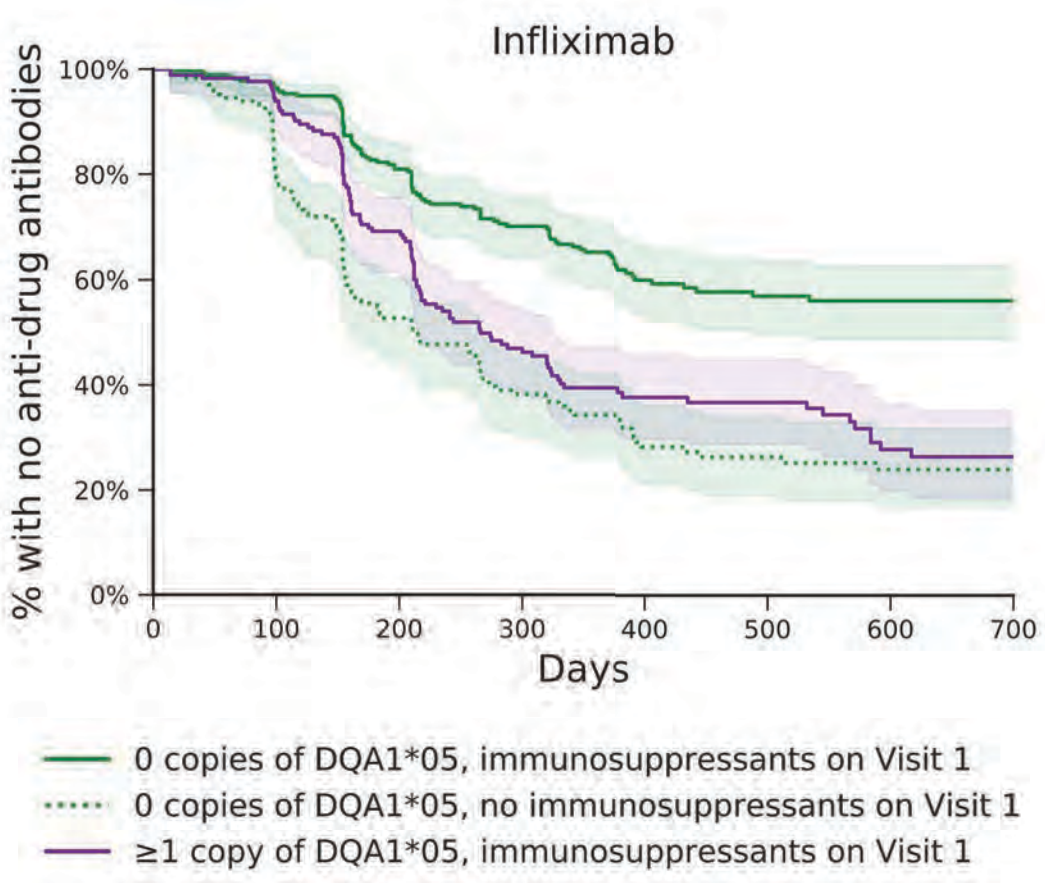
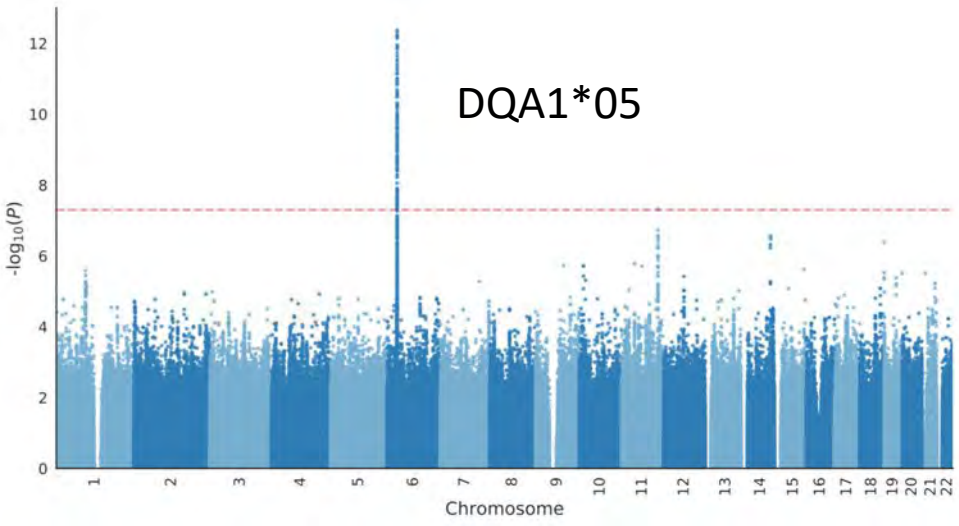


Sazonovs et al. Gastro 2020

Predictive biomarkers - immunogenicity



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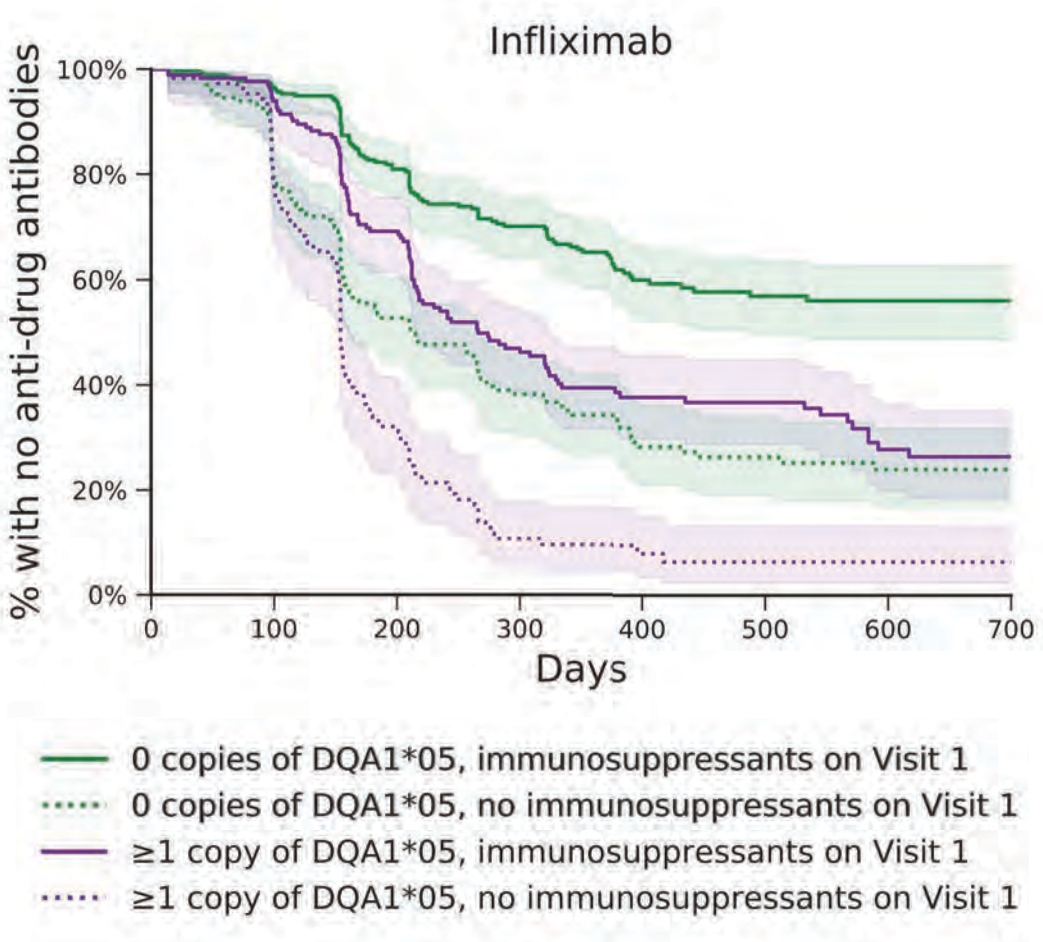
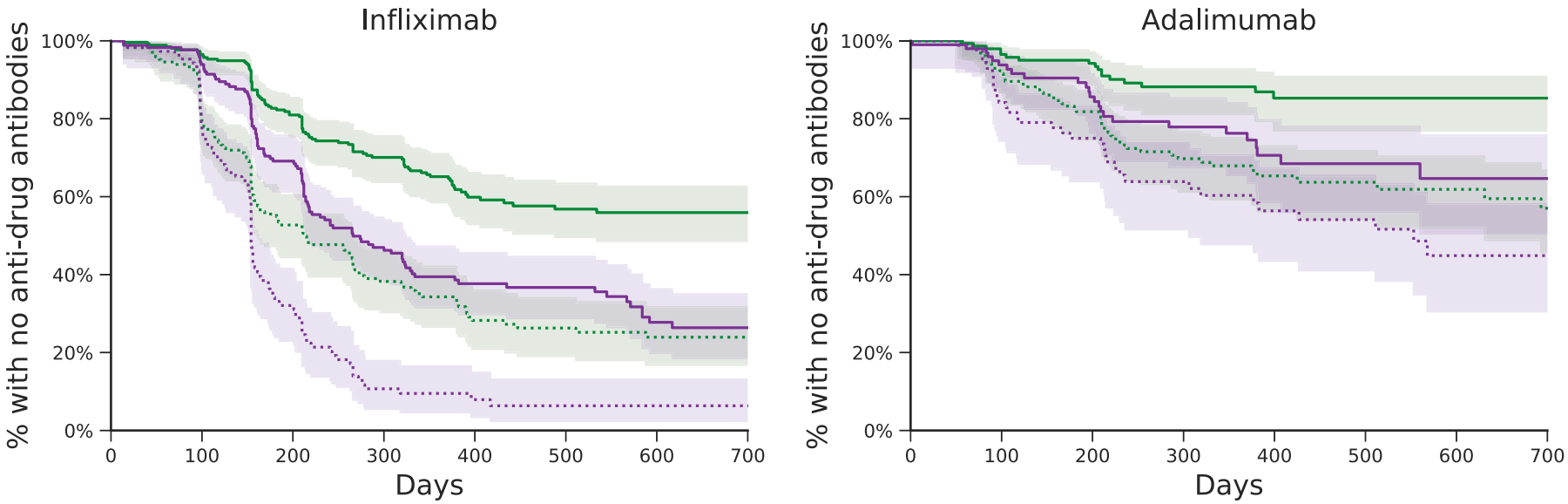


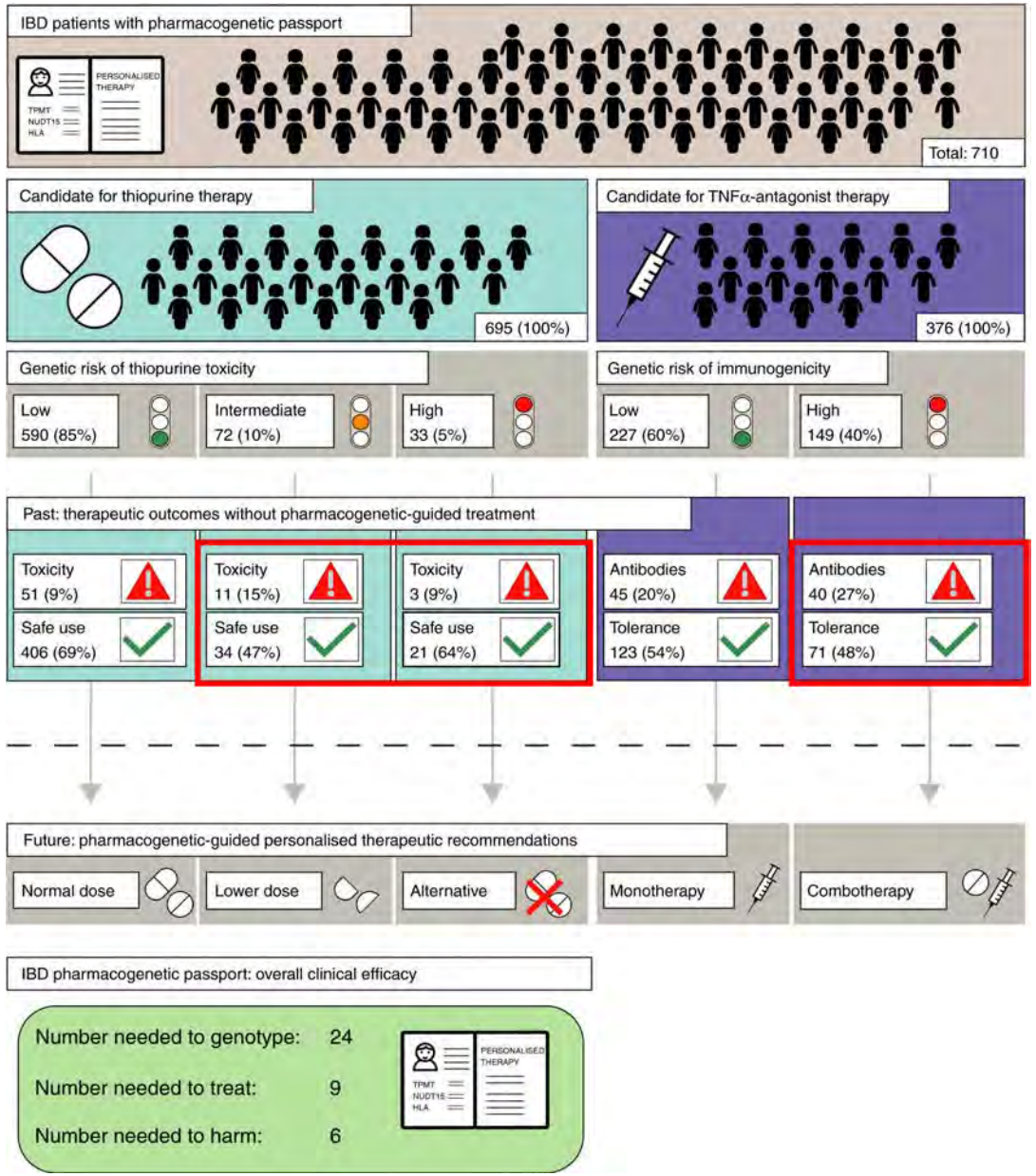
Sazonovs et al. Gastro 2020

Predictive biomarkers - immunogenicity



Sazonovs et al. Gastro 2020

Genetic passports for inflammatory bowel disease

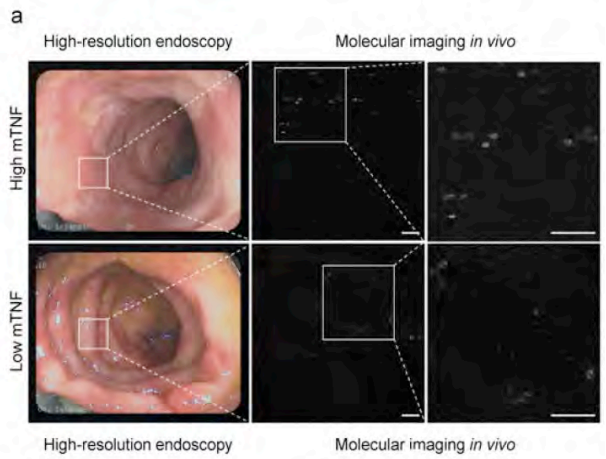


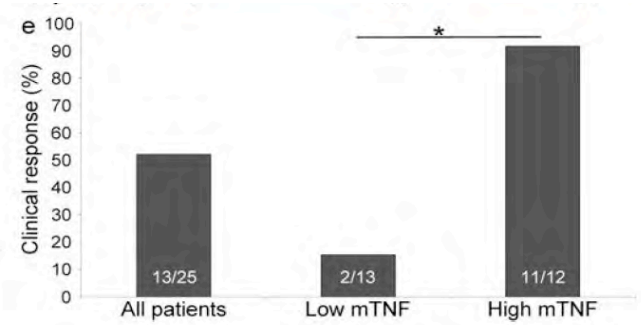
Bangma et al. Aliment Pharmacol Ther, 2020

What about other promising (and plausible) biomarkers?

1. Relating treatment efficacy to presence of drug target

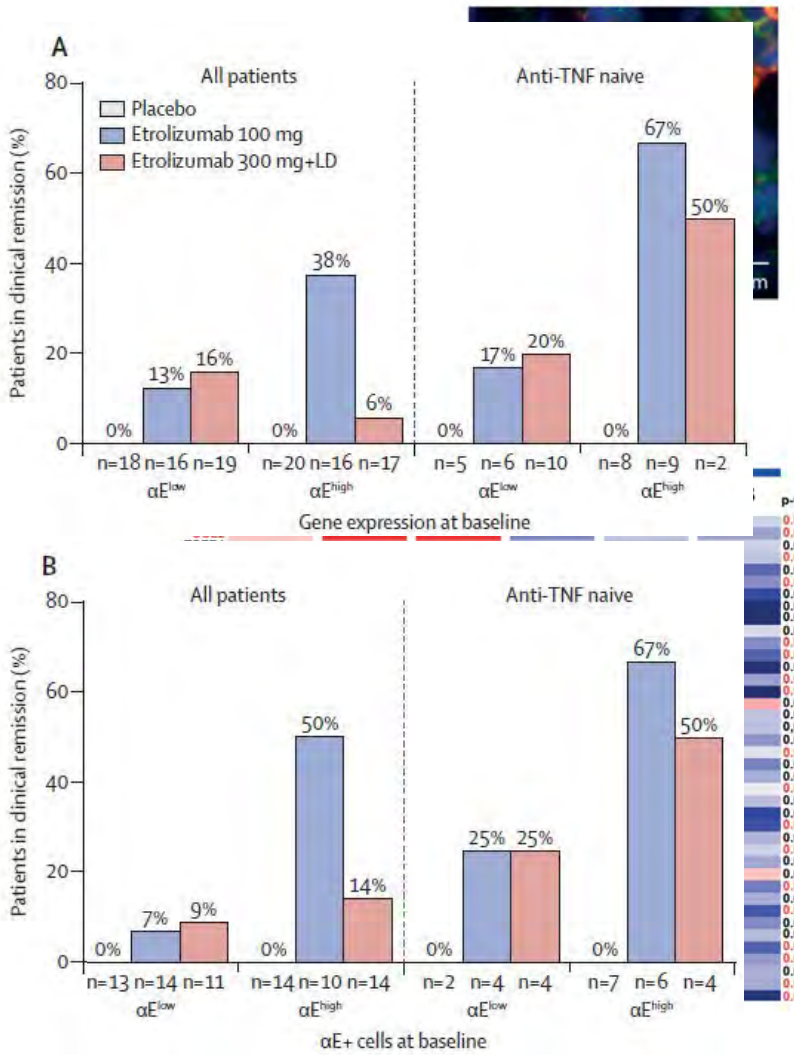
Adalimumab





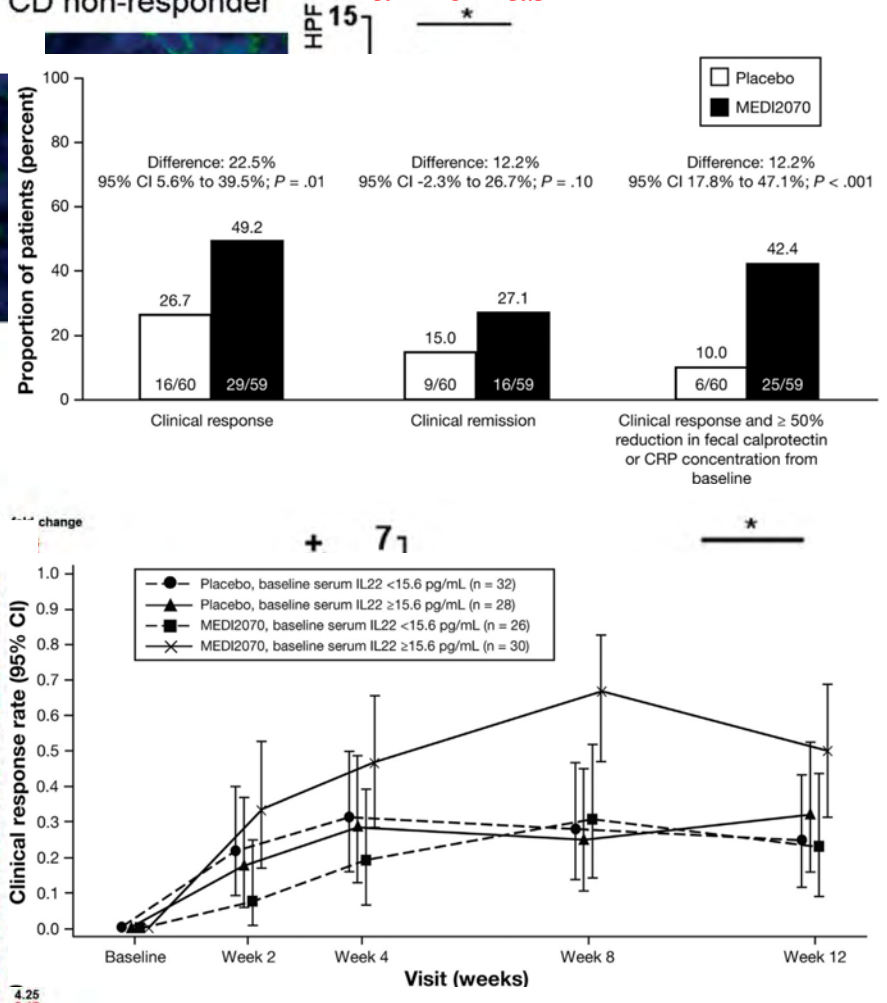
Atreya et al. Nature Medicine (2014)

Etrolizumab



Vermeire et al. Lancet (2014)

Brazikumab

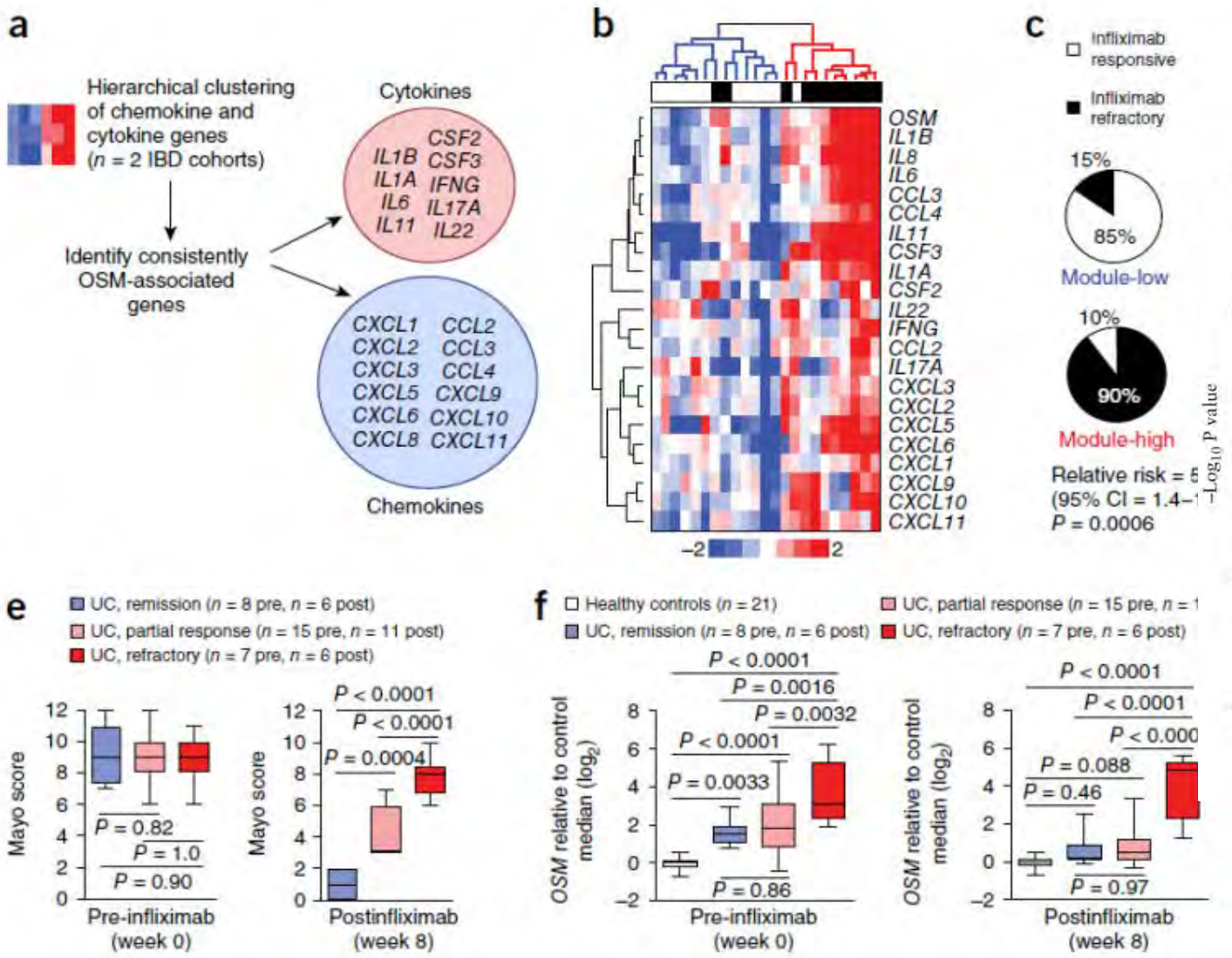


Schmitt et al. Gut (2019)

Sands et al. Gastro (2017)

2. Treatment failure may be due to alternate inflammatory pathways

ONCOSTATIN M

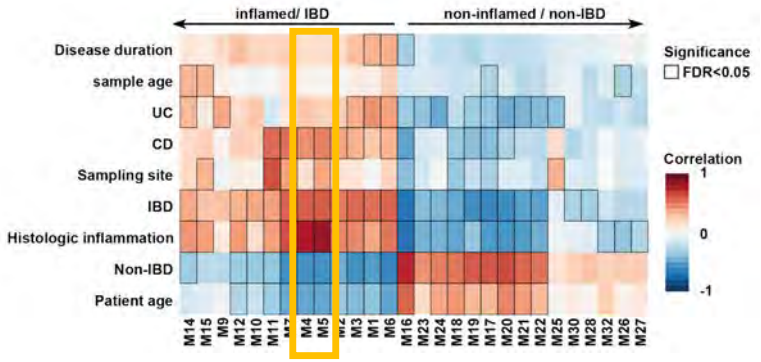


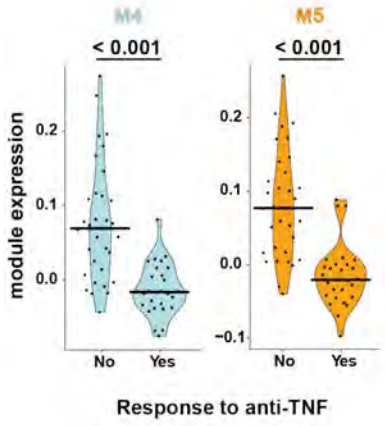
West, Hegazy et al. Nat Med 2017

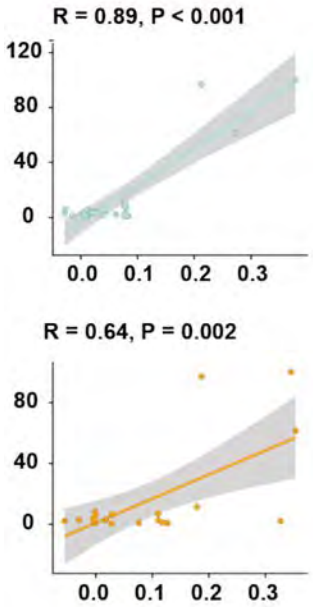
Kalla, Adams et al. JCC 2020

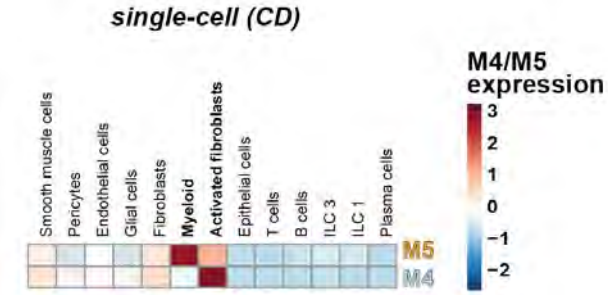
2. Treatment failure may be due to alternate inflammatory pathways

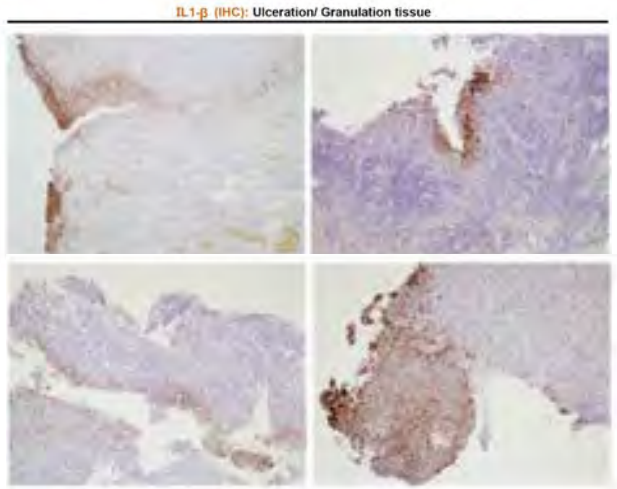
FIBROBLAST – IL1 - NEUTROPHILS

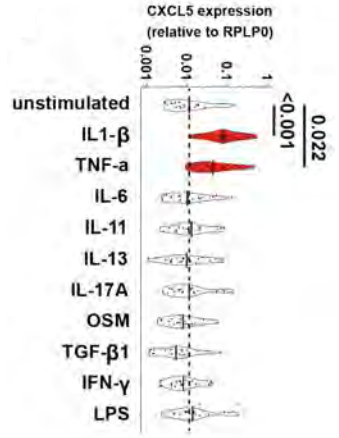


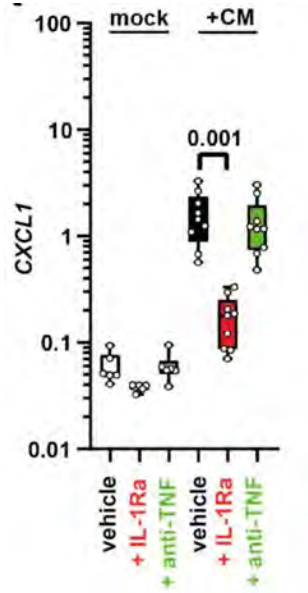






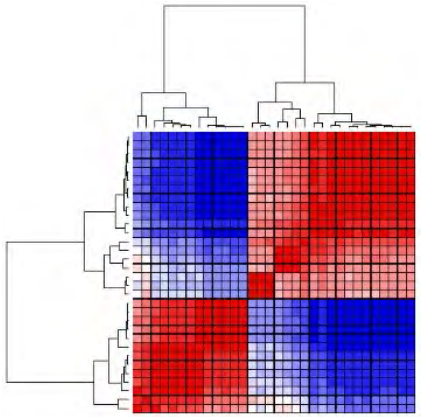


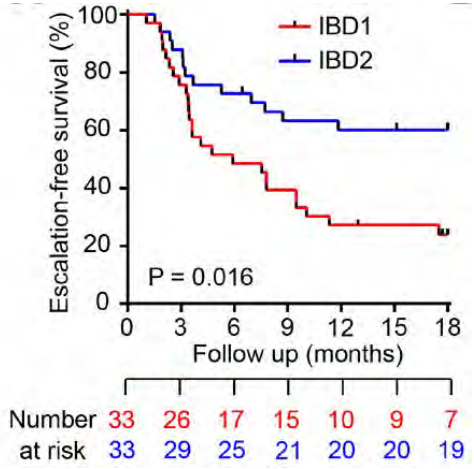




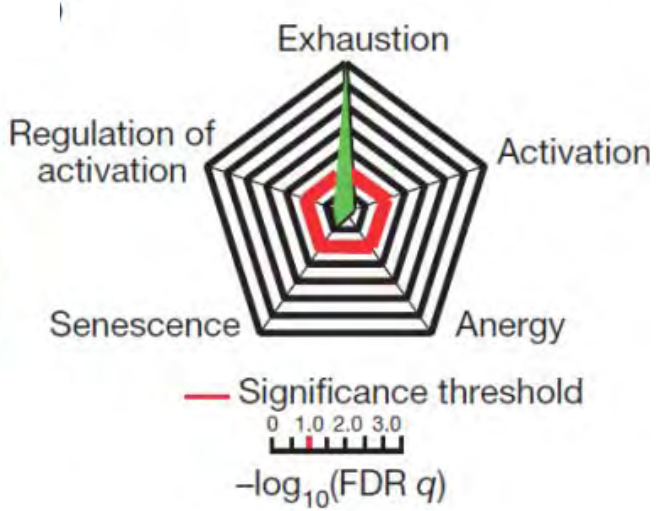
Friedrich et al. 2021 (Nature Medicine)

3. The biology of disease course

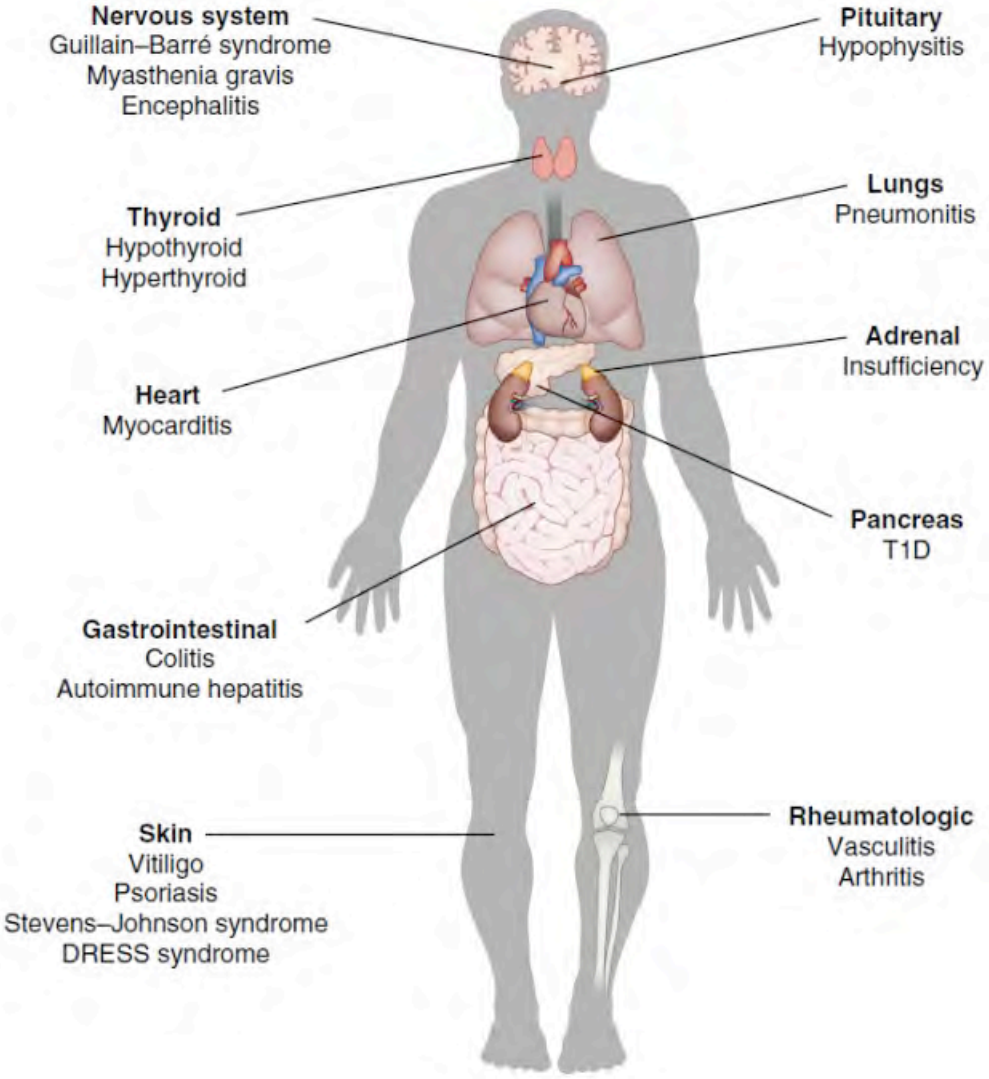




Lee et al. JCI 2011
Biasci et al. Gut 2019



McKinney et al. Nature 2015

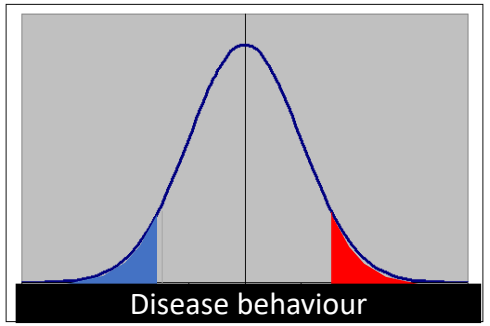


June et al. Nature Medicine 2017

Wherry & Kurachi. Nat Rev Immunol 2015

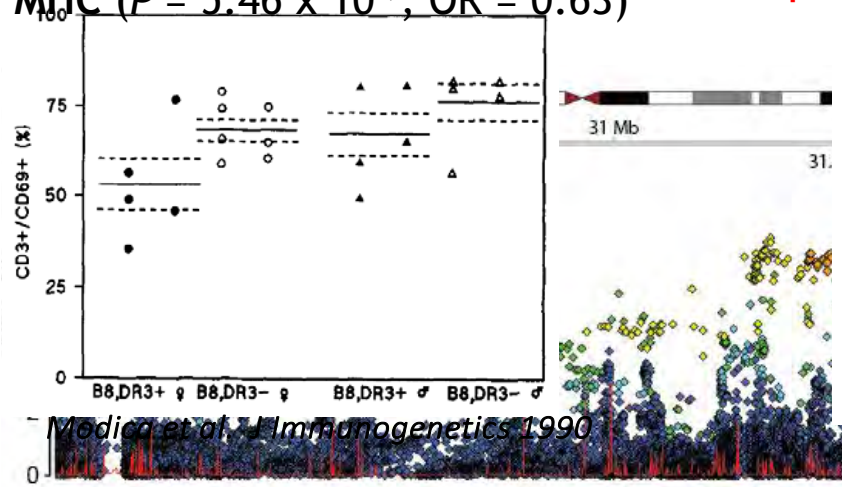
3. The biology of disease course

Prognosis GWAS (Crohn's)



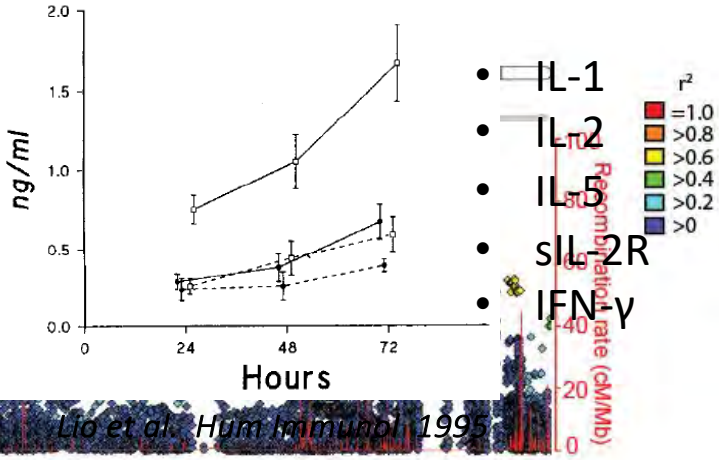
Impaired T cell activation

MHC (P = 5.46 x 10^{-9}, OR = 0.63)



Medica et al. J Immunogenetics 1990

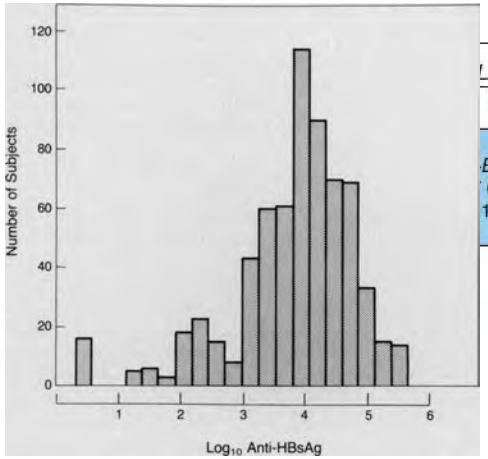
Impaired T cell cytokine production



- IL-1
- IL-2
- IL-5
- sIL-2R
- IFN-γ

Lio et al. Hum Immunol 1995

Reduced vaccine responses



Alper et al. NEJM 1989

More rapid progression of infectious disease

HLA class II region

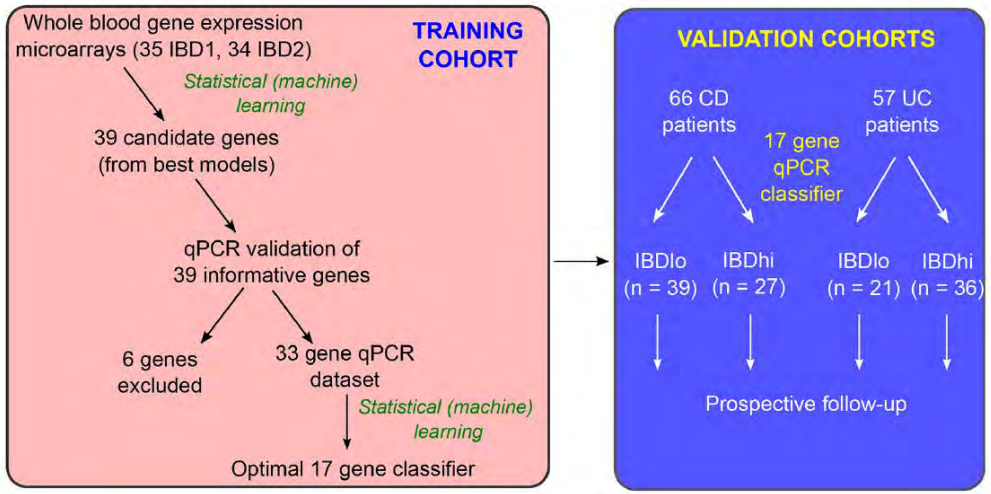
TABLE I—RELATION BETWEEN CD4+ CELL DECLINE AND COMBINATIONS OF HLA ANTIGENS

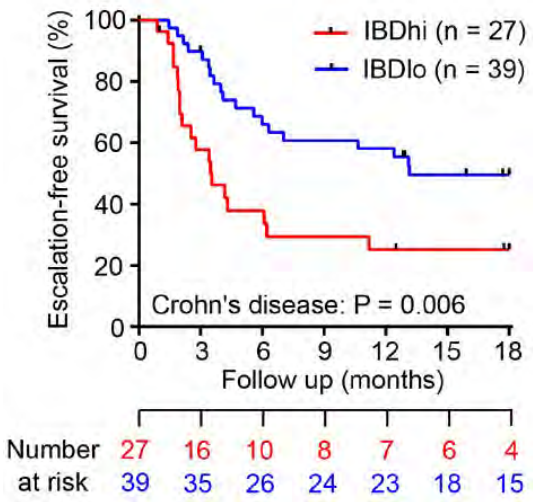
—	No (%) with antigen: Rapid decliners (n = 44–49)	No (%) with antigen: Slow decliners (n = 54–59)	Odds ratio (logit)	p*
A1, Cw7, B8	9 (18·4%)	0	10·3	0·0005
A1, B8	9 (18·4%)	1 (1·7%)	6·1	0·003
A1, Cw7	10 (20·8%)	2 (3·4%)	6·1	0·004
A1, Cw7, B8, DR3	5 (10·6%)	0	7·6	0·01

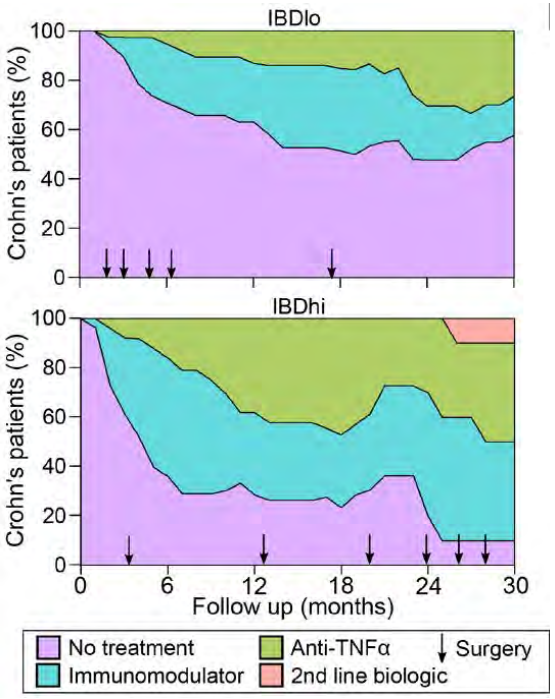
Kaslow et al. Lancet 1990

Lee et al. Nature Genetics 2017

3. The biology of disease course

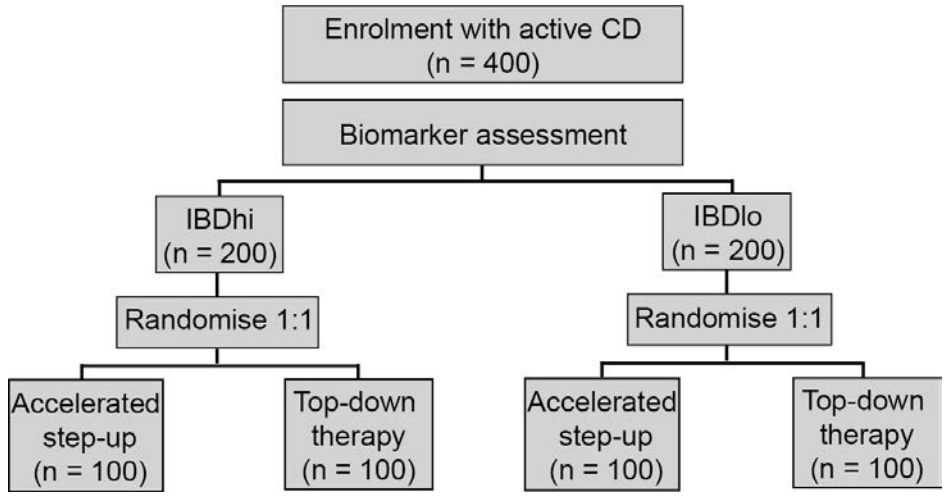






Biasci et al. Gut 2019

PRedicting **O**utcomes **F**or Crohn's d**I**sease using a mo**L**ecular biomark**E**r



"Top-down" therapy

- *Enrolment*: Infliximab & Azathioprine / Methotrexate

"Accelerated Step-up" therapy

- *Enrolment*: Prednisolone 8 week reducing course
- Flare 1: Prednisolone plus Azathioprine / Methotrexate
- Flare 2: Add in Infliximab

- **Recruitment closed (Jan '22)**
- **390 patients recruited**

Is Personalised Medicine possible in IBD?

Yes! BUT…

Can it be used in the real world?

Is it good enough?

Independently validated?

Biologically plausible?

Is it truly predictive?
(not just an association)