

PROFILE trial

*PR*edicting *OU*tcomes *FO*r Crohn's *dI*sease using
*a mo*Lecular *bio*mark*Er*

Dr Nuru Noor

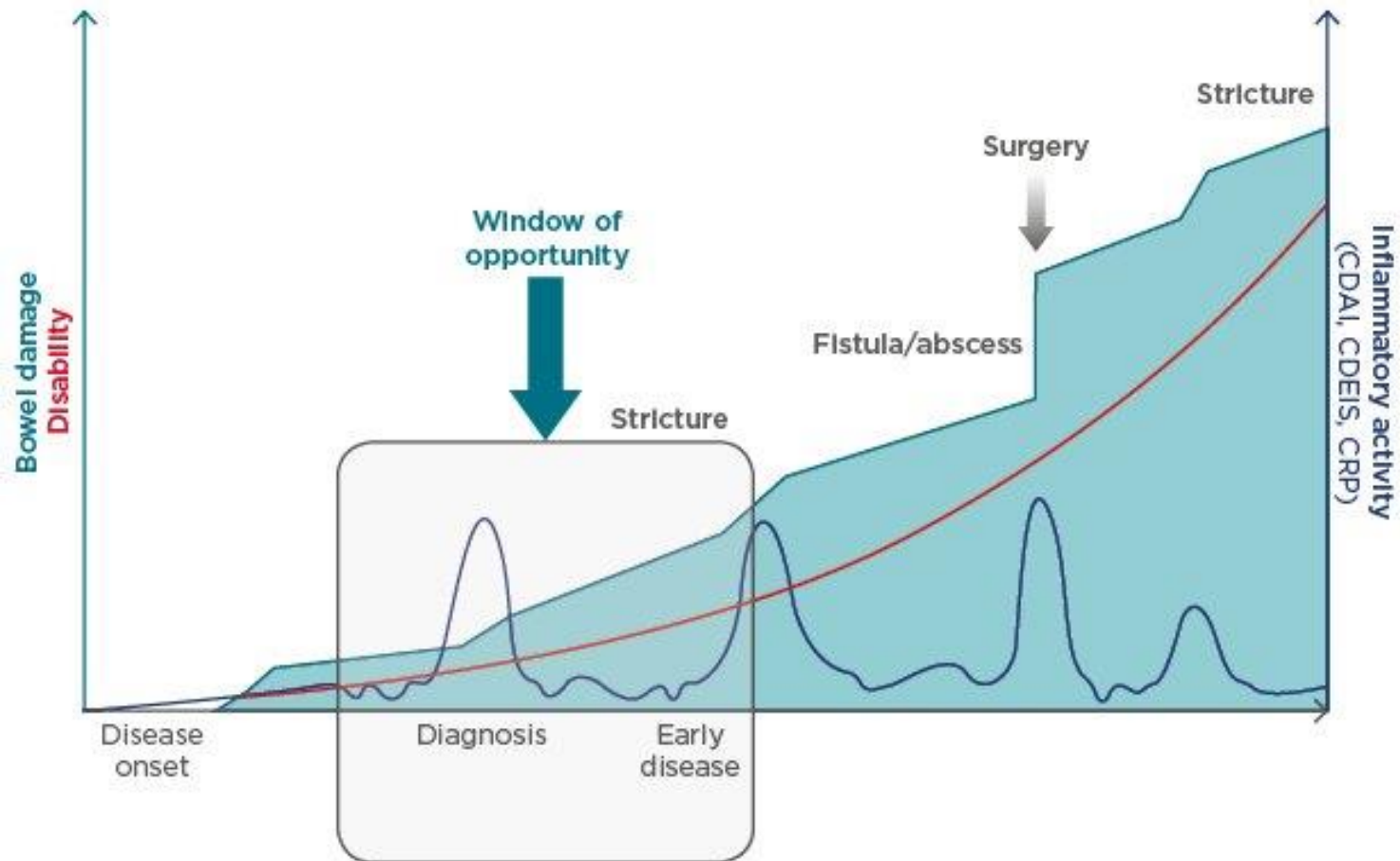
Clinical Lecturer in Gastroenterology
University of Cambridge



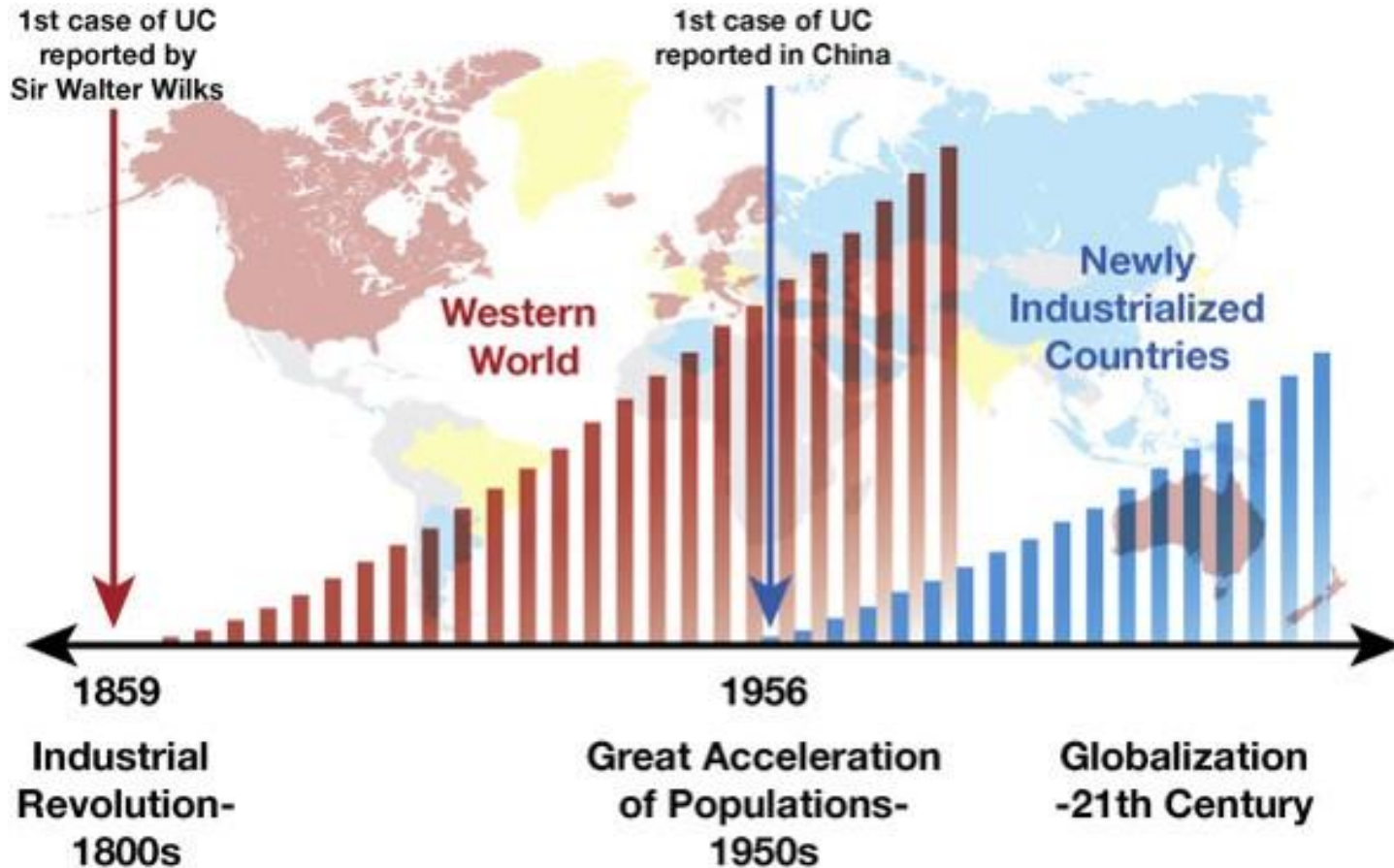
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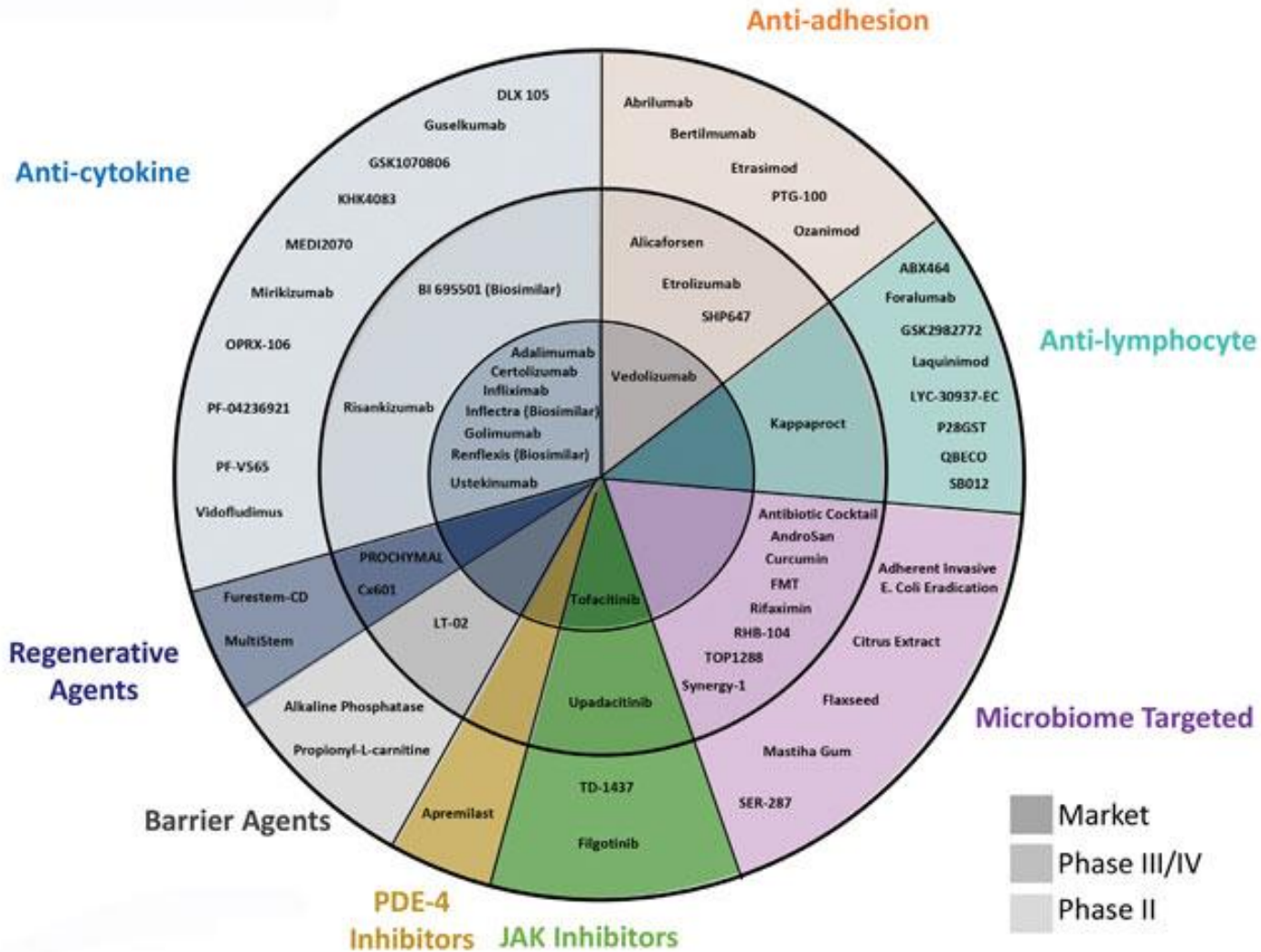
Inflammatory bowel disease is a chronic progressive condition



Inflammatory bowel diseases are a growing and global healthcare problem



More treatments in IBD than ever before (and many more on the way)



HUGE progress in IBD – but clinical care is still mostly trial and error

We've got NEW hormones,
pheromones, bacterials,
arterials, radioactive,
proactive, interactive, and
reactive drugs.
So take your pick...

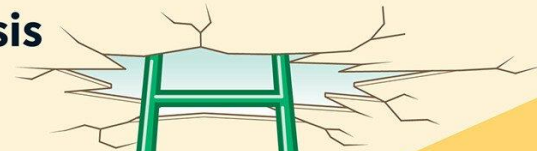
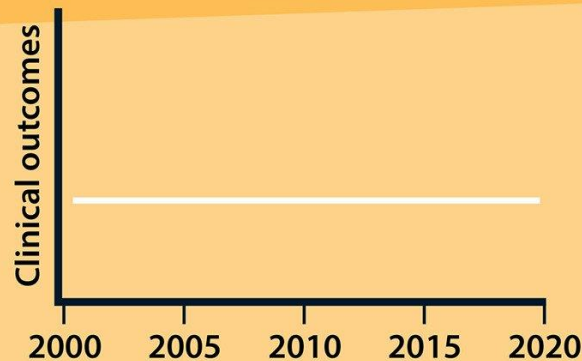
I want the one that
says CURE as part of
the name...



Therapeutic ceiling reached in Crohn's disease for last 20 years

Has the therapeutical ceiling been reached in randomized controlled trials in Crohn's Disease?

A systematic review and meta-analysis



Magro F et al. United European Gastroenterology J. 2022

N=25 trial
8879 patients with CD

Visual abstract created by Susan Tyler

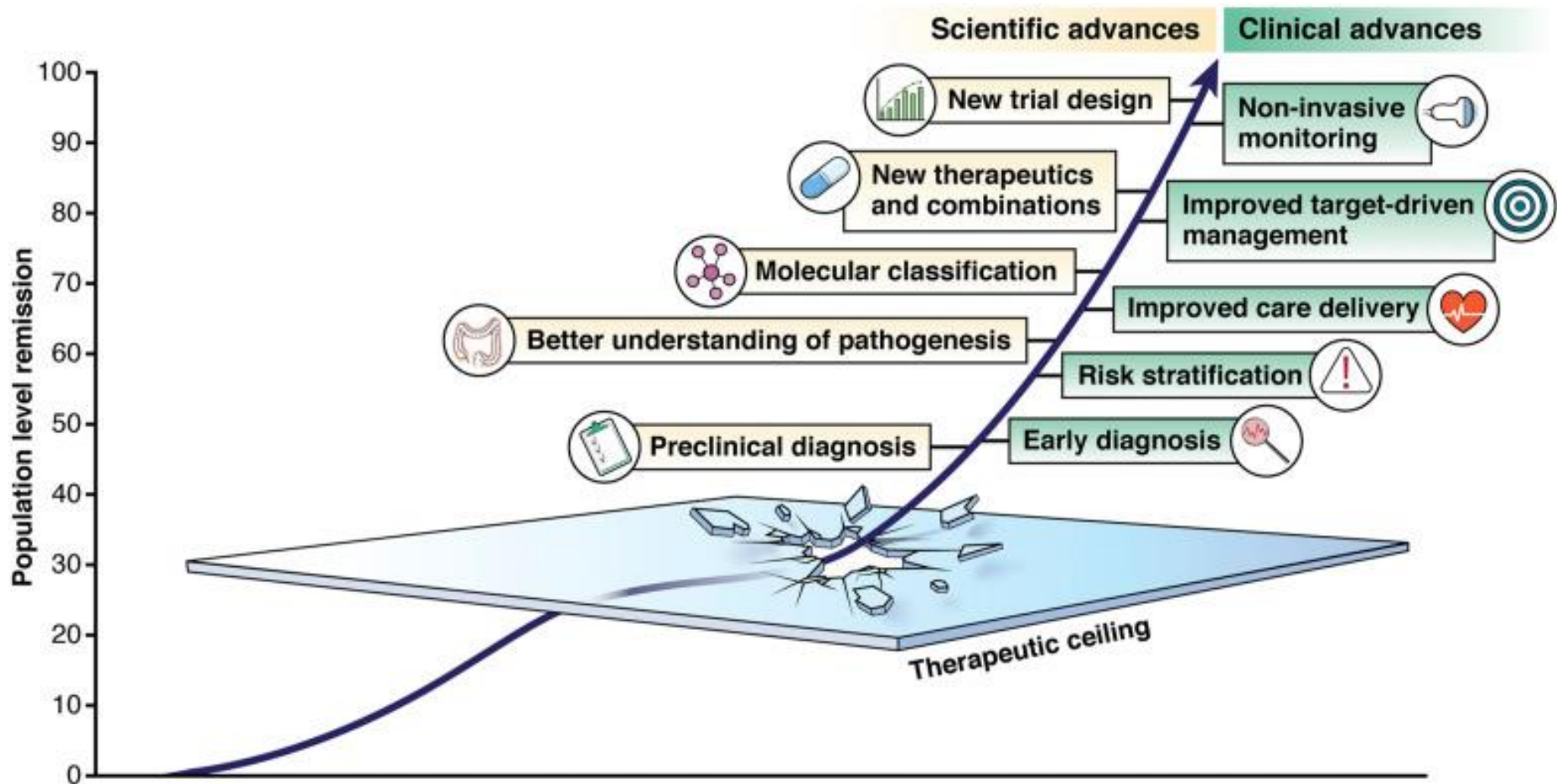
UNITED EUROPEAN GASTROENTEROLOGY
ueg journal

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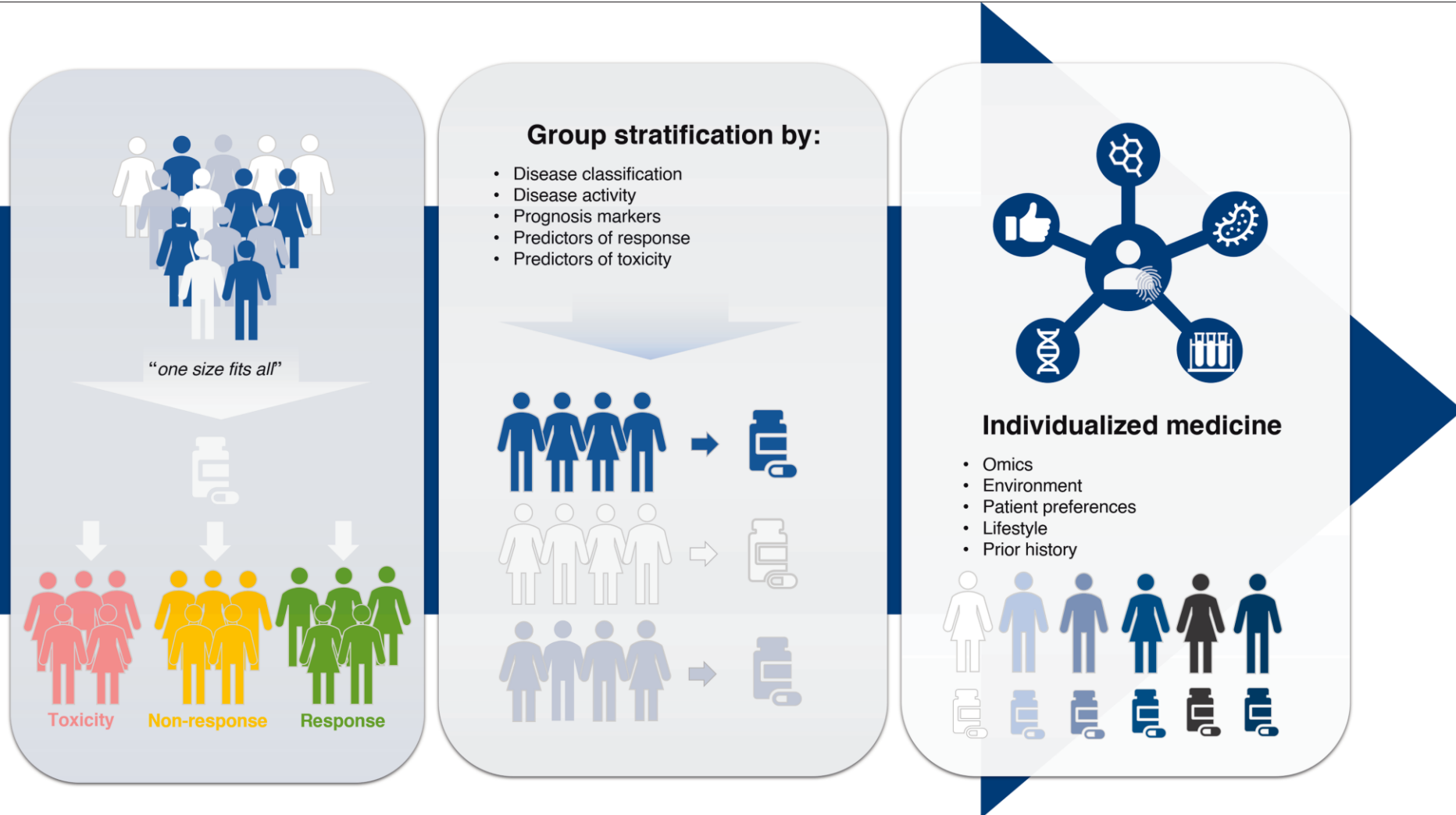
Clinical outcomes of biological therapy vs placebo have been stable in the last decades

Magro F, Moreira PL, Catalano G, et al. UEGJ 2023

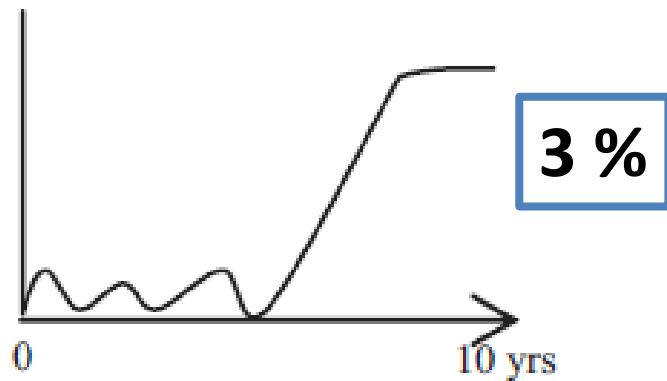
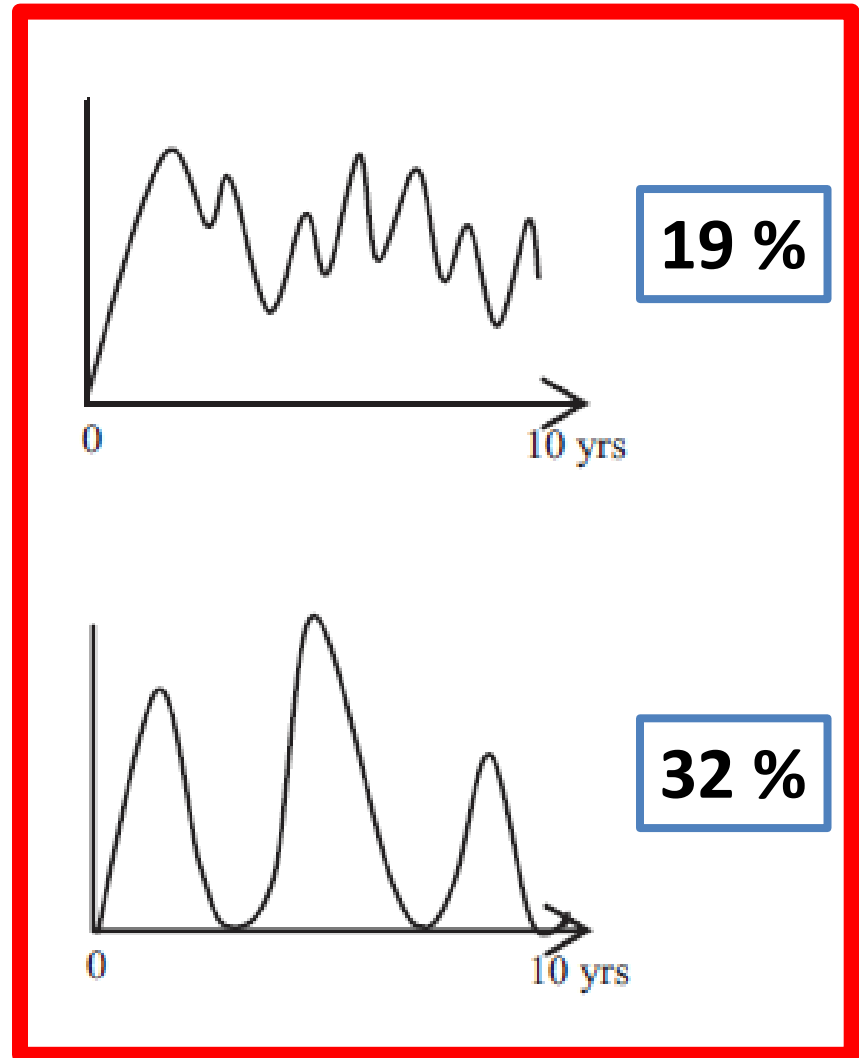
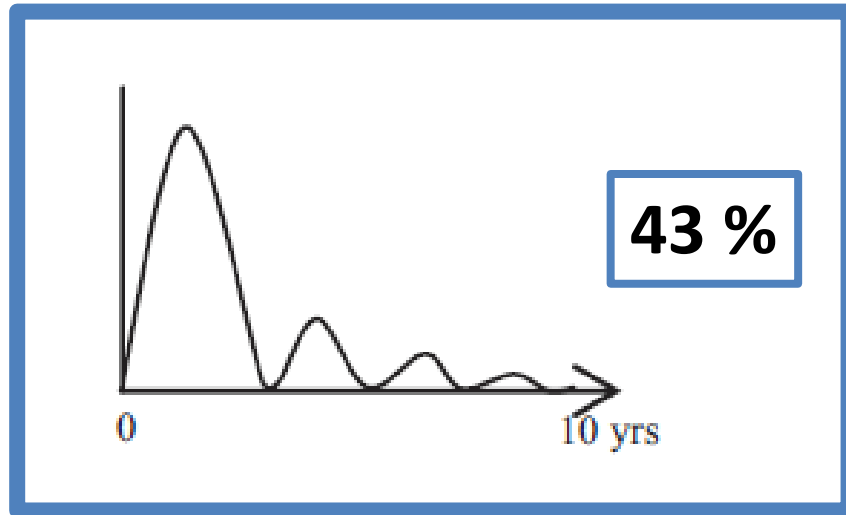
Huge opportunity for research to improve IBD care



Aspiration for personalised medicine in IBD



One issue is highly variable disease course



Need for a personalised approach in most medical conditions

“ The success of personalised medicine depends on having **accurate (biomarker) tests** that identify patients who can benefit from targeted therapies ”

Dr Margaret Hamburg (Commissioner – FDA)

Dr Francis Collins (Director – NIH)

Aggressive disease

Receive stronger therapy as early as possible
(ideally at diagnosis)

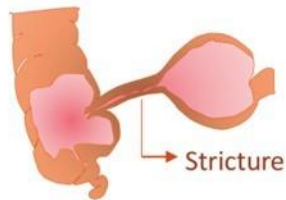
Milder disease

Protected from risks of unnecessary immunosuppression

Need for biomarkers in IBD

BIOMARKER NEEDS IN INFLAMMATORY BOWEL DISEASES

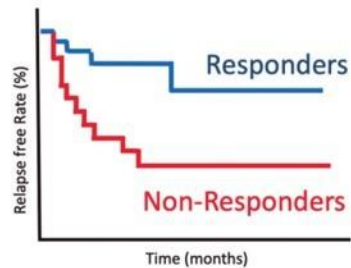
PREDICTING DISEASE COURSE



At diagnosis

PROGNOSTIC BIOMARKERS

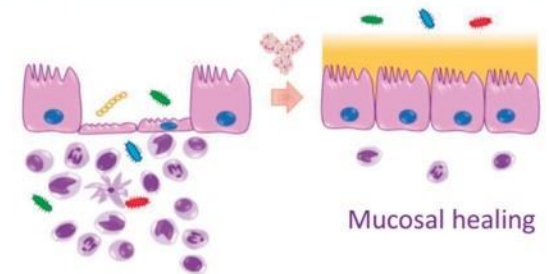
PREDICTING TREATMENT RESPONSE



Before treatment initiation

PREDICTIVE BIOMARKERS

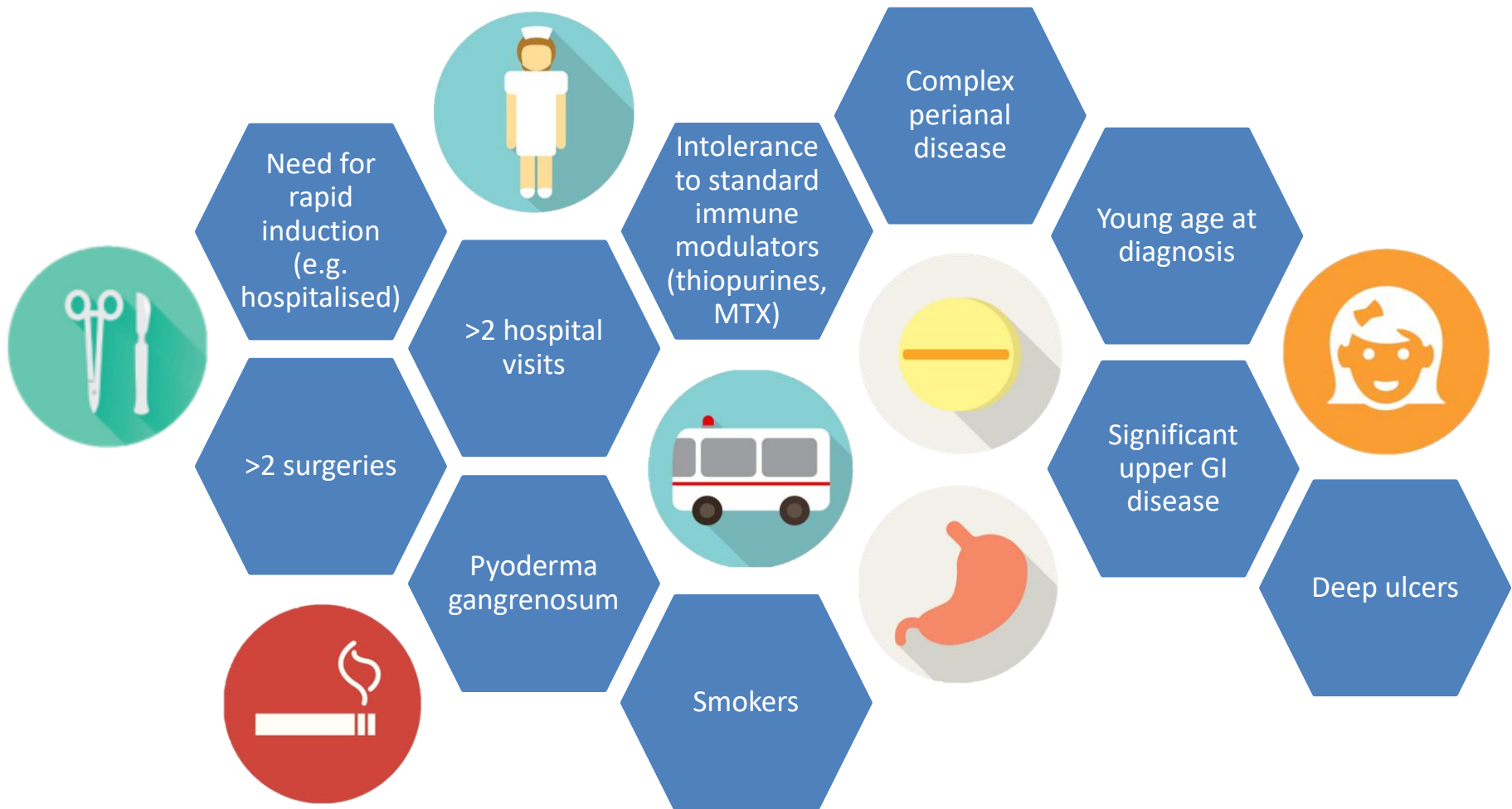
MONITORING TREATMENT RESPONSE



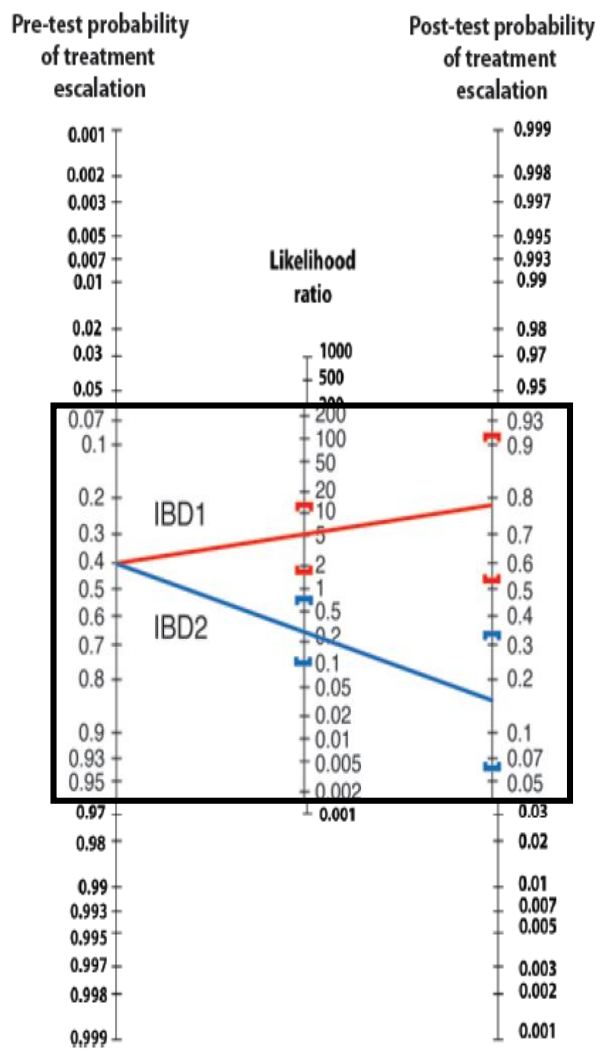
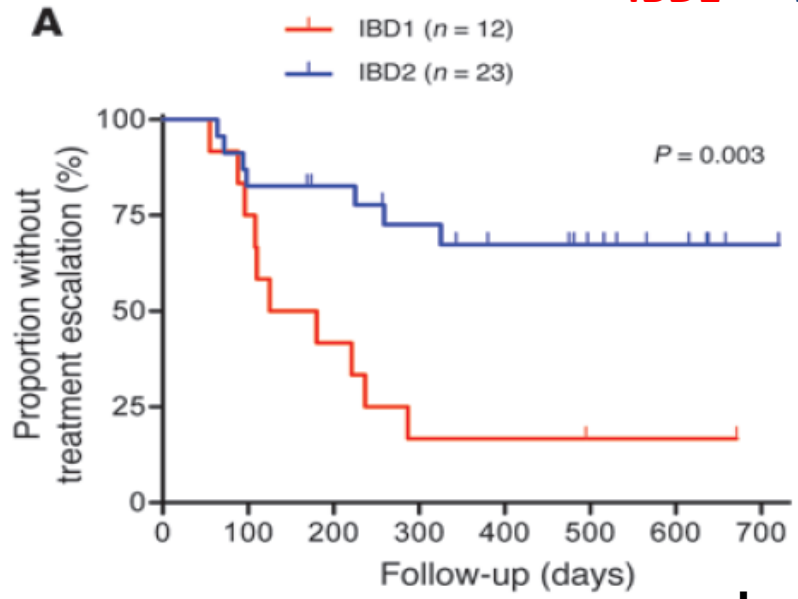
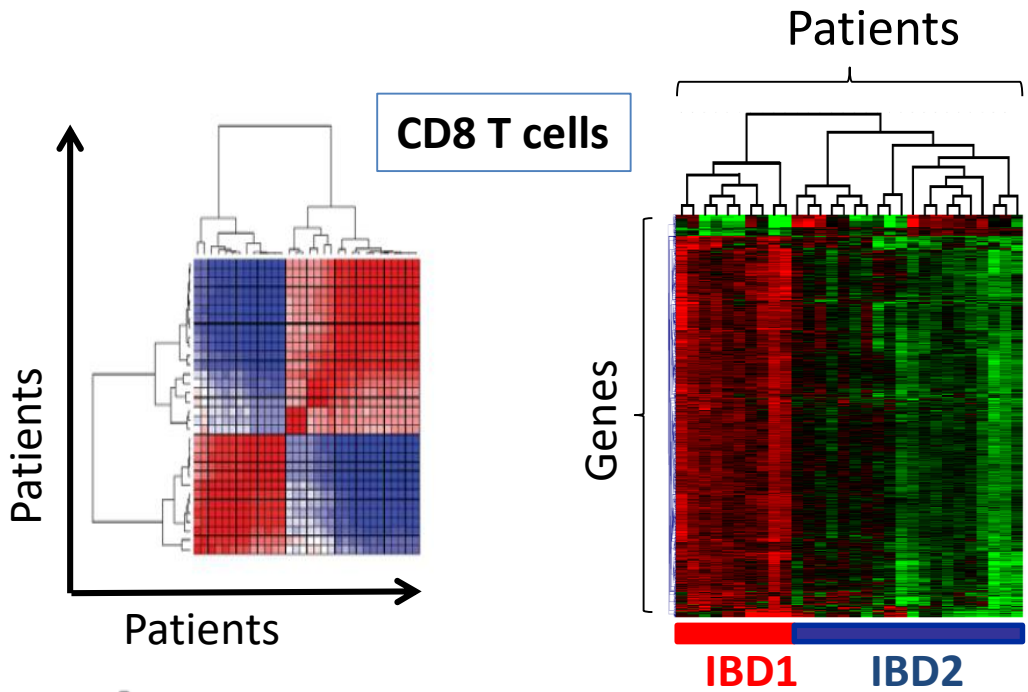
During treatment

MONITORING BIOMARKERS

Can we predict disease course at the moment?



Could we use gene expression to predict outcomes in IBD?

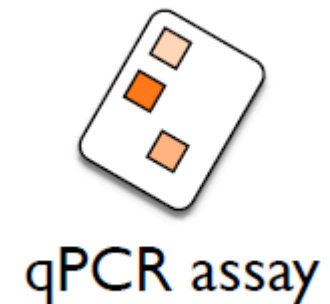
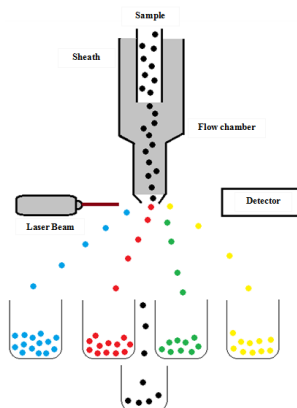
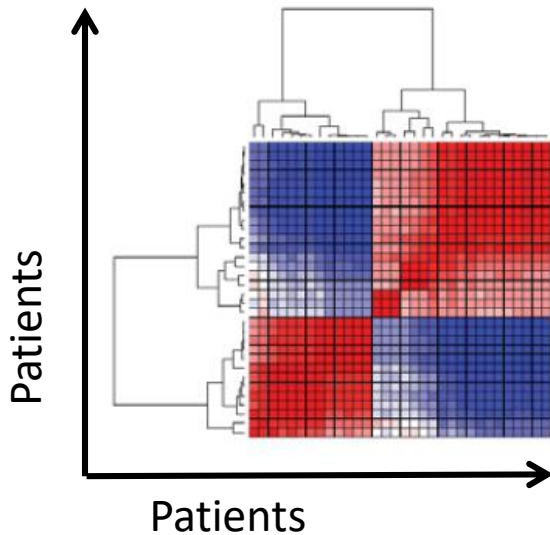
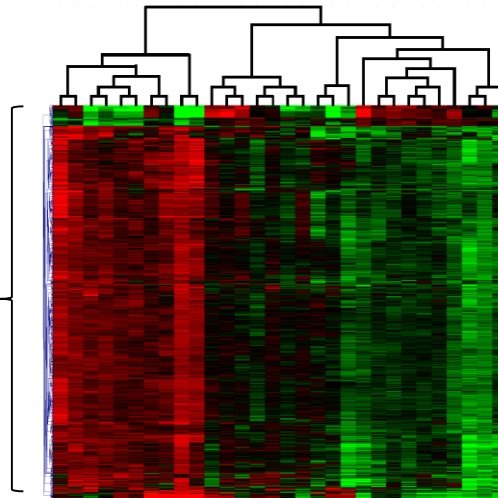


How to translate this back to the clinic?

Patients



Genes

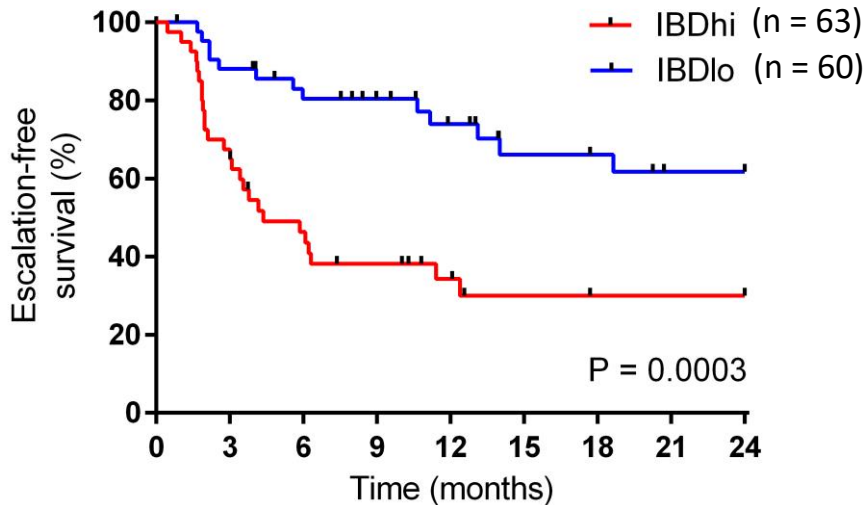


Validation in independent IBD cohort

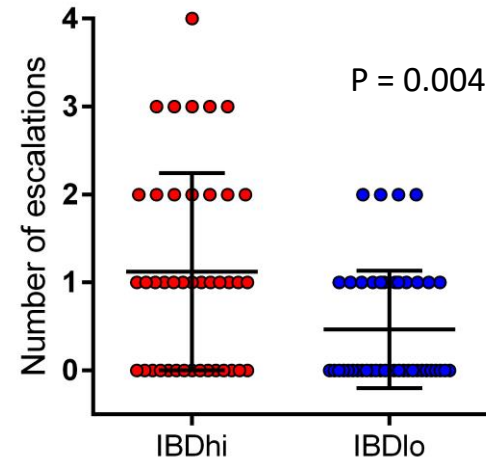


qPCR assay

- 17 genes: 15 informative, 2 reference
- Independent cohort of 123 samples from newly diagnosed IBD patients (Cambridge, Exeter, Nottingham, St Marks)

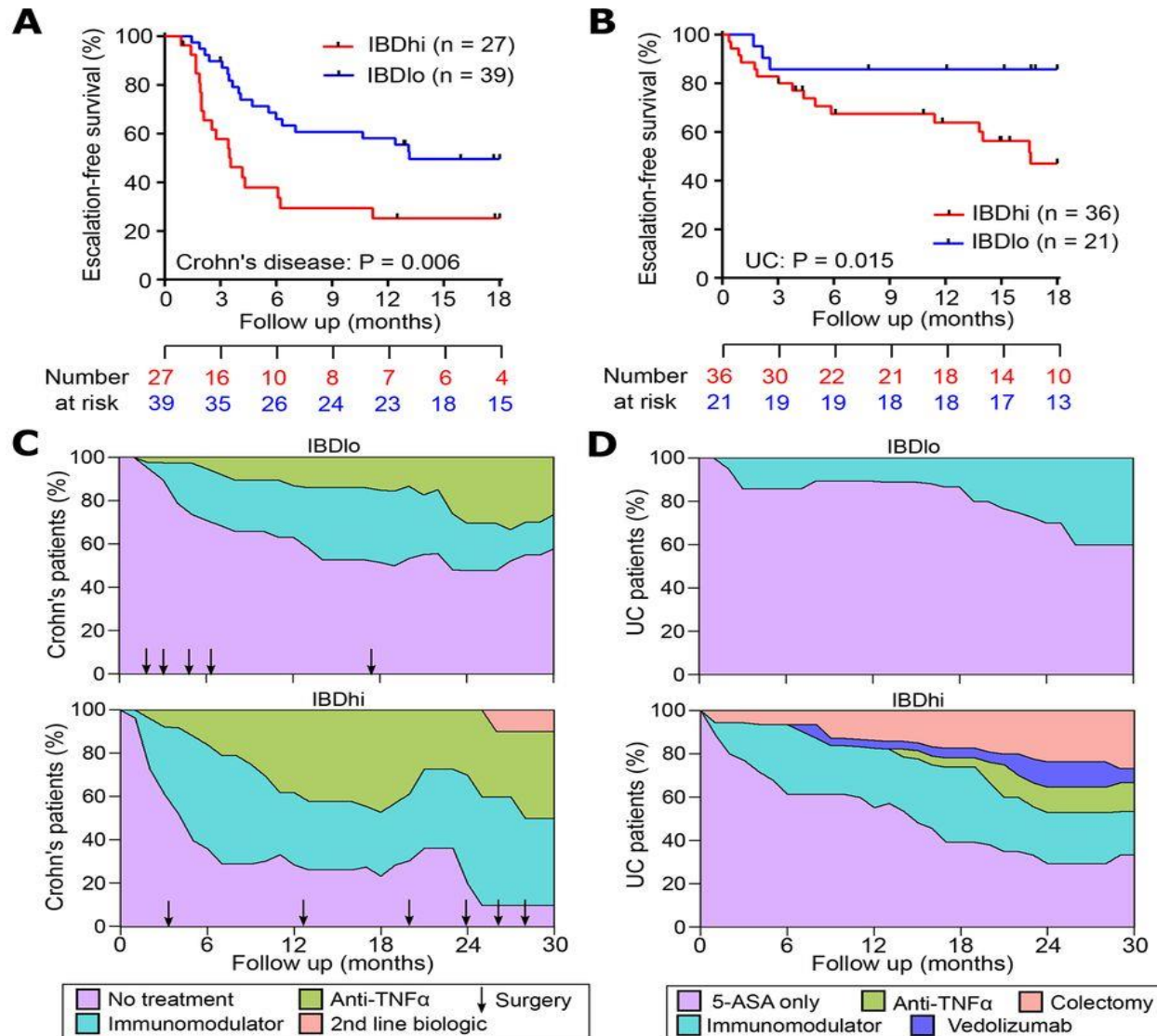


Hazard ratio = 3.34 (95% CI 1.74-6.41)



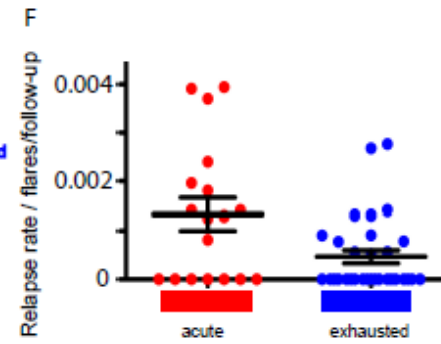
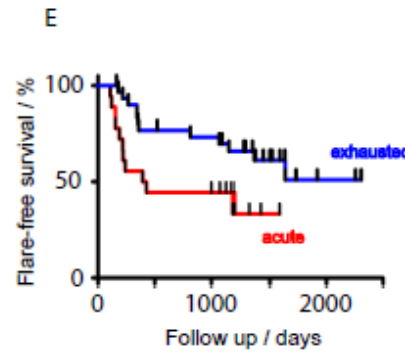
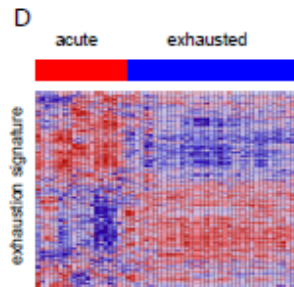
- IBD patients in the high risk group (IBDhi) experience both **earlier and more frequent disease recurrence** (requiring treatment escalation)

CD and UC independent validation cohorts

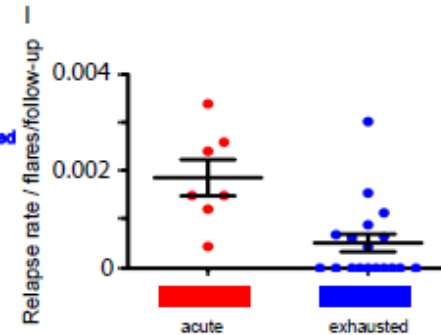
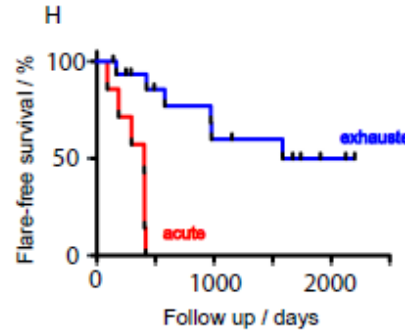
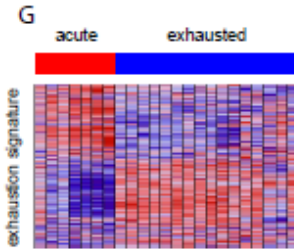


Biological mechanism?

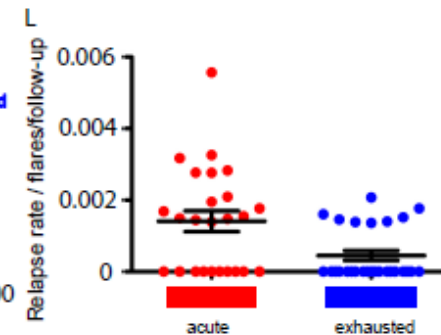
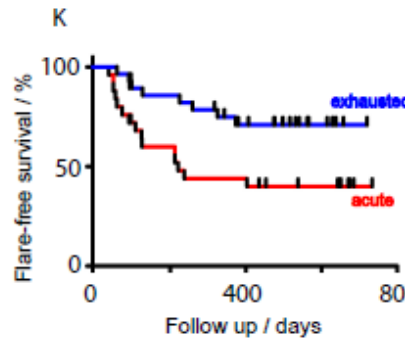
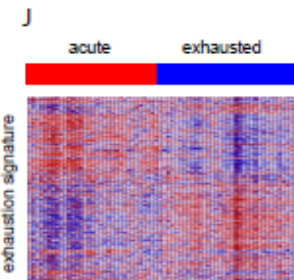
AAV



SLE



IBD



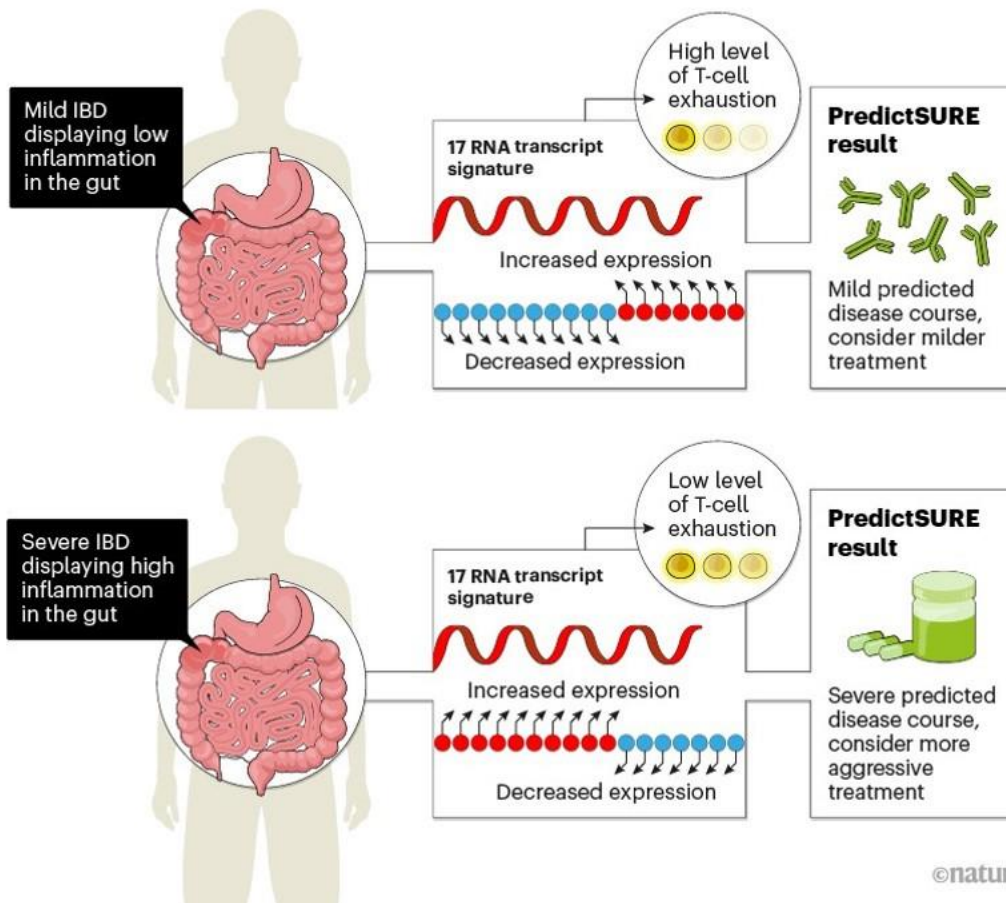
Early relapse

Recurrent relapse

Validated a “biomarker” blood test to predict high or low risk disease

GAUGING AUTOIMMUNE SEVERITY

An expression signature of 17 genes that reveals the level of ‘T-cell exhaustion’ in inflammatory bowel disease (IBD) can guide physicians towards the best therapy. In the test, called PredictSURE, high exhaustion correlates with lower risk of aggressive disease.



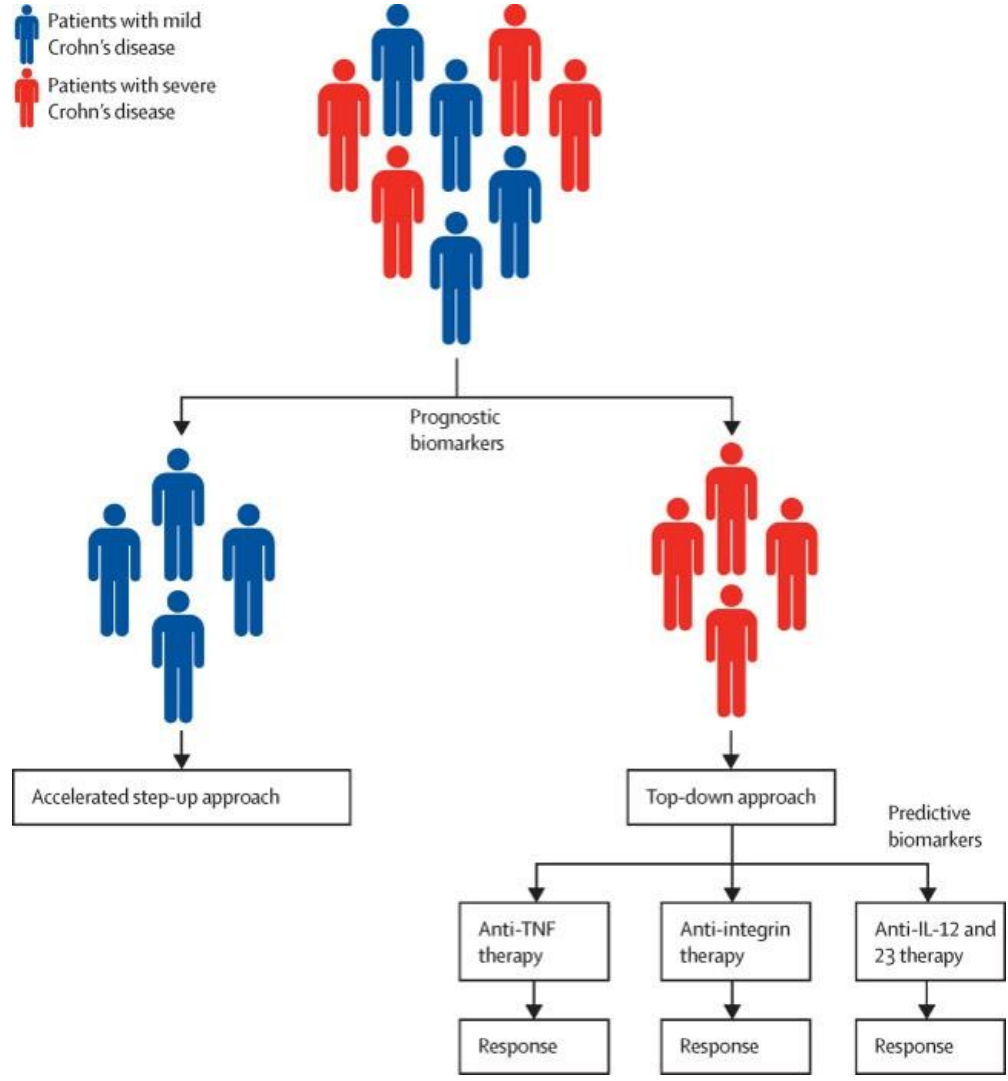
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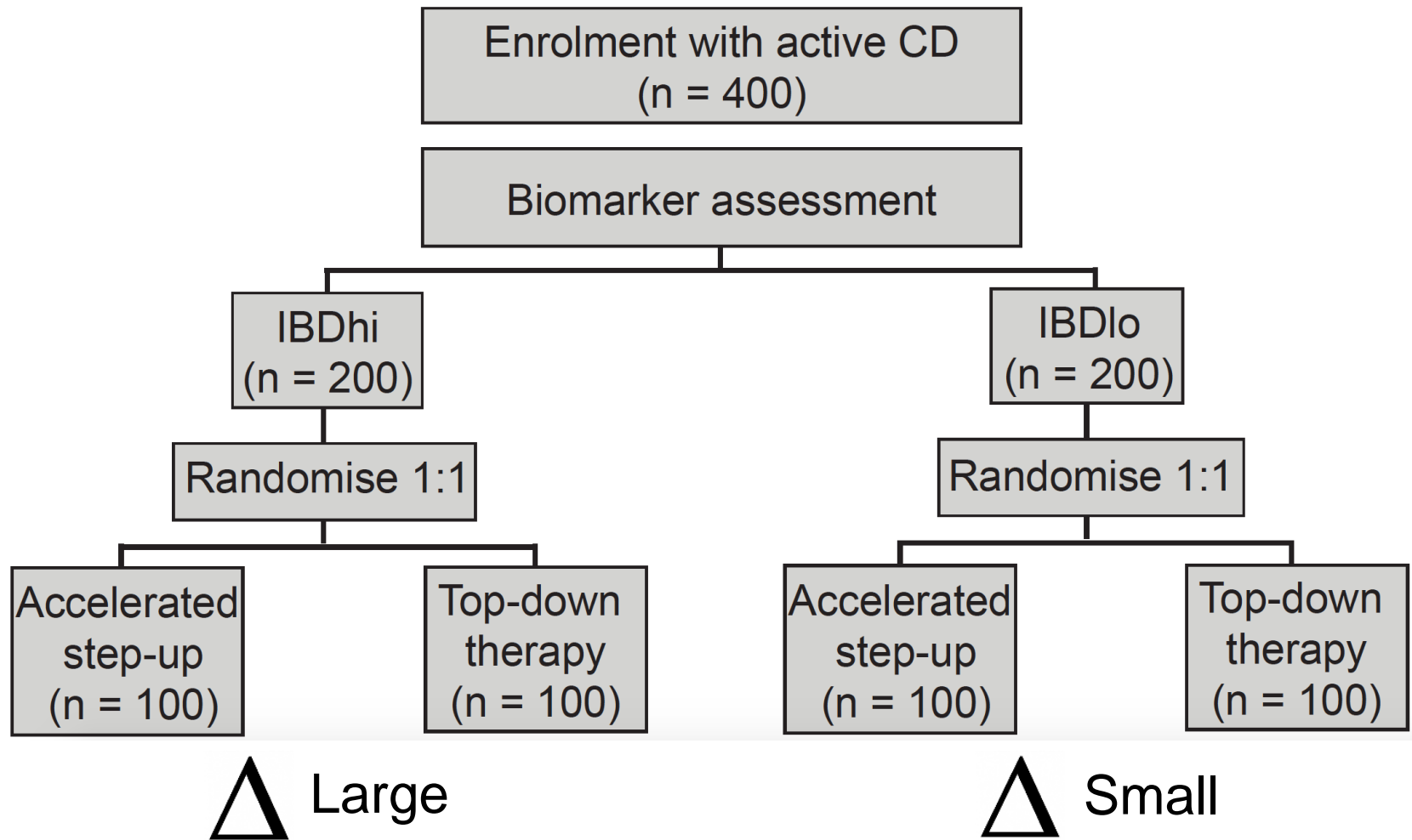
PROFILE trial

***P**redicting **O**utcomes **F**or Crohn's **d**isease
using a **m**olecular biomarker*

What would be rationale for clinical trial?



PROFILE trial schema





Outcome measures

Primary endpoint:

Sustained **steroid and surgery free remission** from completion of steroid induction treatment through to week 48

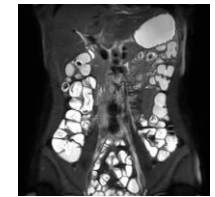
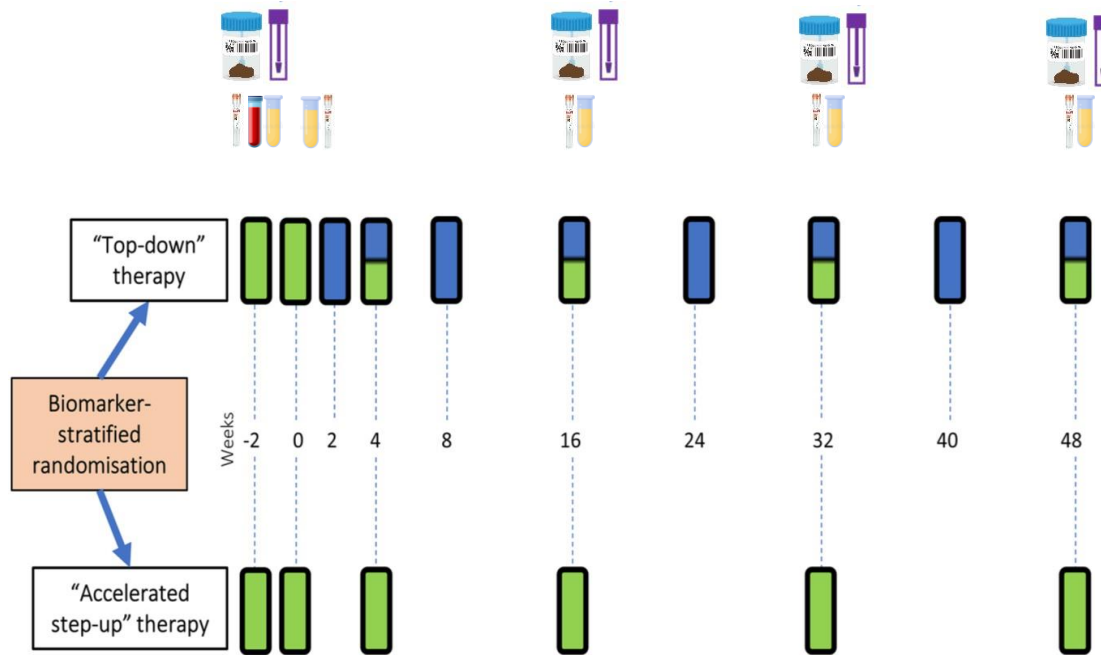
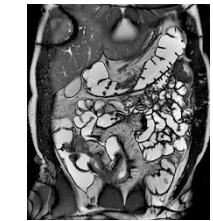
- Absence of symptoms (HBI score <5) + absence of objective markers of inflammation (CRP $<$ ULN and calprotectin <200 OR both)

Secondary endpoints:

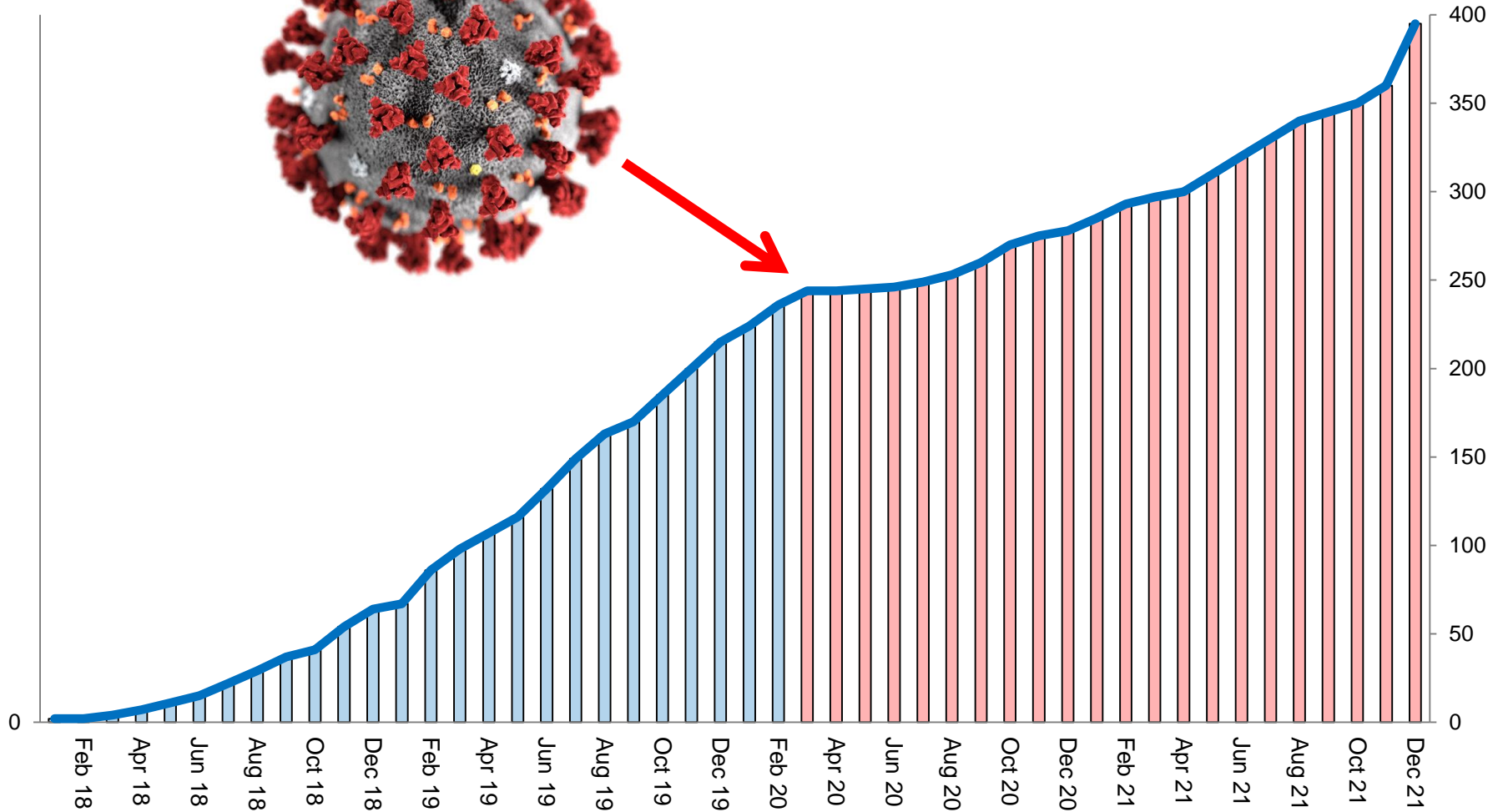
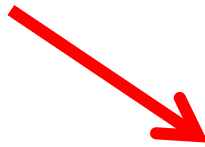
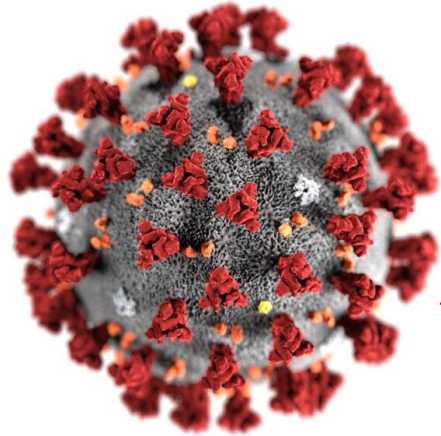
1. Endoscopic remission (absence of ulceration)
2. Quality of life assessment (IBDQ)
3. Number of flares
 - A. i) Cumulative steroid exposure
 - B. ii) Steroid-free remission
 - C. iii) Number of hospital admissions and operations

Tertiary endpoints:

PROFILE schedule of events



PROFILE recruitment pre and peri-COVID



Personalised medicine research cannot just be at ivory towers

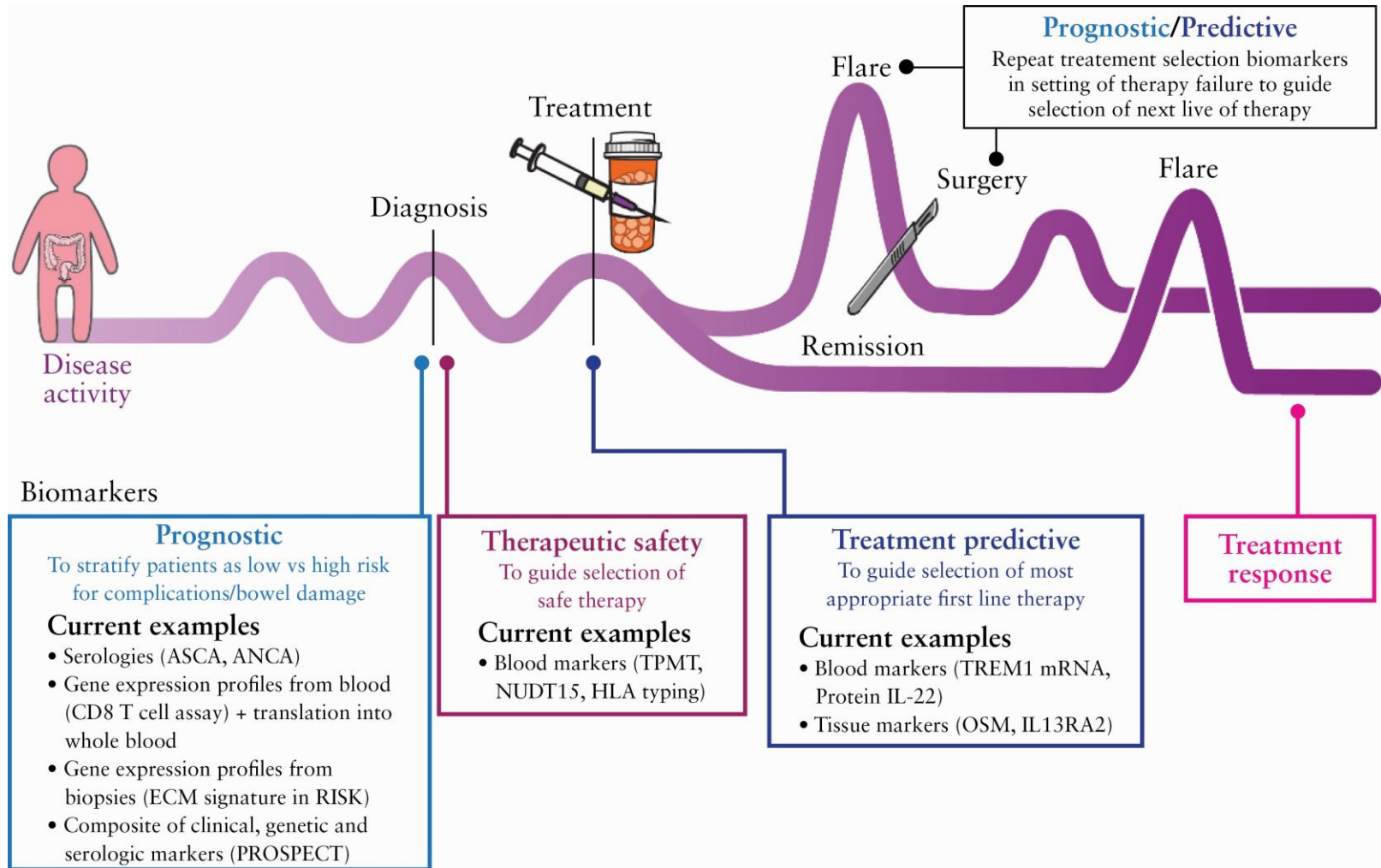


Huge successes PROFILE






- **Largest academic drug trial in IBD** ever delivered from the UK – one of largest in the world
- First ever **biomarker-guided trial in IBD**
- No matter findings will likely result **in major impact on how we deliver IBD clinical care**
- Launched a new generation of **consultants, trainees and research nurses involved**

Prognostic biomarkers are just one piece of the jigsaw

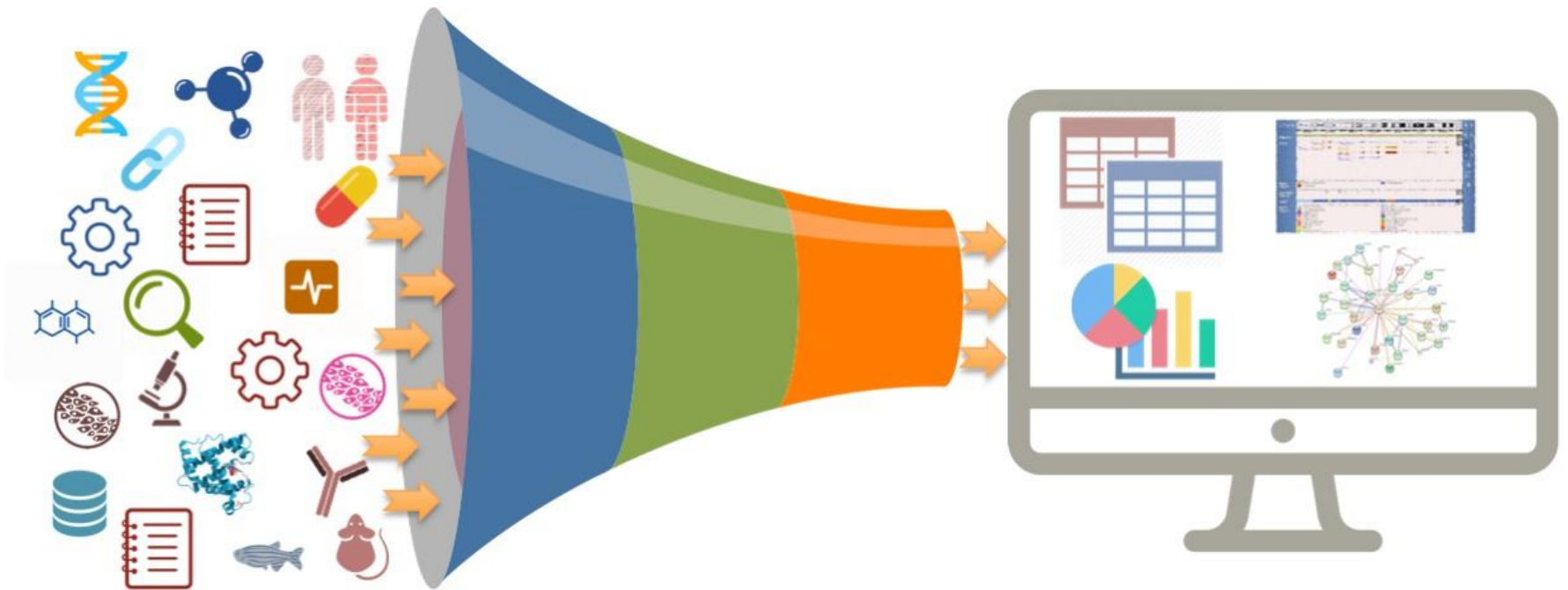


Lots of biomarkers and other tools coming – IBD is going to get even more complex



EARLY STRATIFICATION	
PROGNOSIS 	GWAS <ul style="list-style-type: none"> Distinct genes associated with worse disease outcome but low odds ratios ✖ Polygenic risk scores?
	RISK <ul style="list-style-type: none"> Gene signature of ileal genes controlling extracellular matrix production <ul style="list-style-type: none"> HR 1.70 (95% CI 1.12-2.57) of stricturing behaviour
SAFETY 	TPMT and NUDT15 <ul style="list-style-type: none"> Risk of thiopurine-induced myelosuppression
	HLA-DQA1 and HLA-DRB1 <ul style="list-style-type: none"> Risk of thiopurine-induced pancreatitis
	Fluorescent targeting <ul style="list-style-type: none"> Anti-TNF response – cells with membrane bound TNF <ul style="list-style-type: none"> Clinical response at week 12: 92% vs 15%, p<0.01
	HLA-DQA1*05 (PANTS) <ul style="list-style-type: none"> Associated with greater likelihood of immunogenicity to infliximab and adalimumab <ul style="list-style-type: none"> HR of 1.90 (95% CI 1.69-2.25)
RESPONSE and NON-RESPONSE 	OSM <ul style="list-style-type: none"> High pre-treatment OSM expression strongly associated with anti-TNF non-response <ul style="list-style-type: none"> RR 5.00 (95% CI 1.4-17.9)
	TREM-1 <ul style="list-style-type: none"> Colonic biopsies predicting clinical non-response <ul style="list-style-type: none"> AUC 0.82
	GIMATS <ul style="list-style-type: none"> Unique cellular module associated with anti-TNF non-response

The promise (dream) of multi-omics



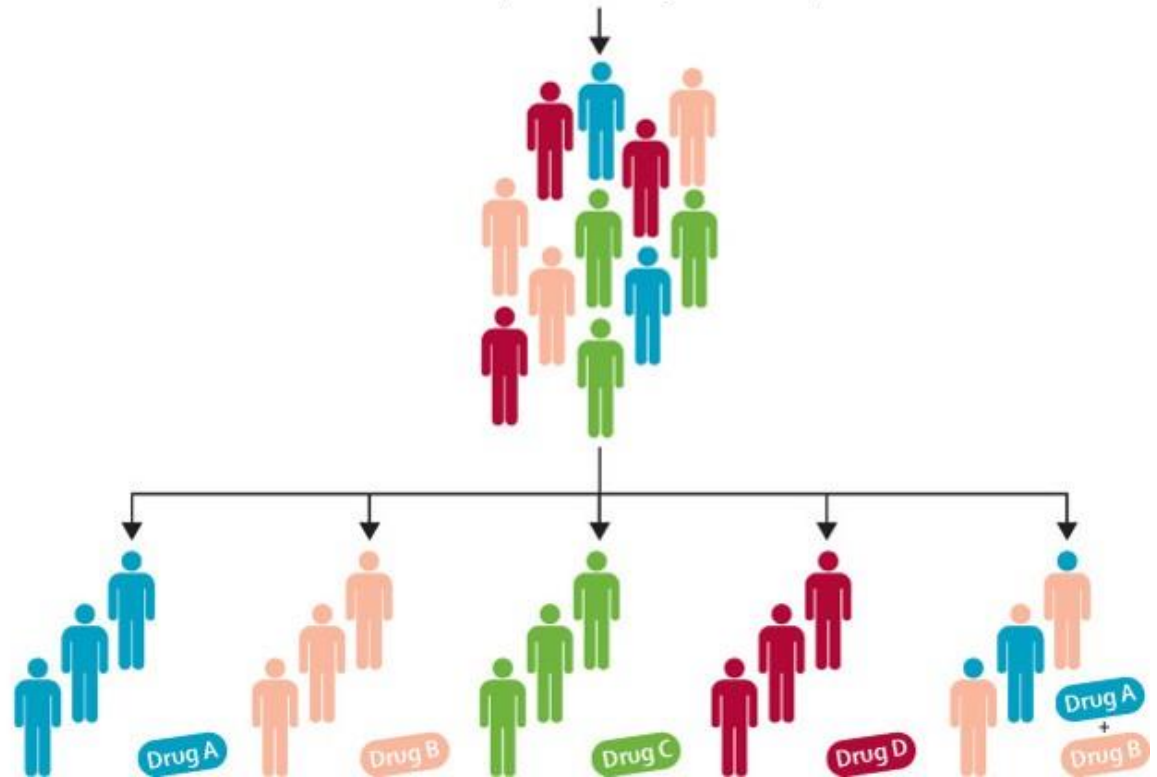
Future likely multiple integrated biomarkers and multi-omic approaches

A One-size-fits-all approach

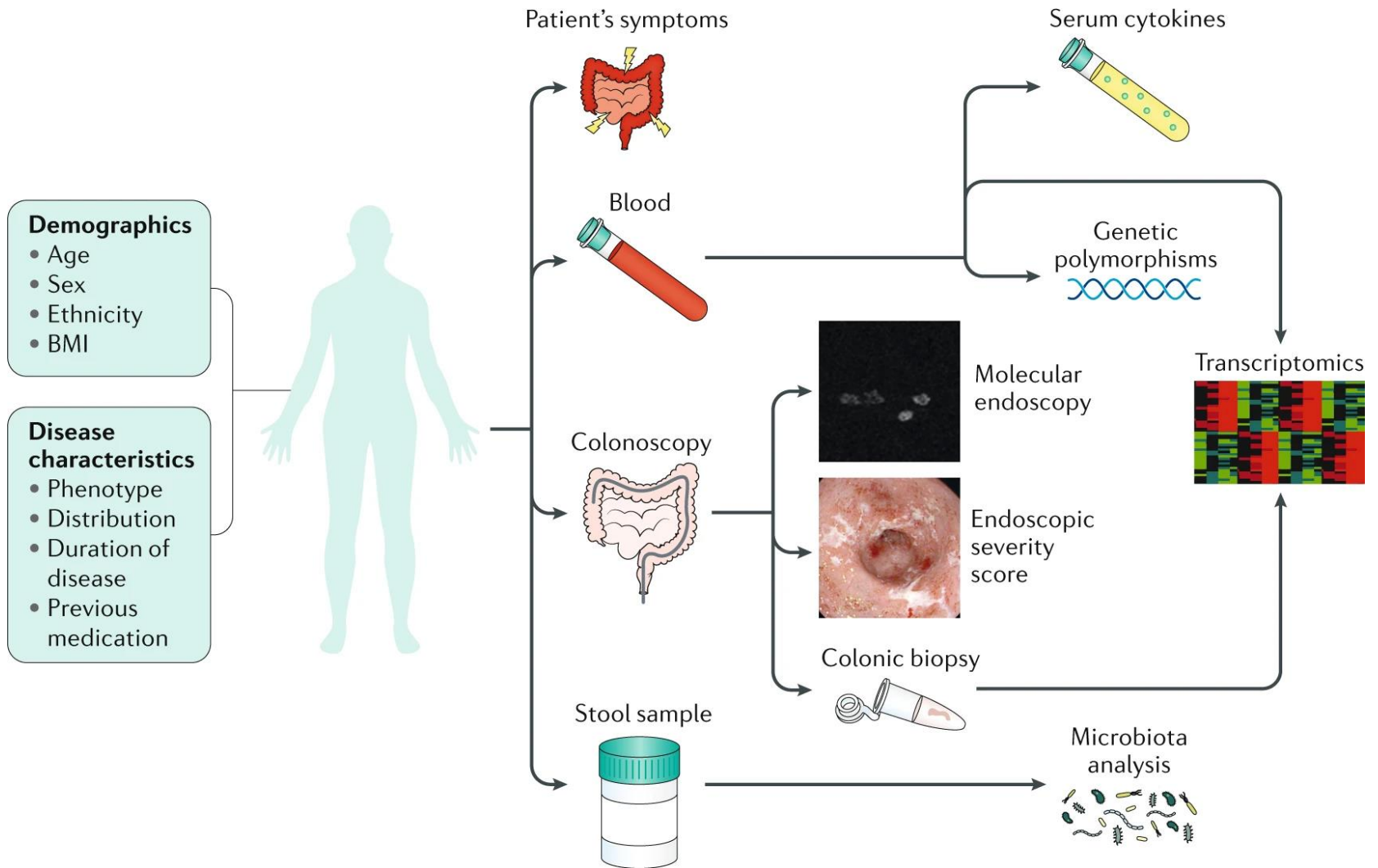


B Multiomics approach

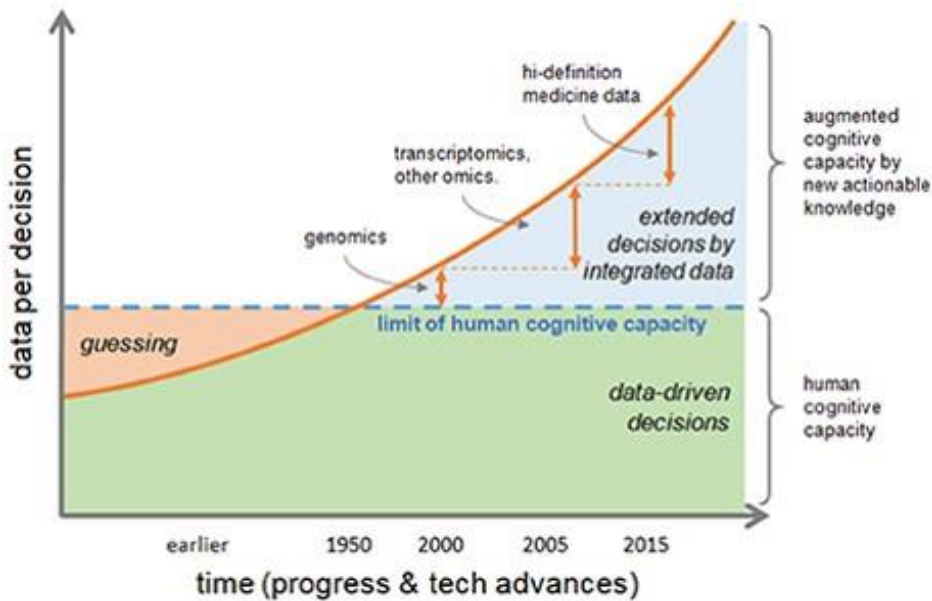
- Phenomics
- Proteomics
- Genomics and epigenetics
- Metabolomics and metagenomics
- Tissue transcriptomics and single cell transcriptomics



What we might be doing in the clinics of the future?



More data may not necessarily = better decision-making

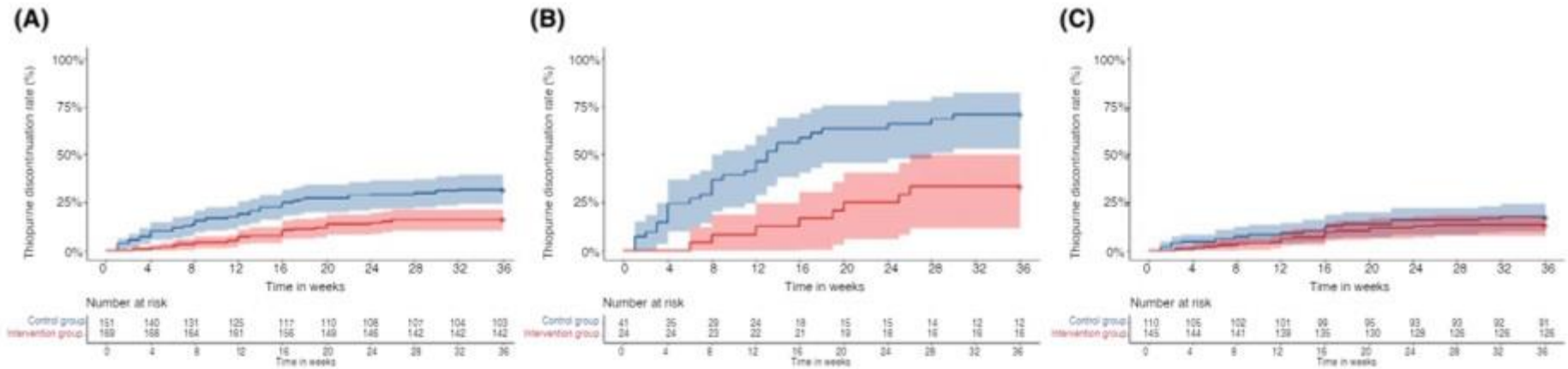


No test is perfect, biomarkers are tools to guide – the patient is always key



Personalized profiles for disease risk must capture all facets of health

Do we need clinical trials? Can't we just use biomarkers straight away if validated?



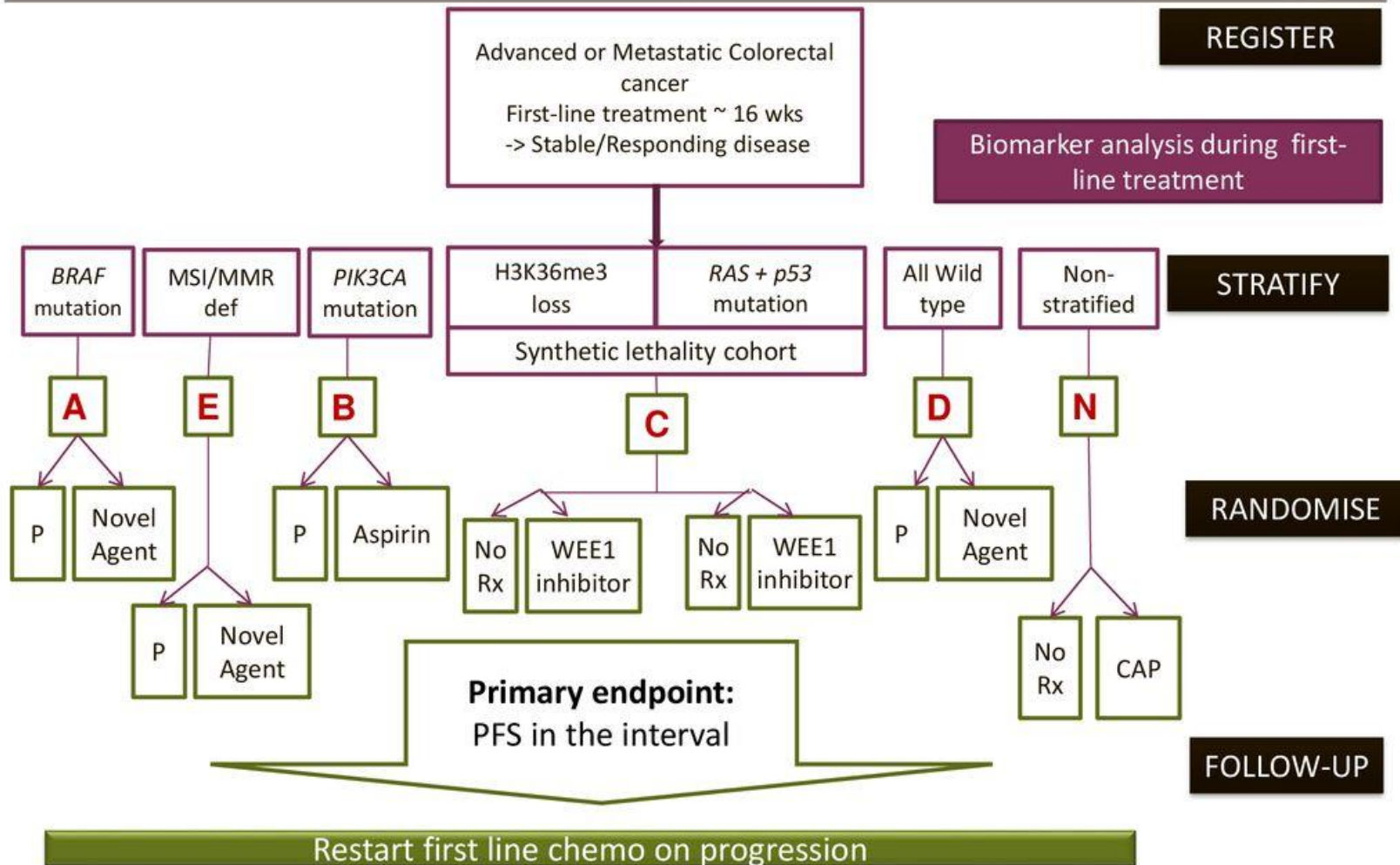
Yang SK, Hong M, Baek J, et al. Nature Genetics 2014
Walker GJ, Harrison JW, Heap GA, et al. JAMA 2019
Chao K, Huang Y, Zhu X, et al. APT 2021
Verstockt B, Noor NM, Marigorta UM, et al. JCC 2021

So many biomarkers and treatments coming? Do we need to do an RCT for each one?

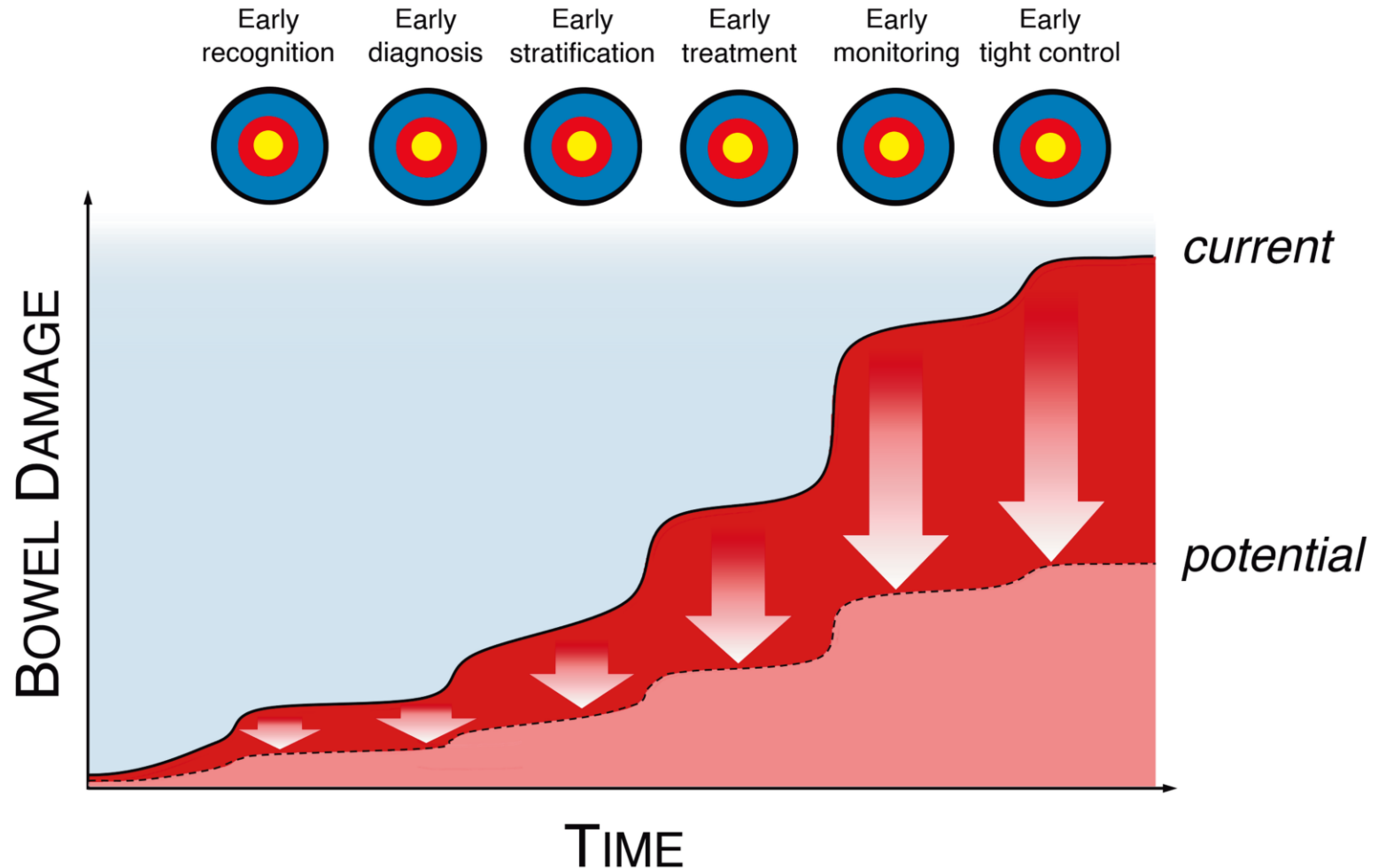


FOCUS4

FOCUS4



No point in personalised medicine tools if we don't do the basics



Conclusions



- **Personalised medicine for IBD is closer than ever** but need to do basics alongside using new, fancy tools
- Need to remember that translation of research findings to clinical practice **takes a LONG time**
- **PROFILE is first biomarker-stratified trial** in Inflammatory Bowel Disease
- Hope to demonstrate that personalised therapy for individuals as **early as possible, leads to better outcomes for patients**

Clinical trials are the ultimate team science!



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