Cambridge University Hospitals NHS
NHS Foundation Trust

CCTU
Cambridge Clinical Trials Unit

PROFILE

PROFILE trial

PRedicting Outcomes For Crohn's dIsease using a moLecular biomarkEr

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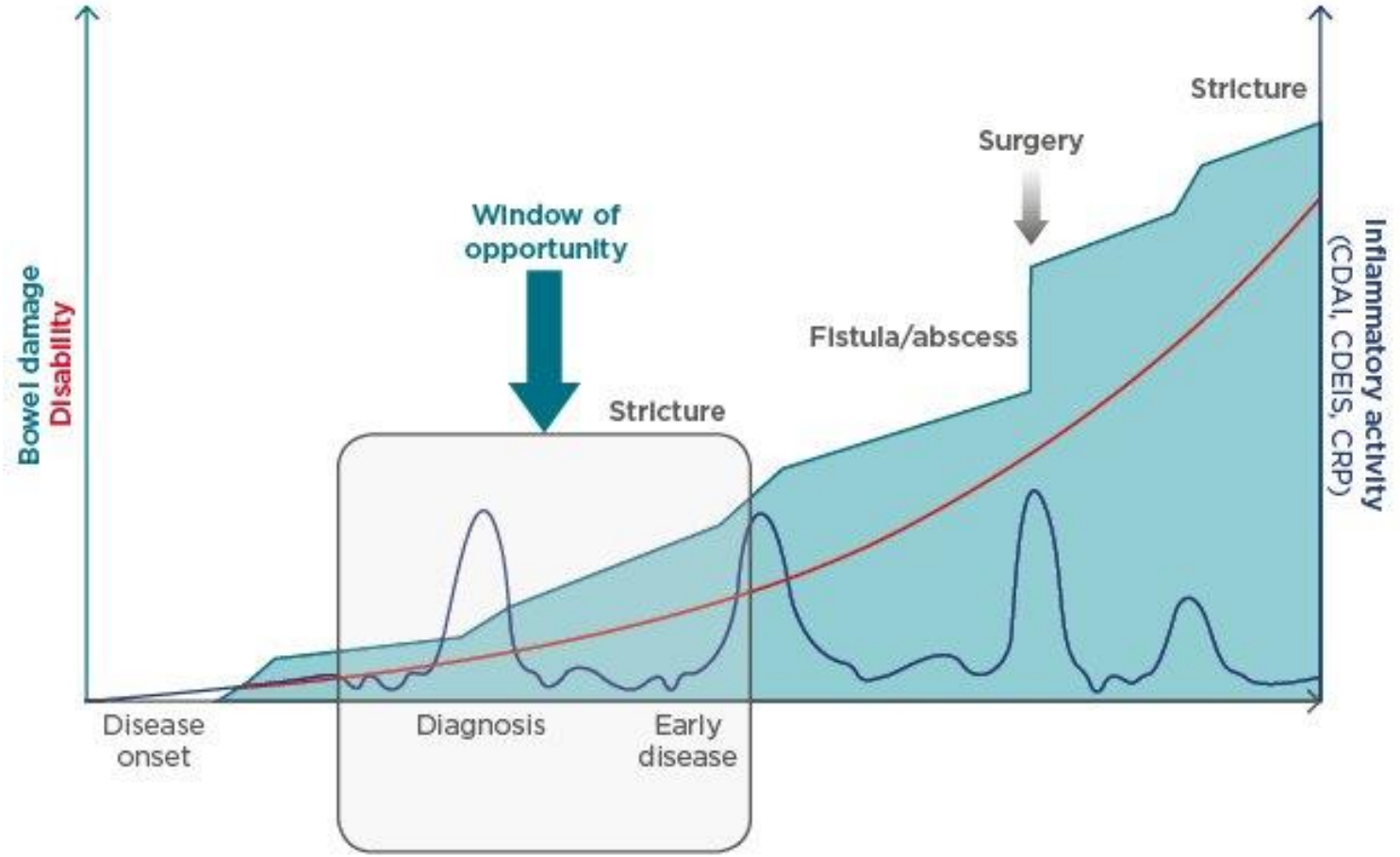
UNIVERSITY OF CAMBRIDGE

predict IMMUNE

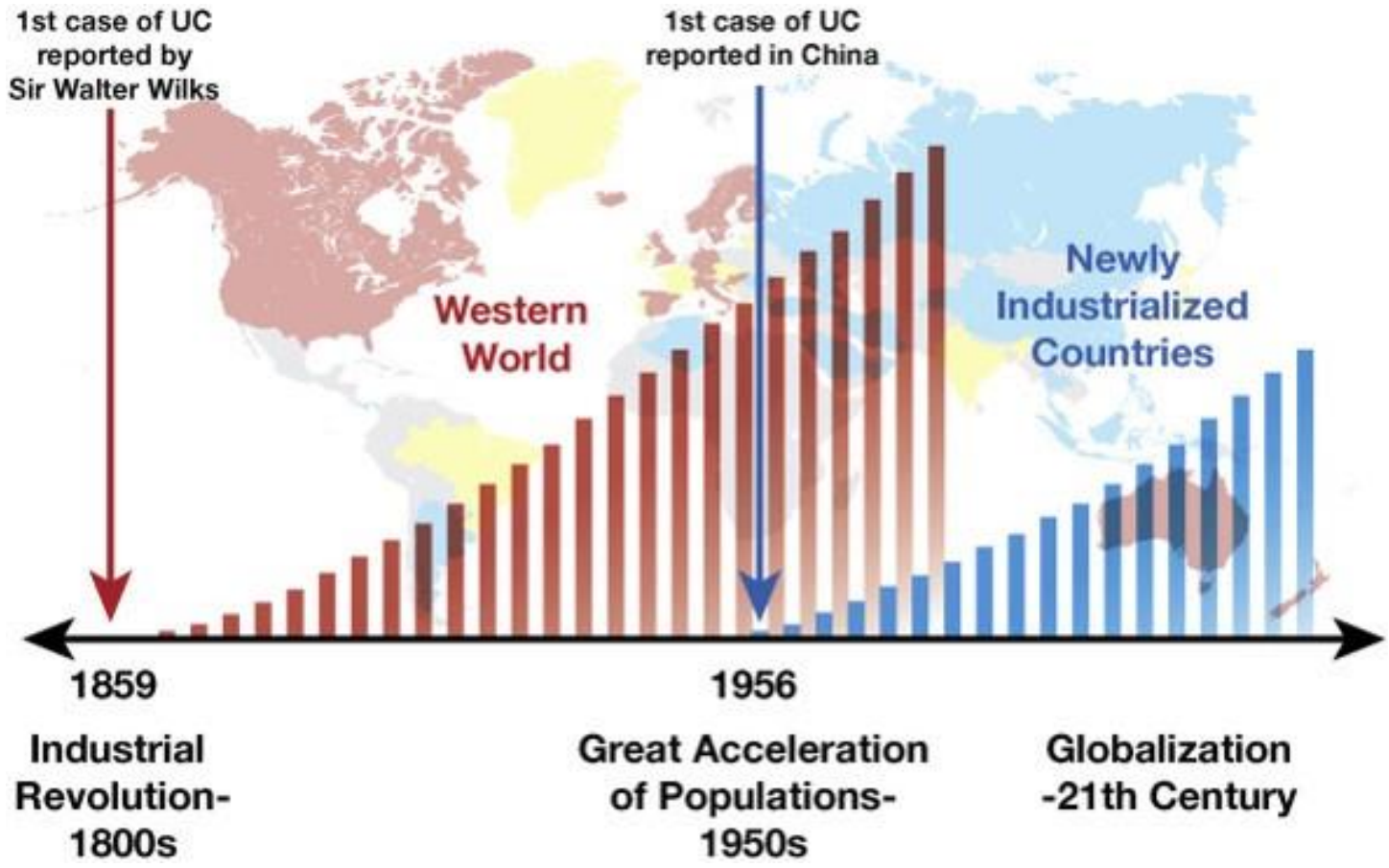
wellcome

Inflammatory bowel disease is a chronic progressive condition



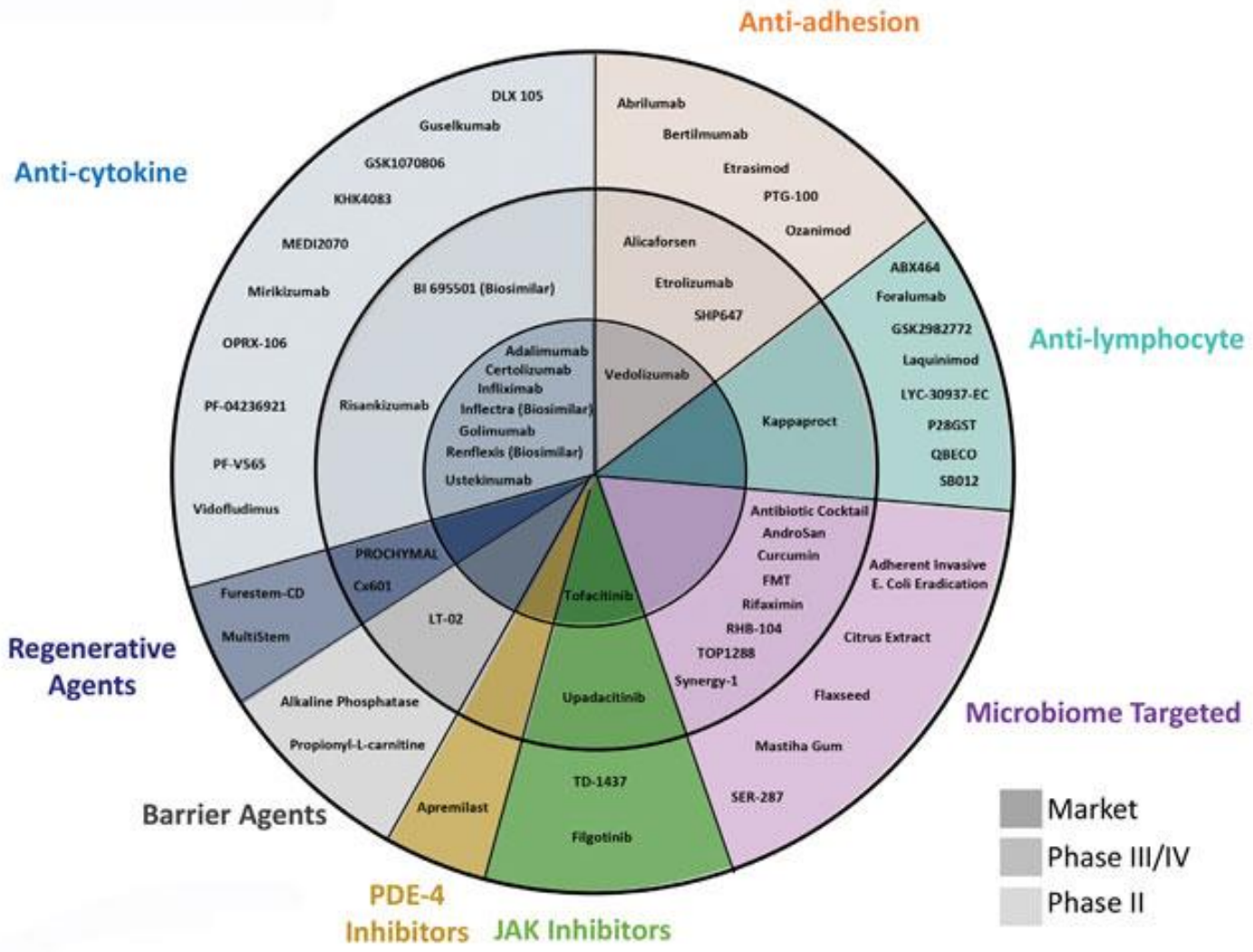
Pariente B, Cosnes J, Danese S, et al. IBD 2011

Inflammatory bowel diseases are a growing and global healthcare problem



Ng S, Kaplan G. Gastro 2017

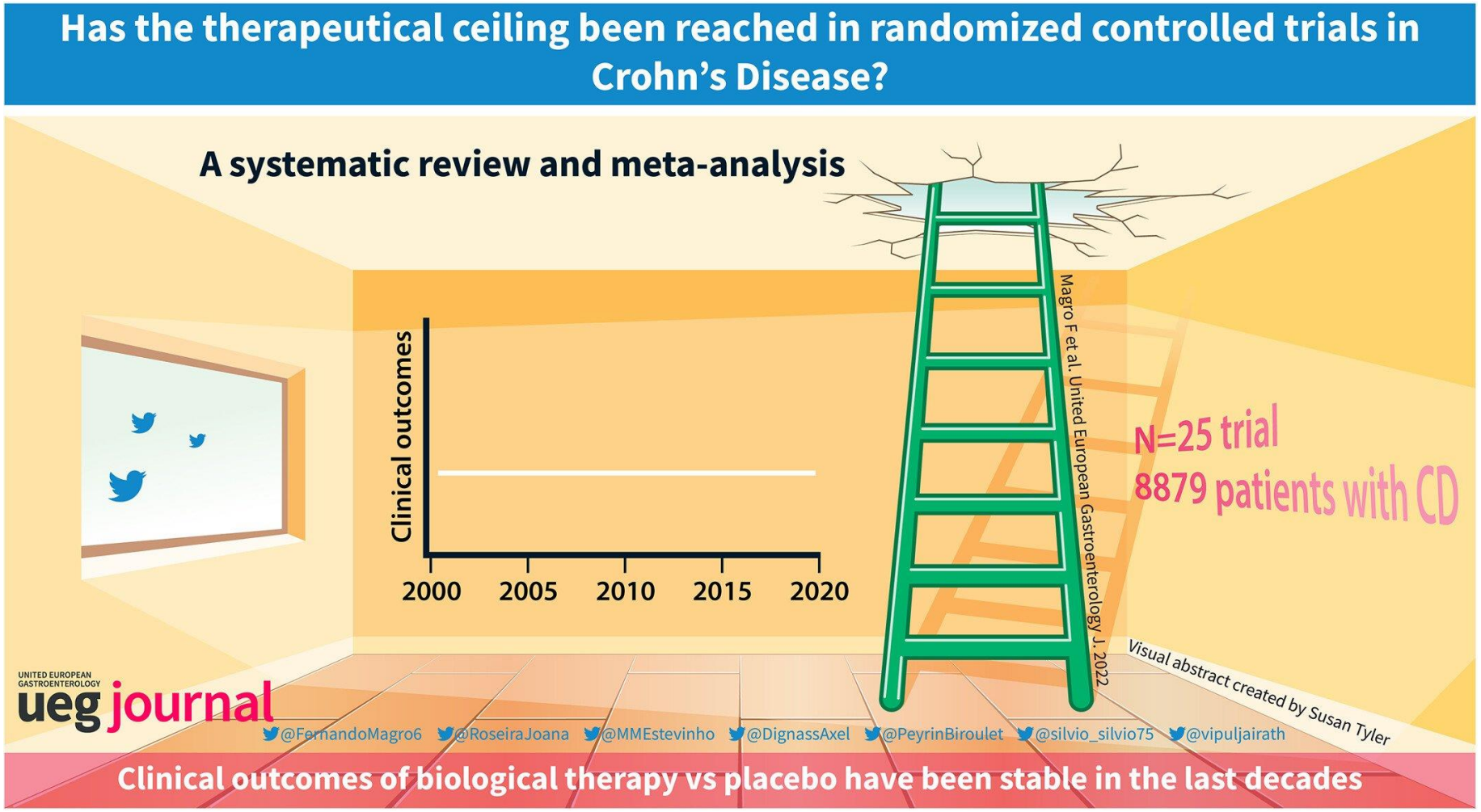
More treatments in IBD than ever before (and many more on the way)



Steiner CA, Berinstein JA, Higgins PDR. Practical Gastro 2019

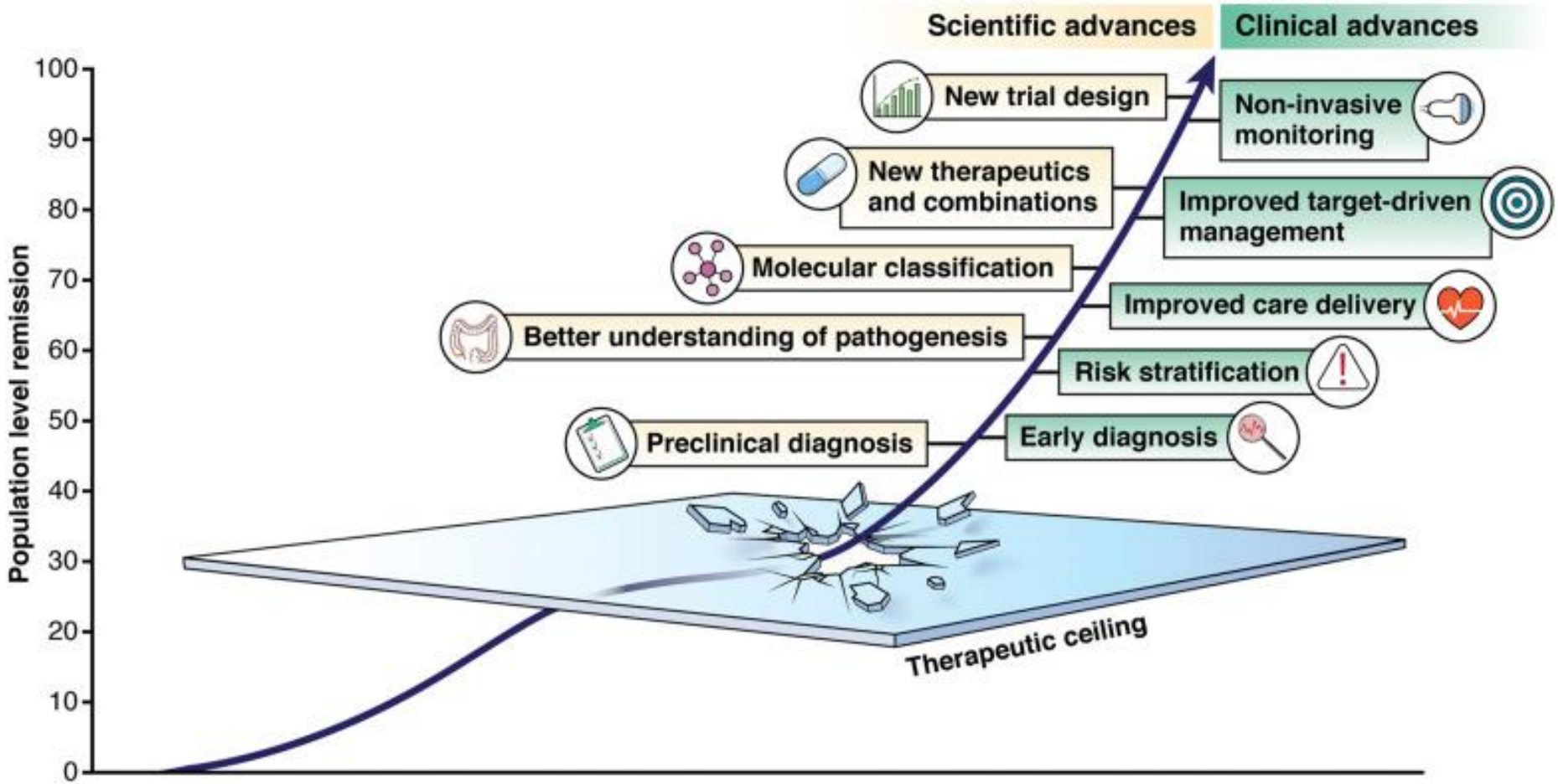
HUGE progress in IBD – but clinical care is still mostly trial and error

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



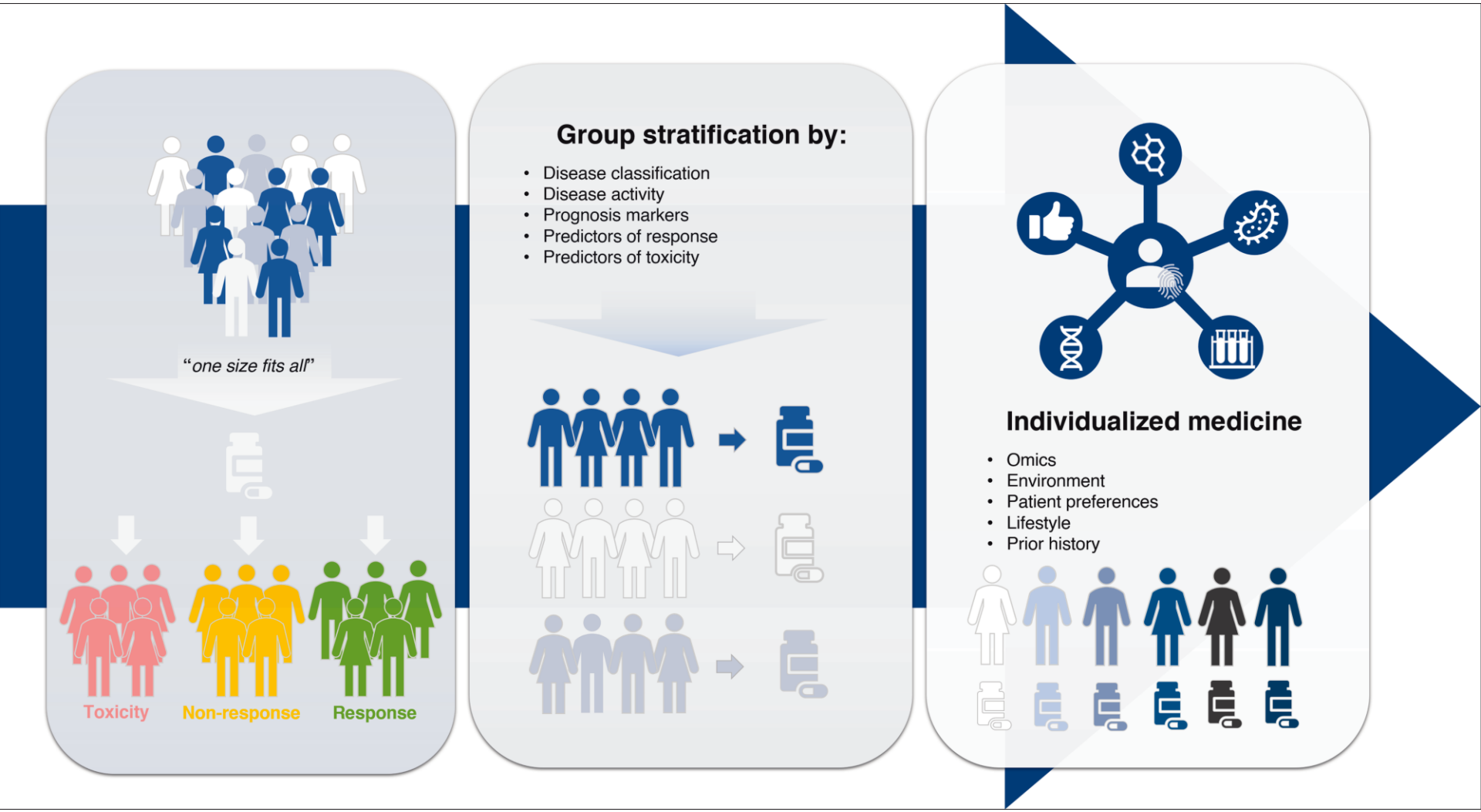
Magro F, Moreira PL, Catalano G, et al. UEGJ 2023

Huge opportunity for research to improve IBD care



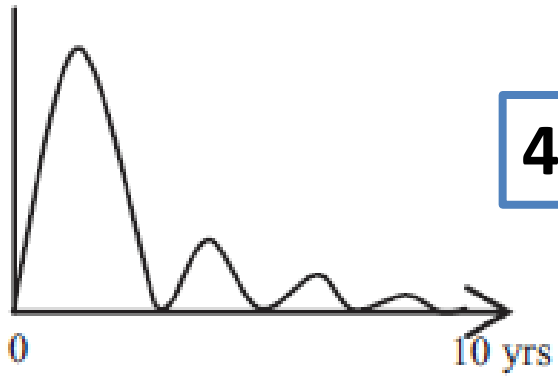
Raine T, Danese S. Gastro 2022

Aspiration for personalised medicine in IBD

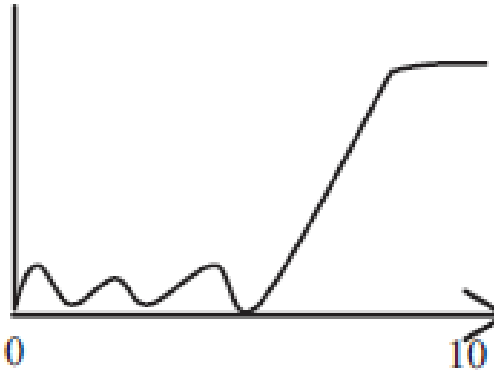


Noor NM*, Sousa P*, Paul S, et al. IBD 2022

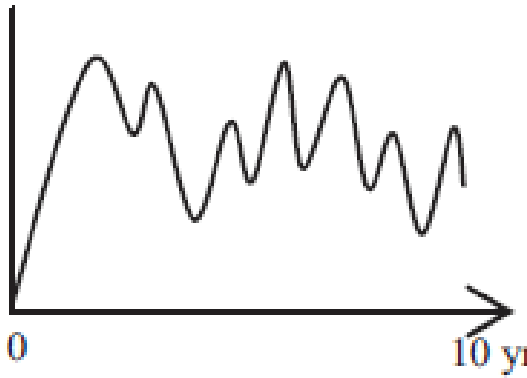
One issue is highly variable disease course



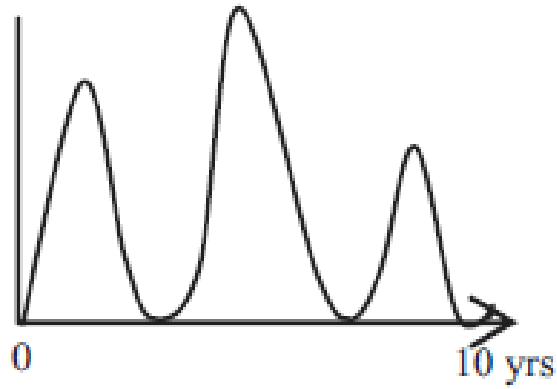
43 %



3 %



19 %



32 %

Solberg IC, Vatn MH, Hoie O, et al. CGH 2007

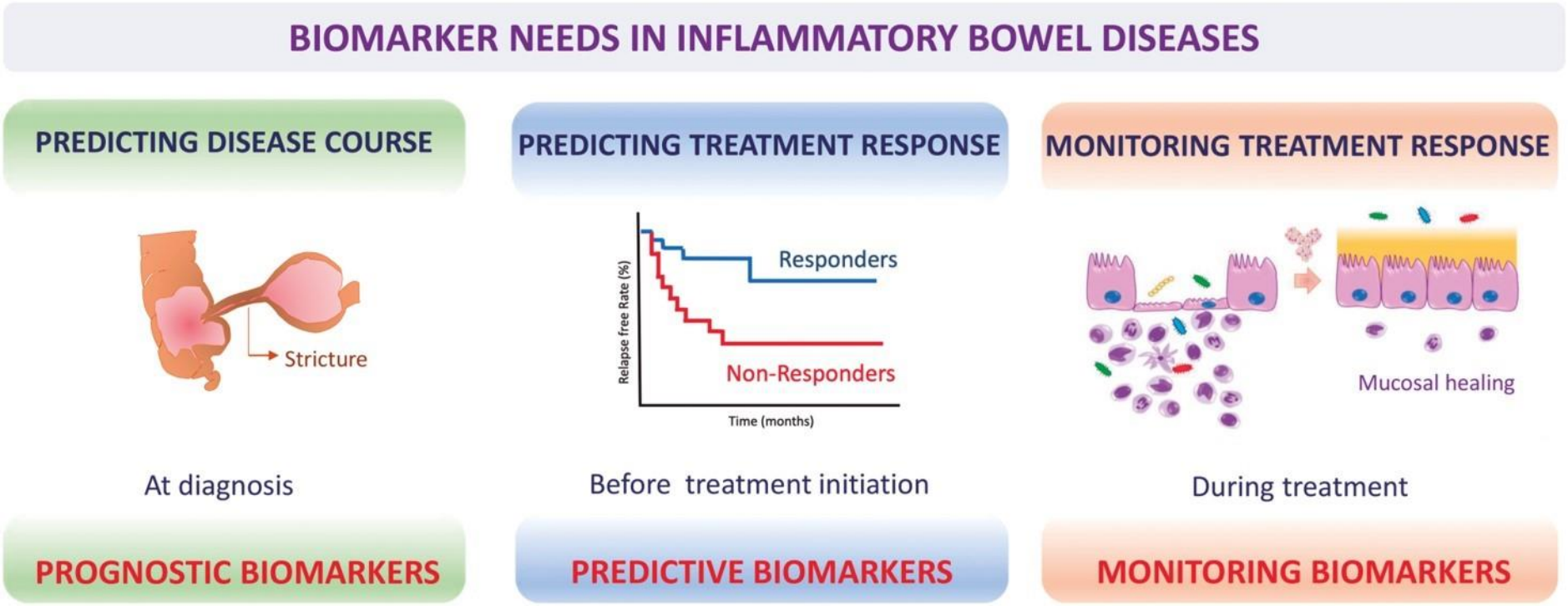
Need for a personalised approach in most medical conditions

> “ 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)

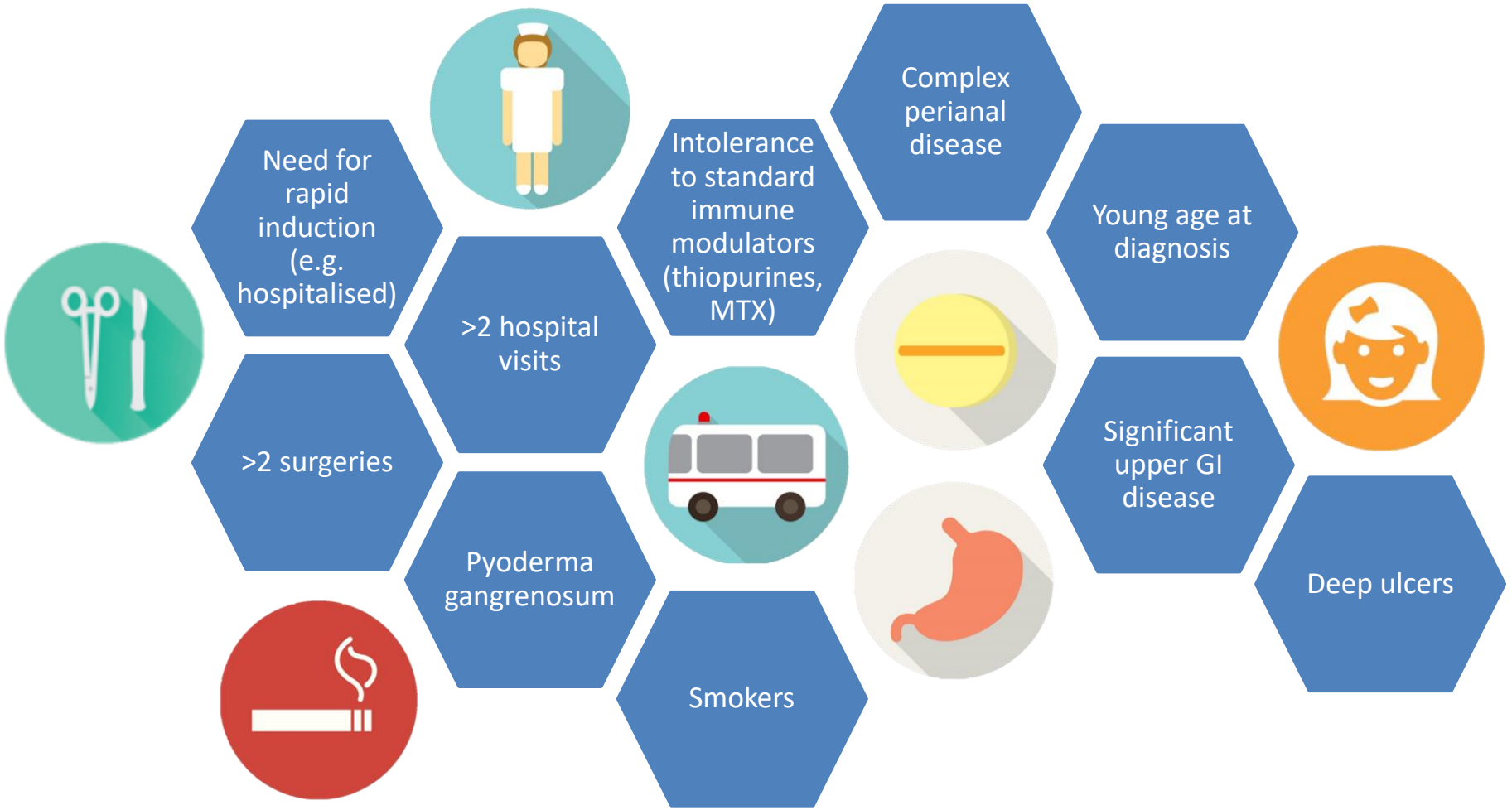
Milder disease
Protected from risks of unnecessary immunosuppression

Need for biomarkers in IBD

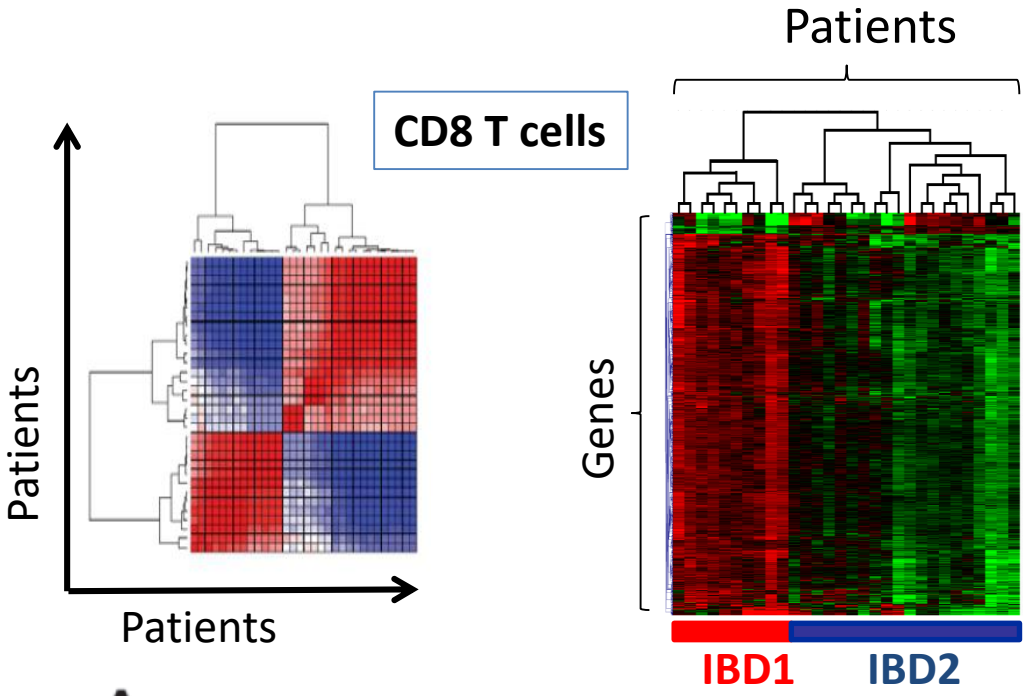


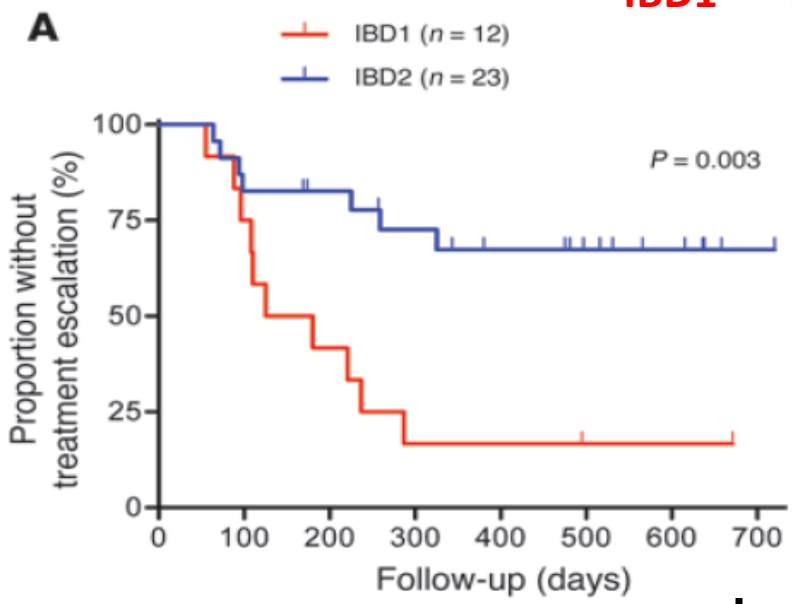
Honig G, Heller C, Hurtado-Lorenzo A. IBD 2020

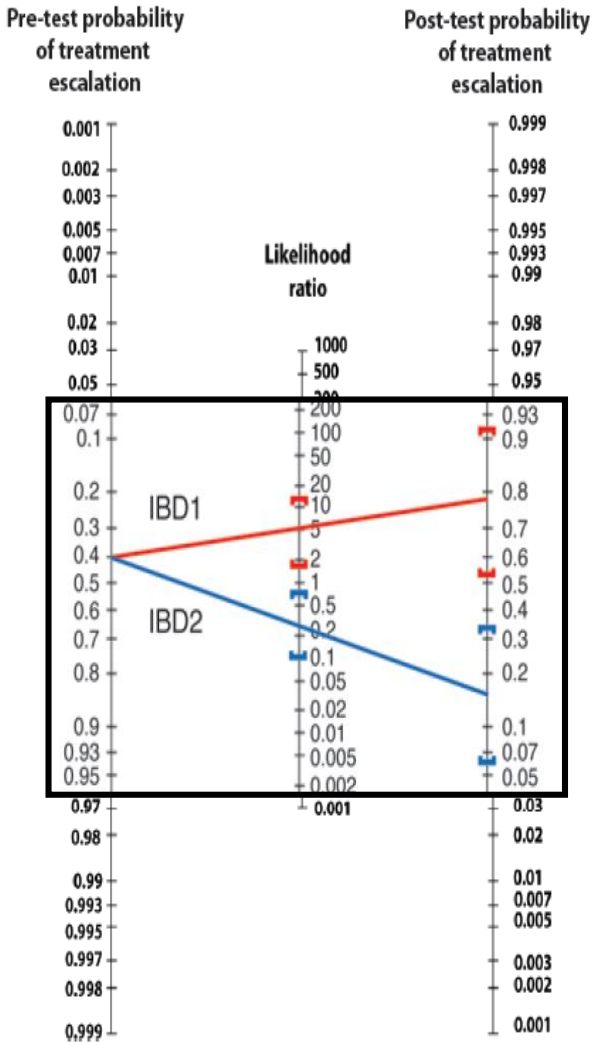
Can we predict disease course at the moment?



Could we use gene expression to predict outcomes in IBD?

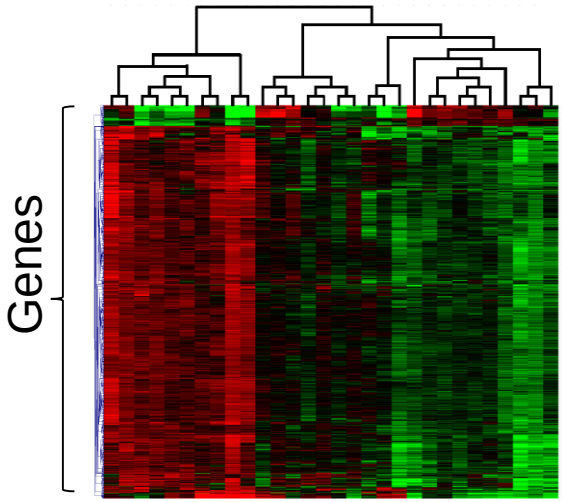


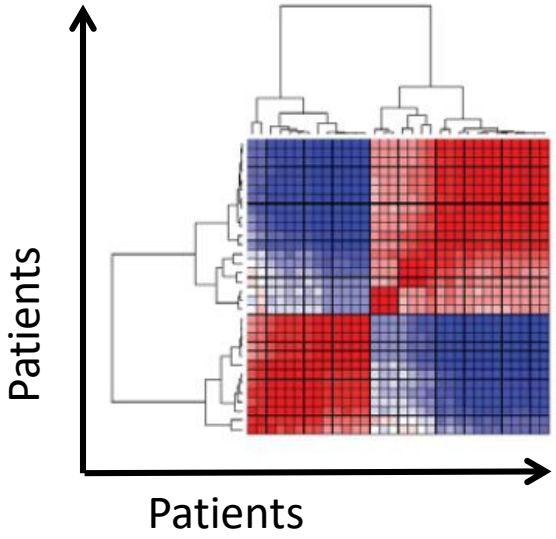


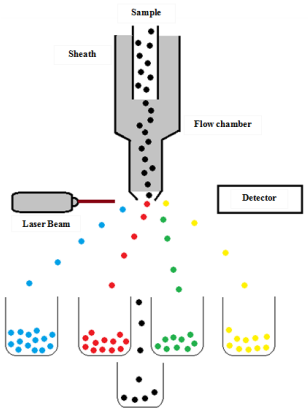


Lee JC, Lyons PA, McKinney EF, et al. JCI 2011

How to translate this back to the clinic?





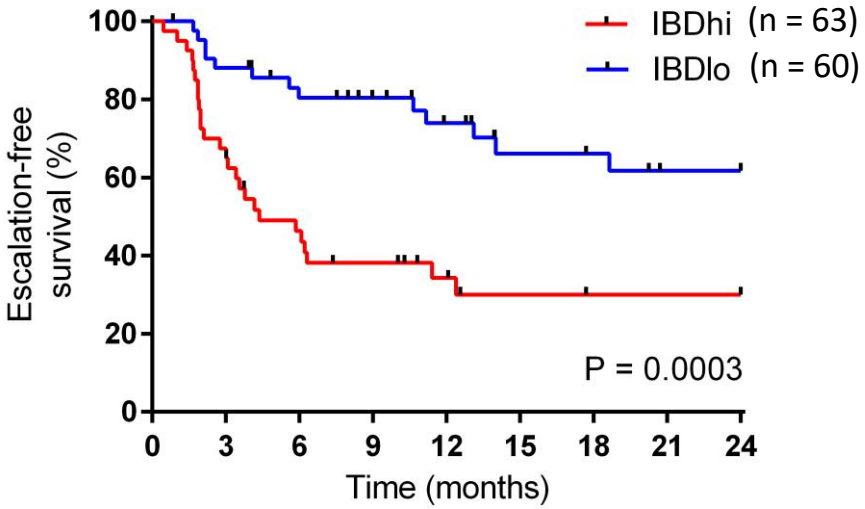


qPCR assay

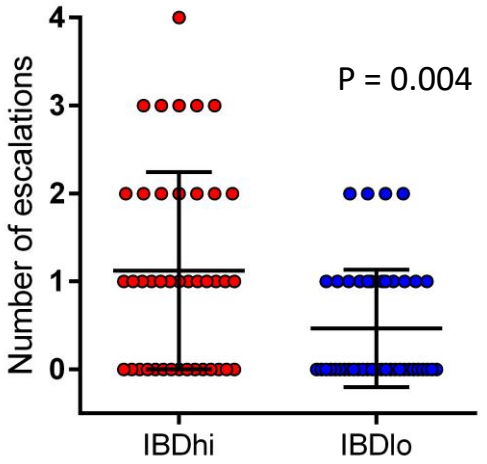
Validation in independent IBD cohort

qPCR assay

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



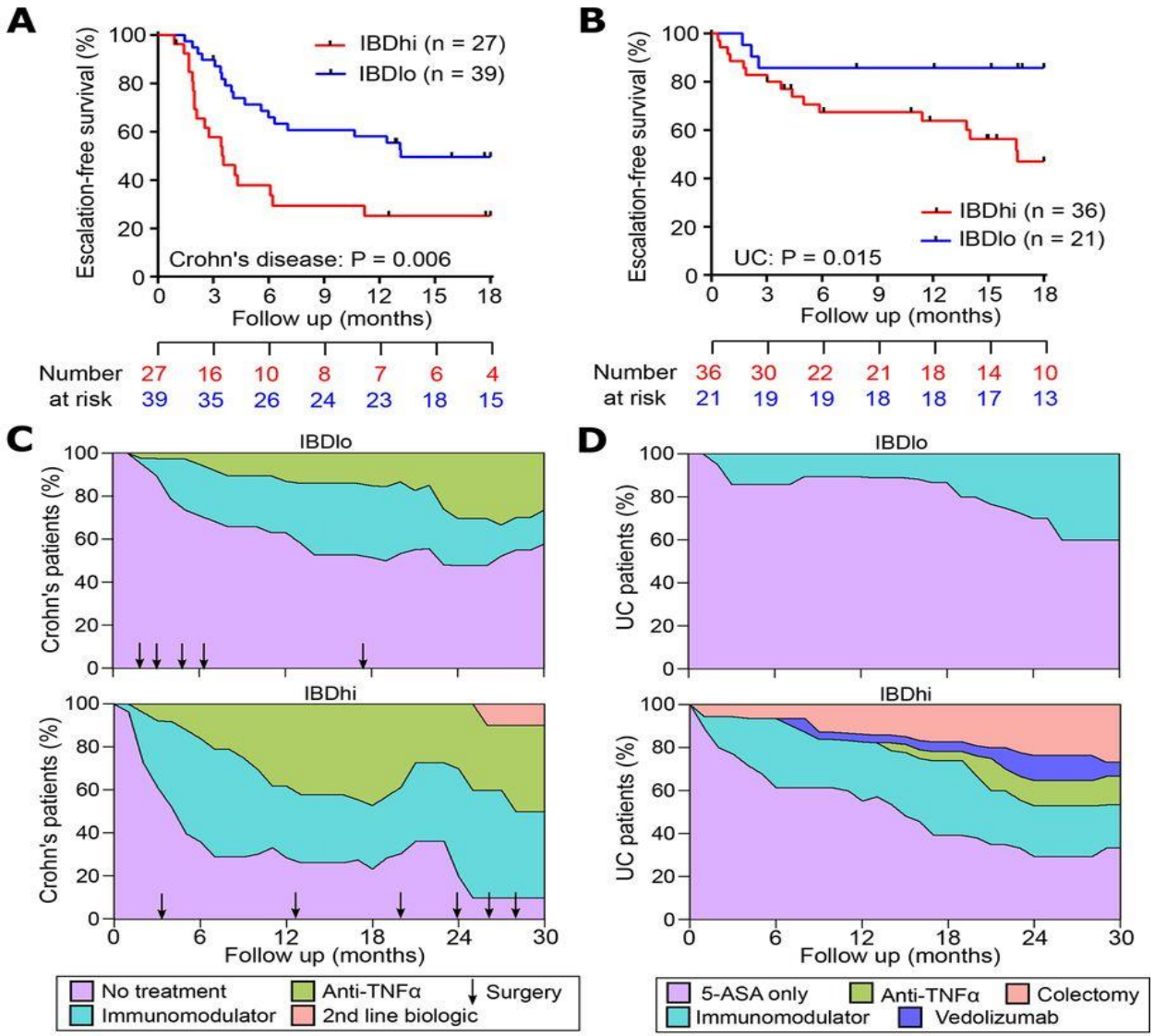
Hazard ratio = 3.34 (95% CI 1.74-6.41)



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

Biasci D*, Lee JC*, Noor NM, et al. Gut 2019

CD and UC independent validation cohorts



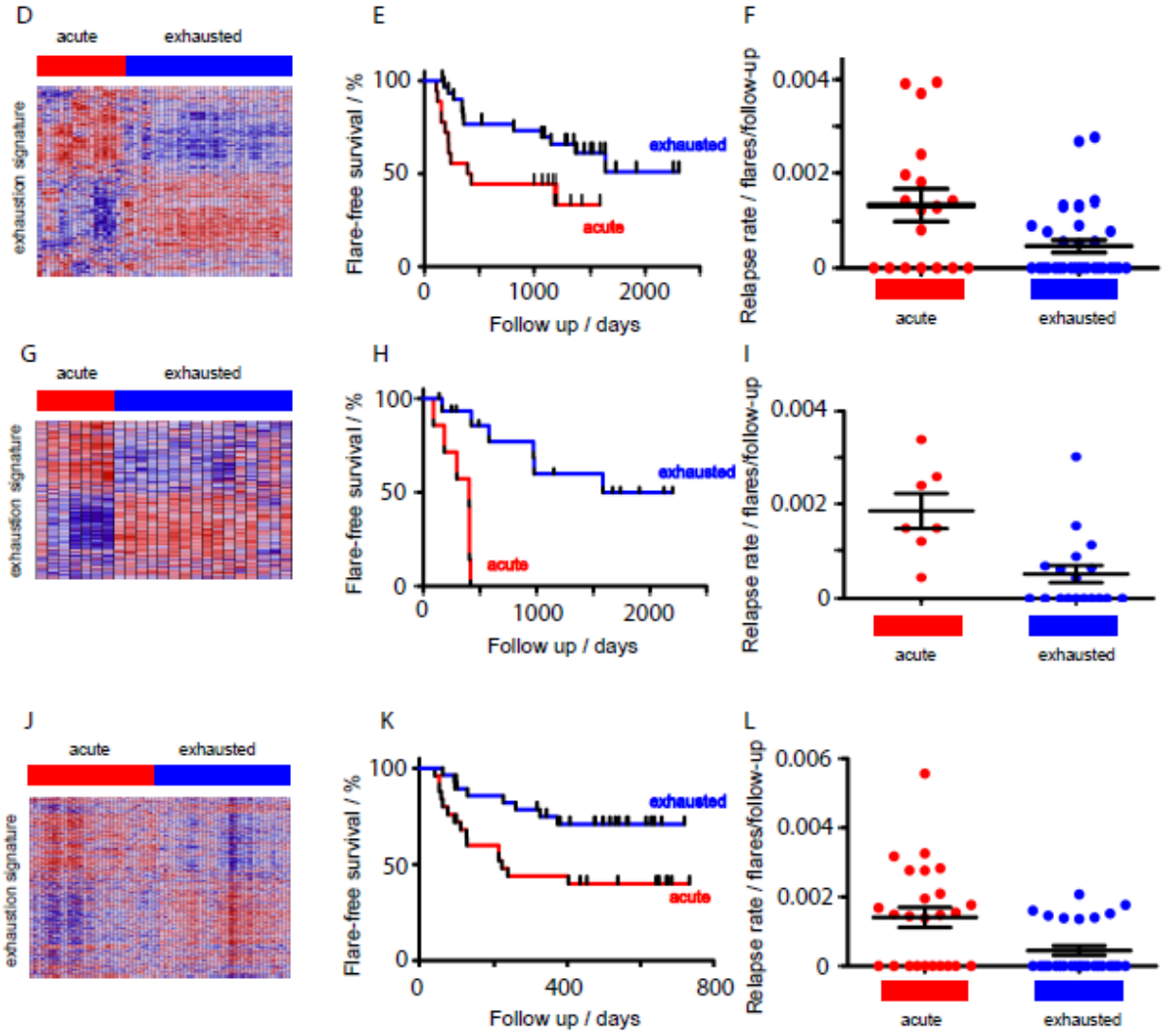
Biasci D*, Lee JC*, Noor NM, et al. Gut 2019

Biological mechanism?

AAV

SLE

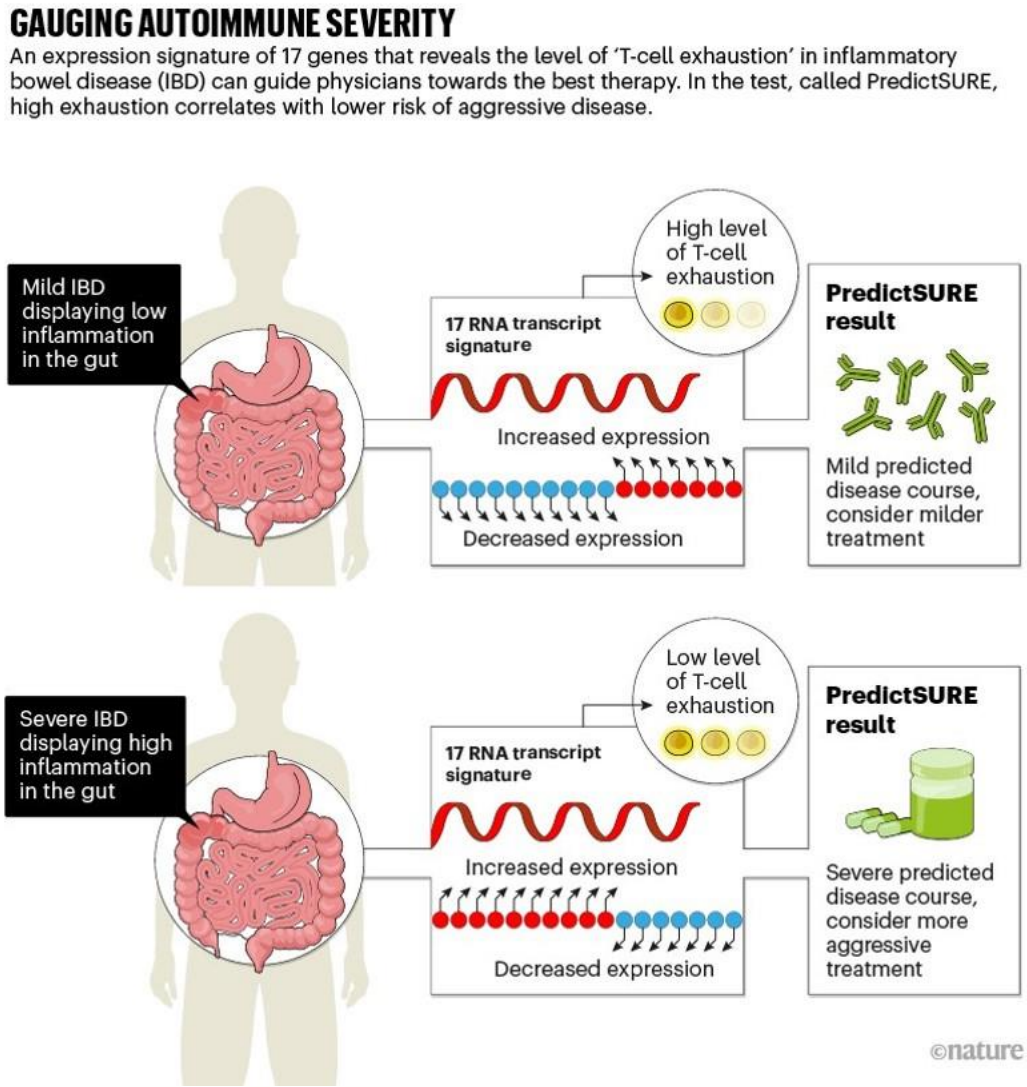
IBD



Early relapse Recurrent relapse

McKinney EF, Lee JC, Jayne DR, et al. Nature 2015

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



Dolgin E. Nature 2020

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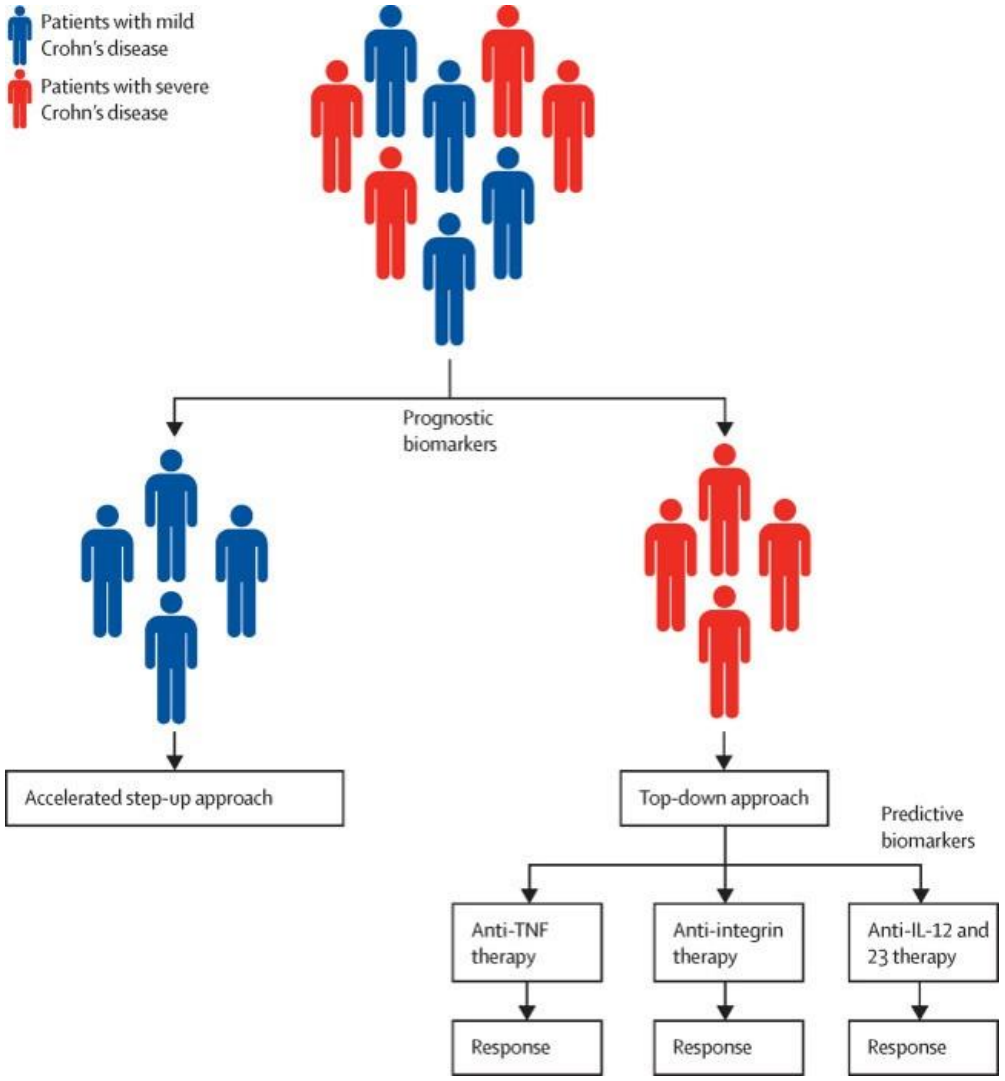
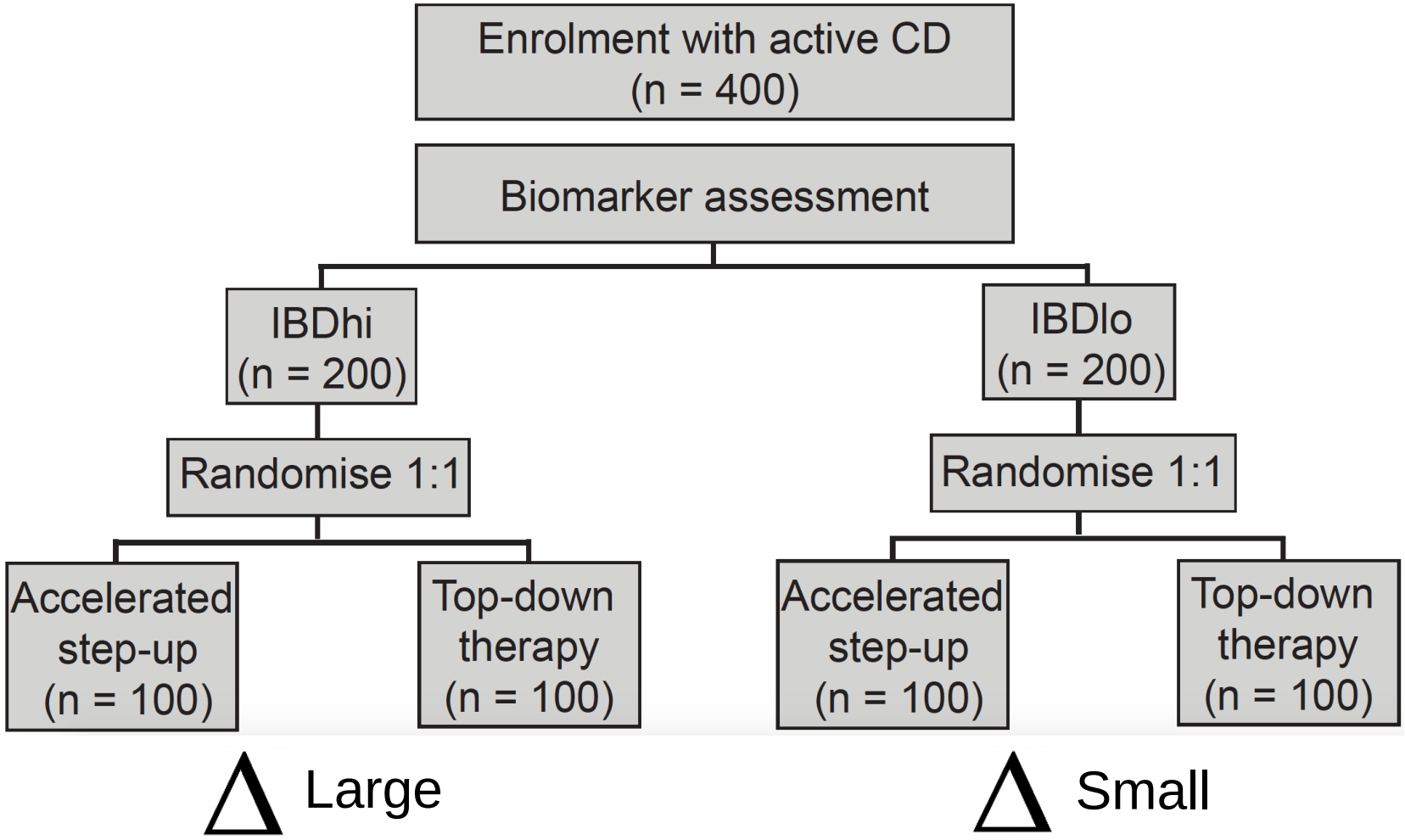
What would be rationale for clinical trial?



Noor NM, Verstockt B, Parkes M, et al. Lancet Gastro 2020

PROFILE trial schema



Parkes M*, Noor NM*, Dowling F, et al. BMJ Open 2018

Outcome measures

PROFILE

Primary endpoint:

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

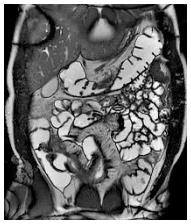
- Absence of symptoms (HBI score <5) + absence of objective markers of inflammation (CRP<ULN and calprotectin <200 OR both)

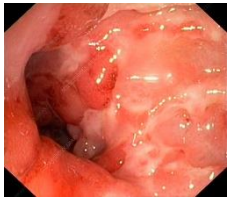
Secondary endpoints:

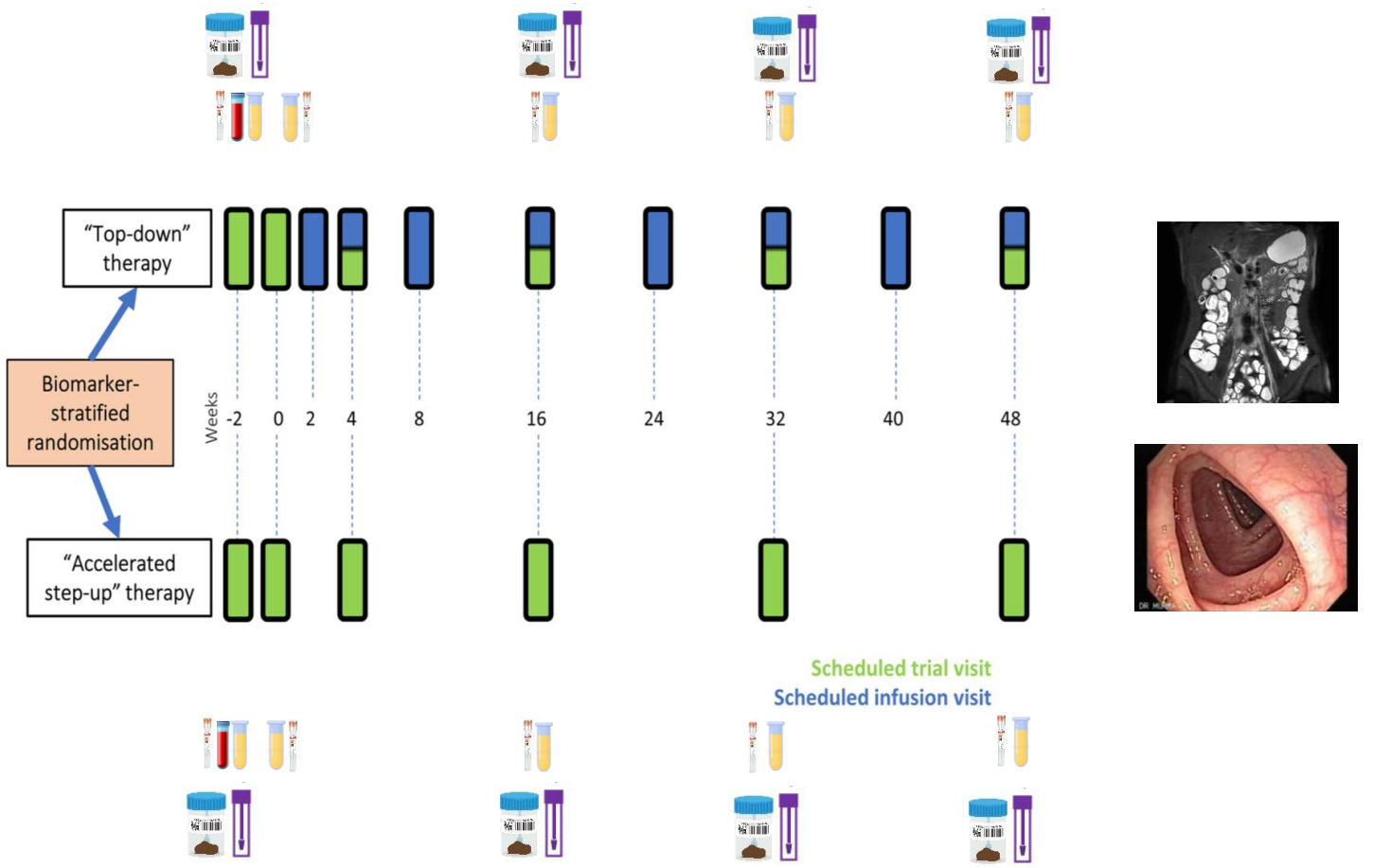
1. Endoscopic remission (absence of ulceration)
2. Quality of life assessment (IBDQ)
3. Number of flares
   A. i) Cumulative steroid exposure
   B. ii) Steroid-free remission
   C. iii) Number of hospital admissions and operations

Tertiary endpoints:

PROFILE schedule of events

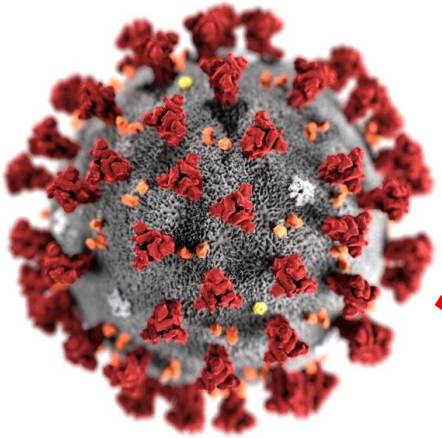






PROFILE recruitment pre and peri-COVID

PROFILE



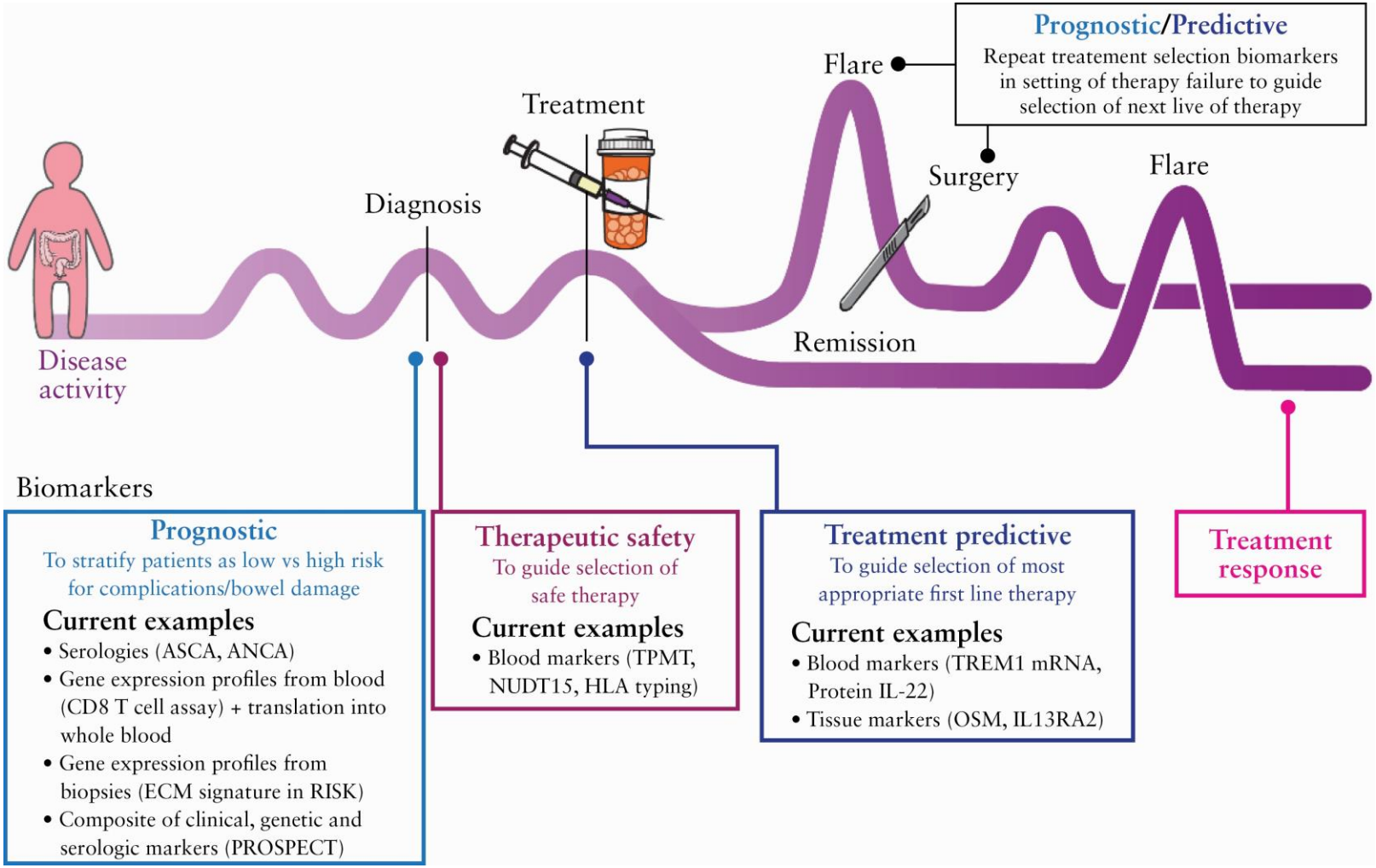
Personalised medicine research cannot just be at ivory towers

PROFILE

Huge successes PROFILE

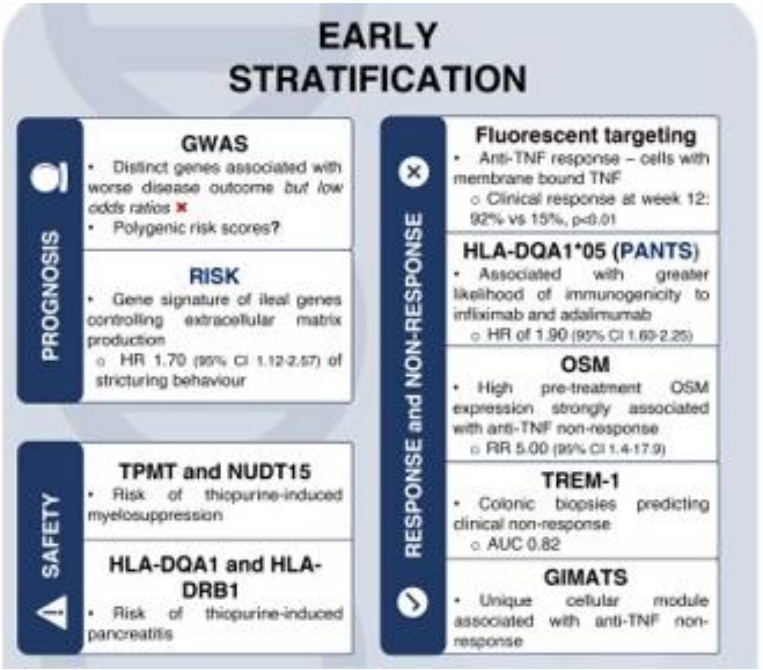
- **Largest academic drug trial in IBD** ever delivered from the UK – one of largest in the world
- First ever **biomarker-guided trial in IBD**
- No matter findings will likely result **in major impact on how we deliver IBD clinical care**
- Launched a new generation of **consultants, trainees and research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

Prognostic biomarkers are just one piece of the jigsaw



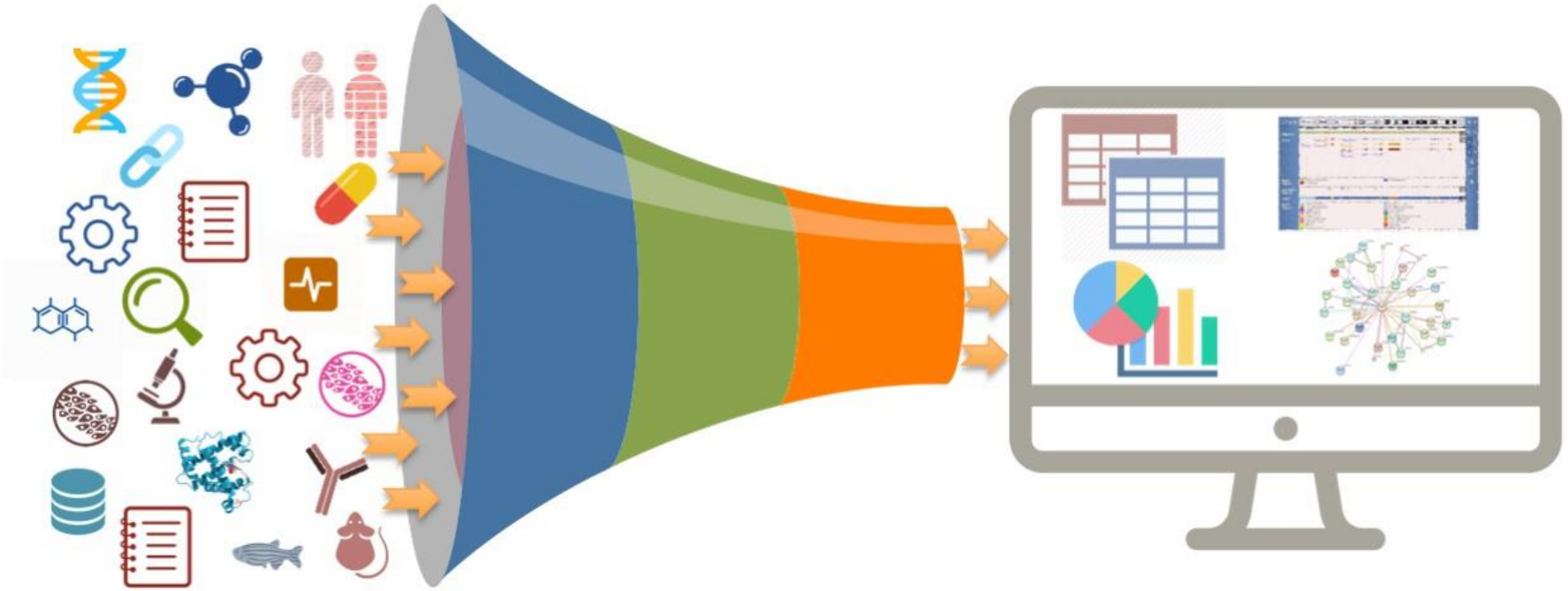
Verstockt B, Noor NM, Marigorta UM, et al. JCC 2021

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

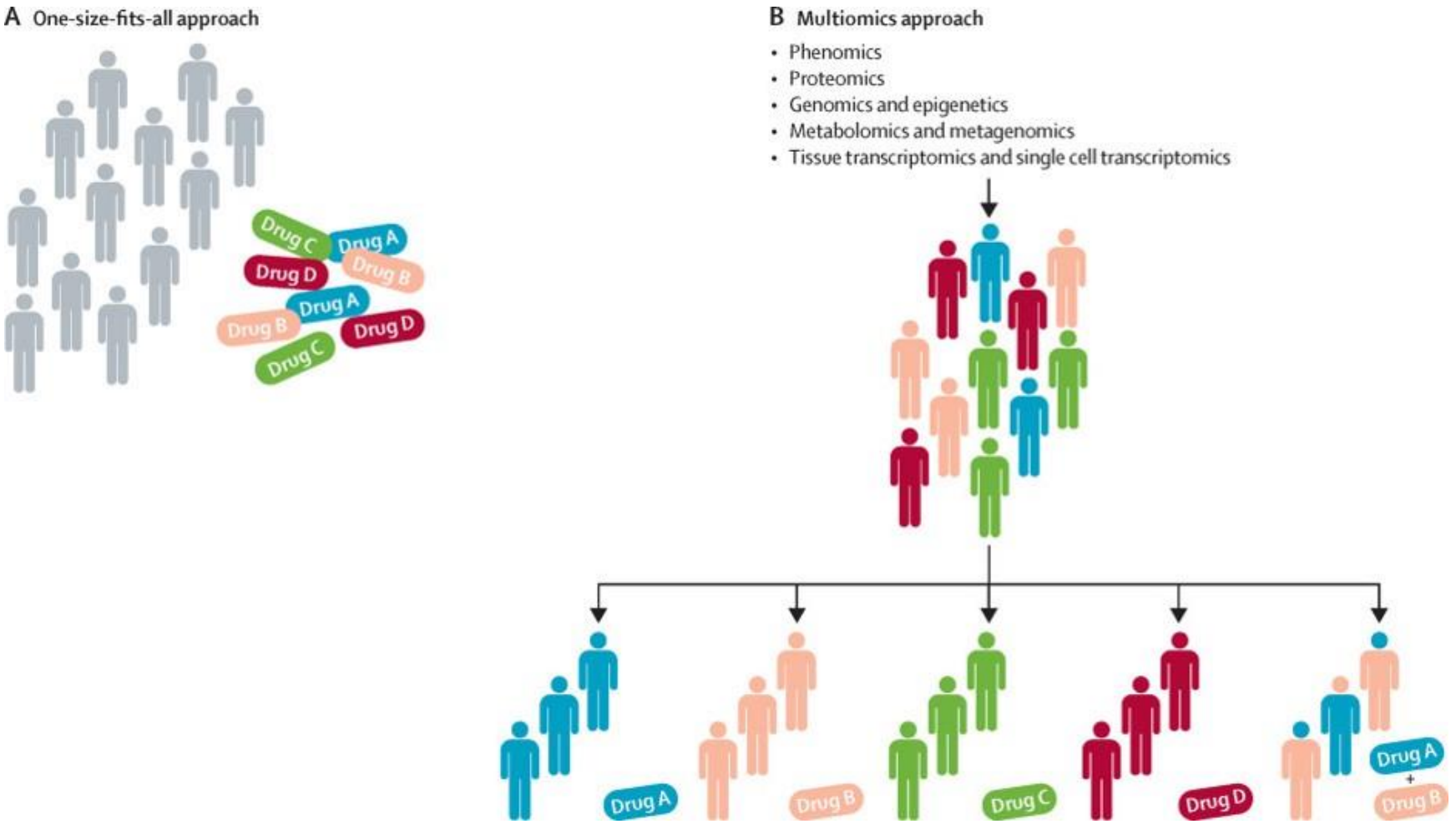


Noor NM, Sousa P, Paul S, et al. IBD 2022

The promise (dream) of multi-omics

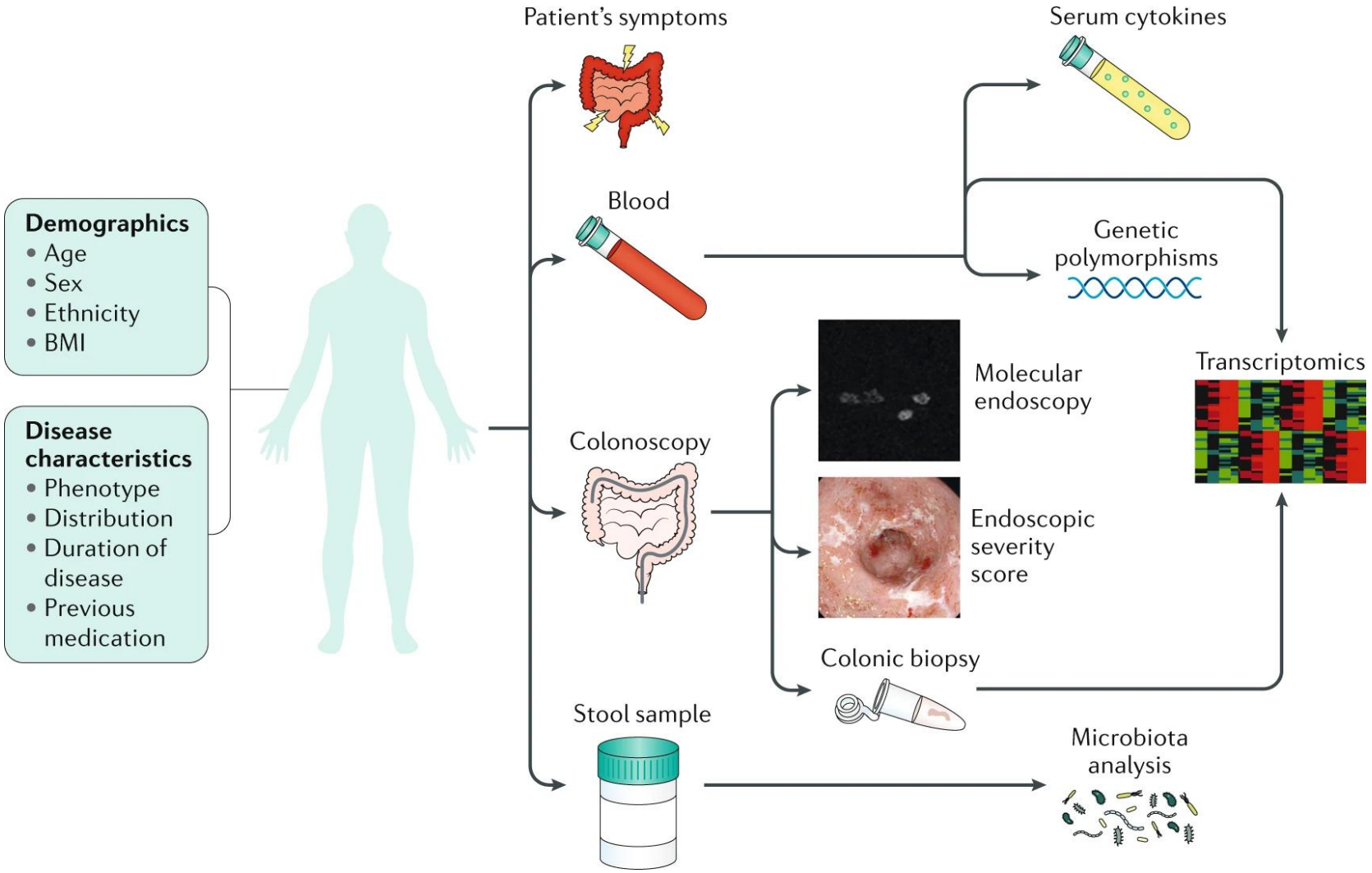


Future likely multiple integrated biomarkers and multi-omic approaches



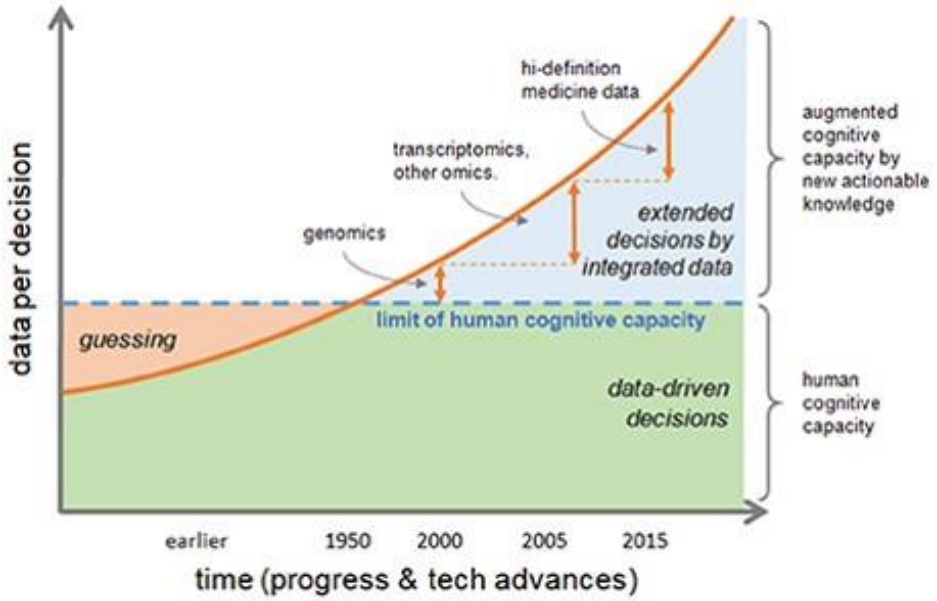
Noor NM, Verstockt B, Parkes M, et al. Lancet Gastro 2020

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



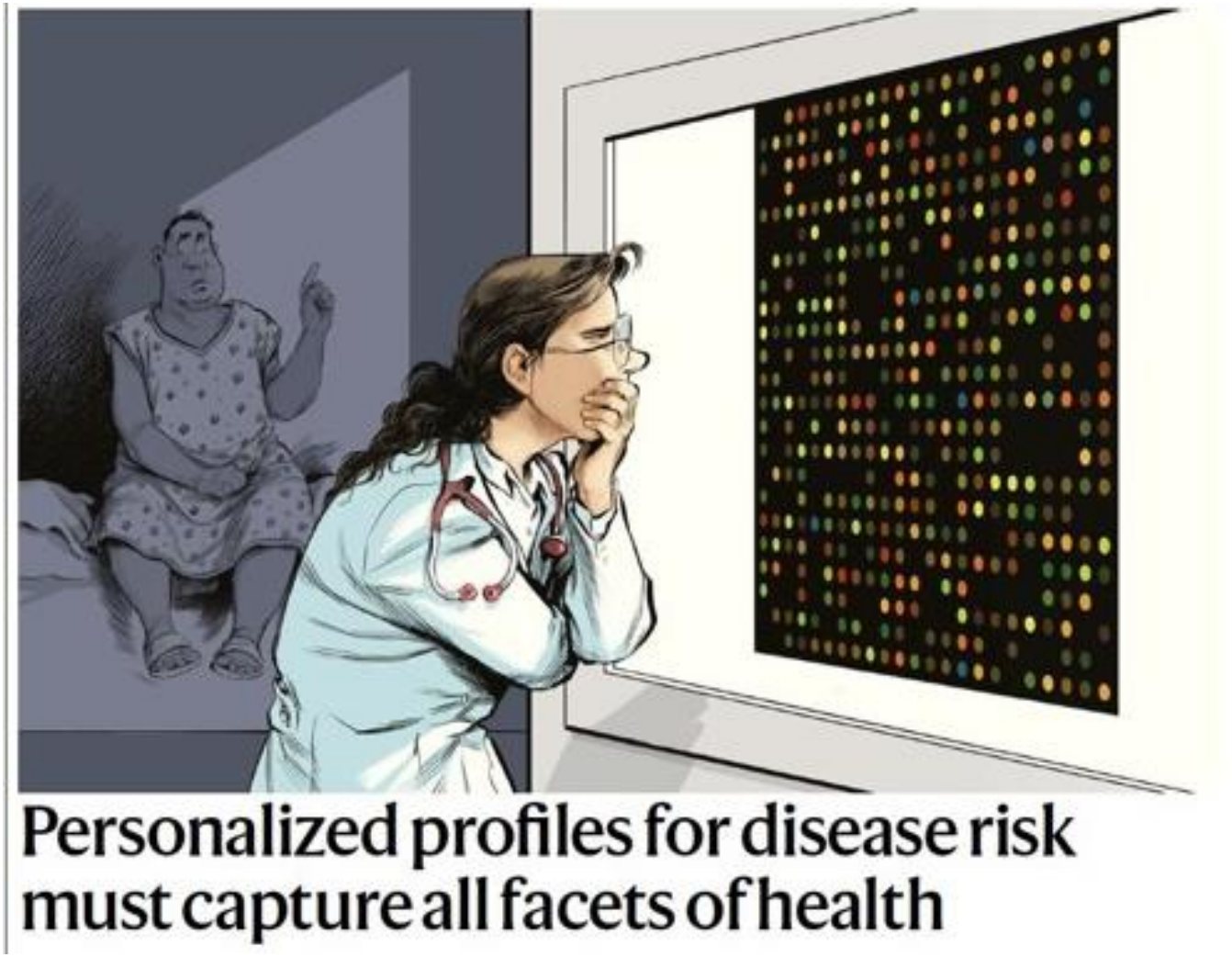
Digby-Bell J, Atreya R, Monteleone G, et al. Nature Rev Gastro 2019

More data may not necessarily = better decision-making



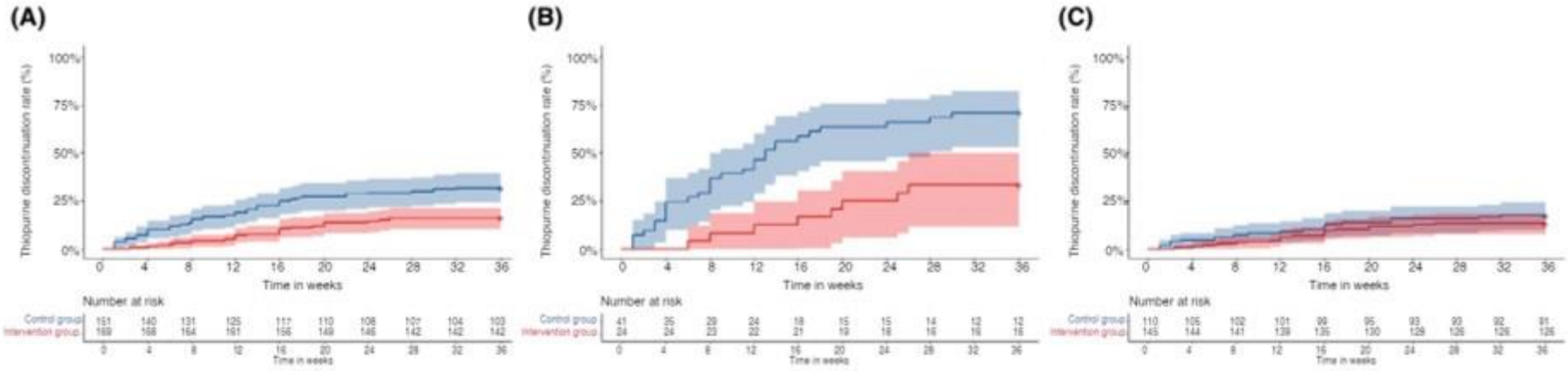
Rossi RL, Grifantini RM. Front Dig Hum, 2018

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



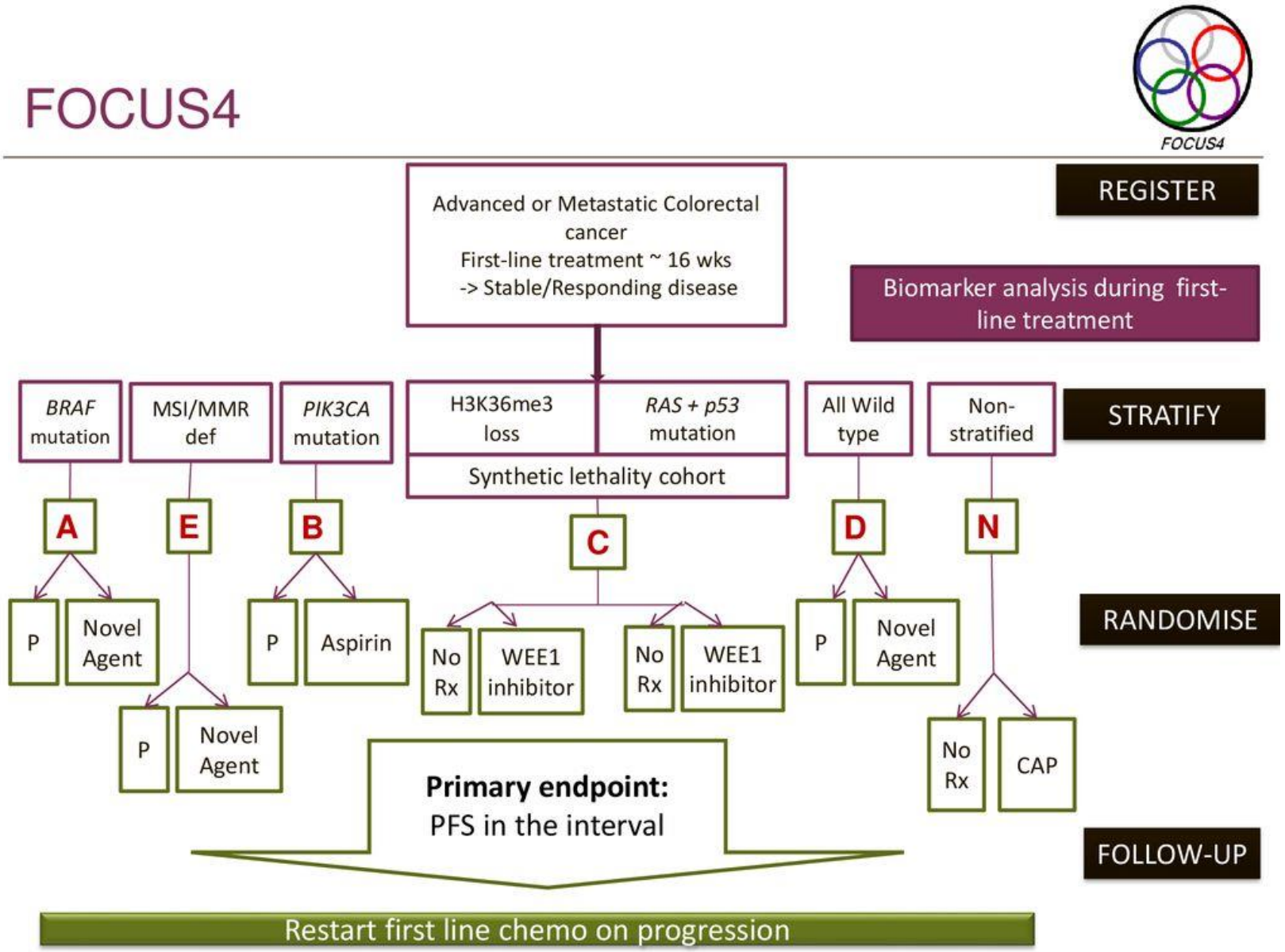
McCarthy M, Birney E. Nature 2021

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

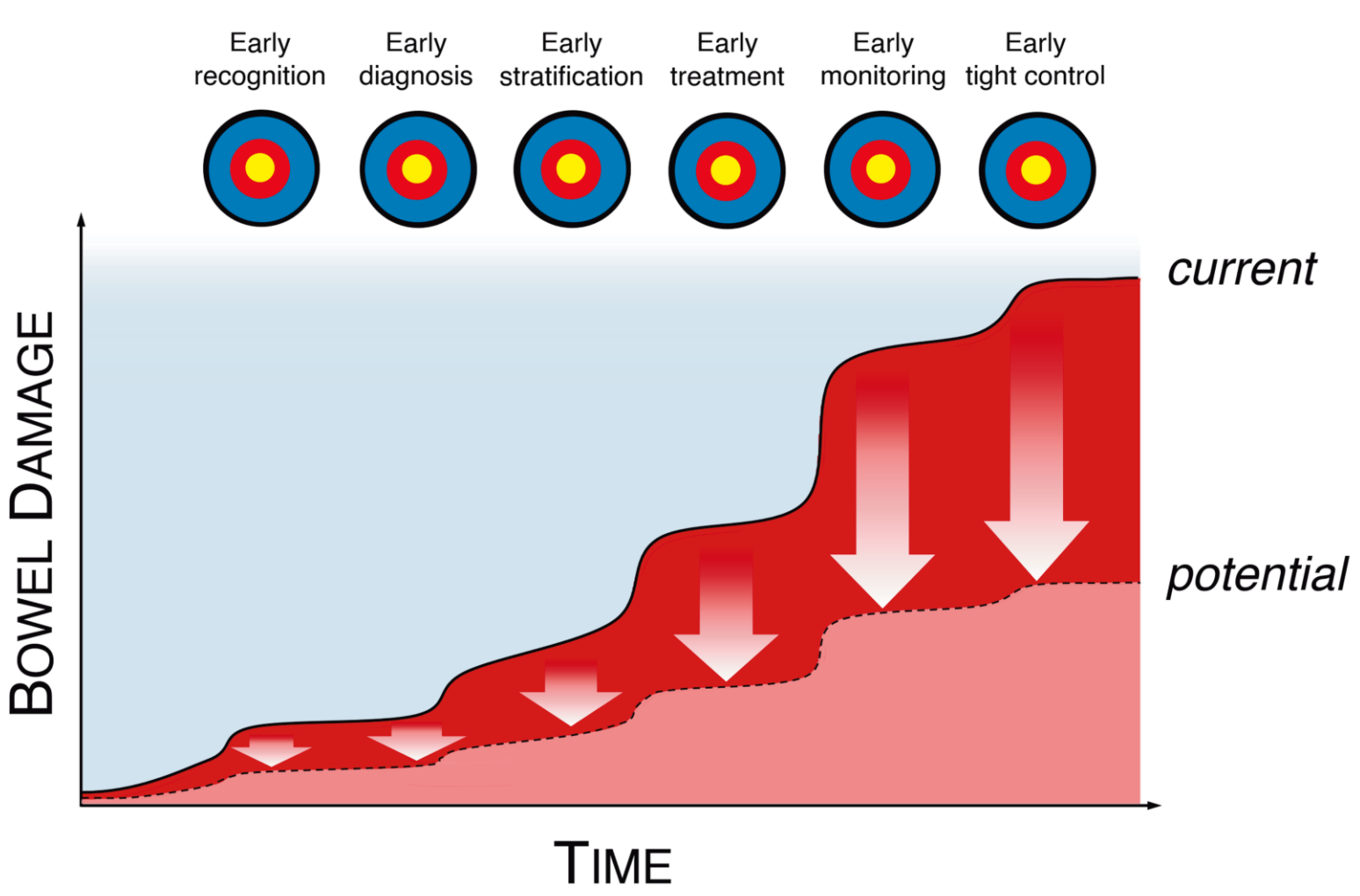


Yang SK, Hong M, Baek J, et al. Nature Genetics 2014
Walker GJ, Harrison JW, Heap GA, et al. JAMA 2019
Chao K, Huang Y, Zhu X, et al. APT 2021
Verstockt B, Noor NM, Marigorta UM, et al. JCC 2021

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



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



Noor NM*, Sousa P*, Paul S, et al. IBD 2021

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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