# 20 years after the first biologic in IBD

## What do we still need from drugs?

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THE UNIVERSITY of EDINBURGH
PREdiCCt
CHIEF SCIENTIST OFFICE
CENTRE FOR GENOMIC & EXPERIMENTAL MEDICINE

# Disclosures

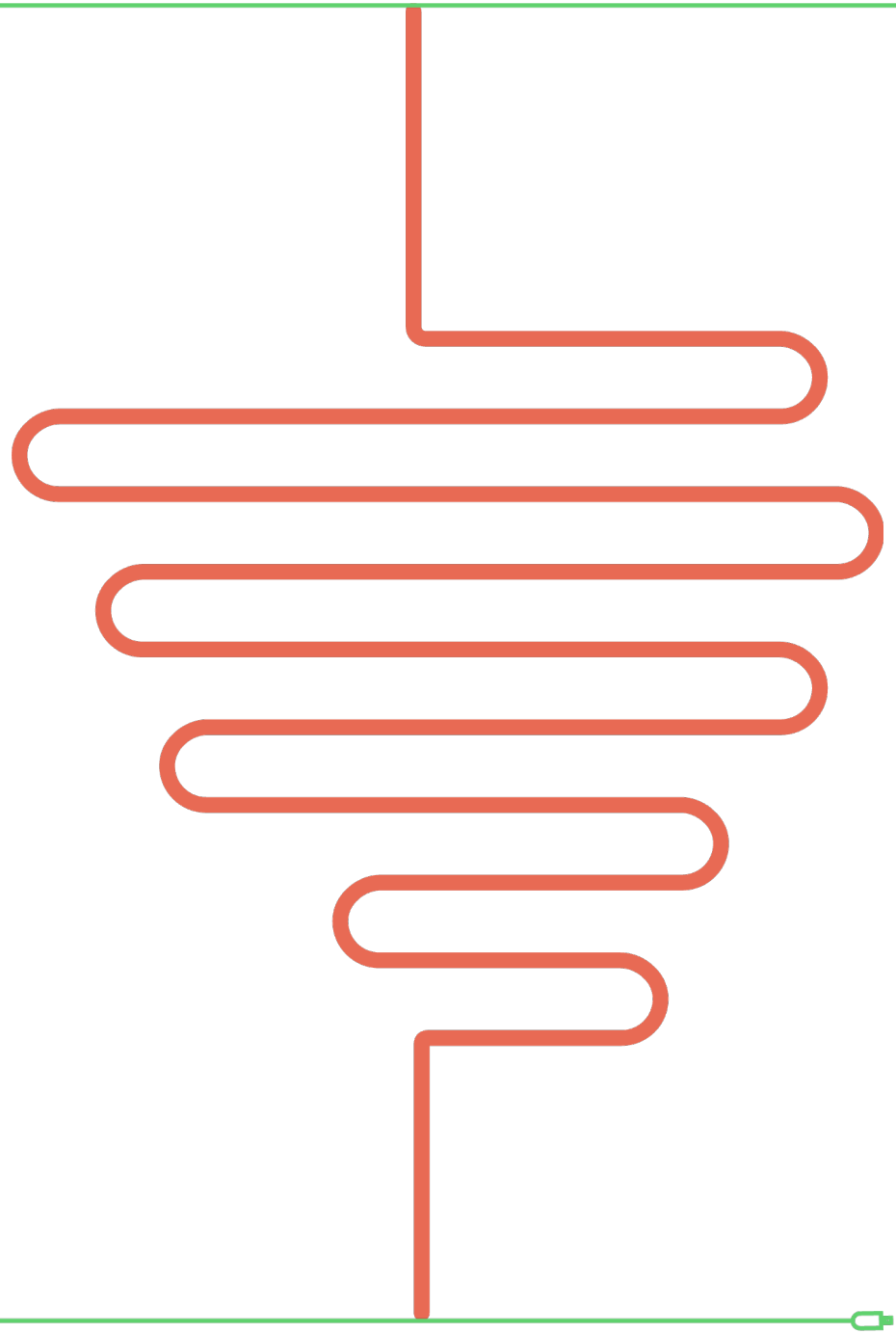
**Professor Lees is funded by a UKRI Future Leaders Fellowship**

**Additional research support from:**
Chief Scientist's Office, Cure Crohn's Colitis

**Consultancy fees from:**
Abbvie, Pfizer, Janssen, Gilead, Galapagos, BMS, Boehringer Ingelheim, Dr Falk, Trellus Health, Iterative Scopes and Vifor Pharma

**Speaking fees and travel support from:**
Abbvie, Pfizer, Janssen, Gilead, Galapagos, BMS, Sandoz, Novartis, Dr Falk, Ferring, Fresnius Kabi and Takeda

***All cases presented with written consent of patients***



# OVERVIEW

Our patients and life without proper therapy

The different phases of IBD therapy

- **IBD-1.0** through to **IBD-2.0**

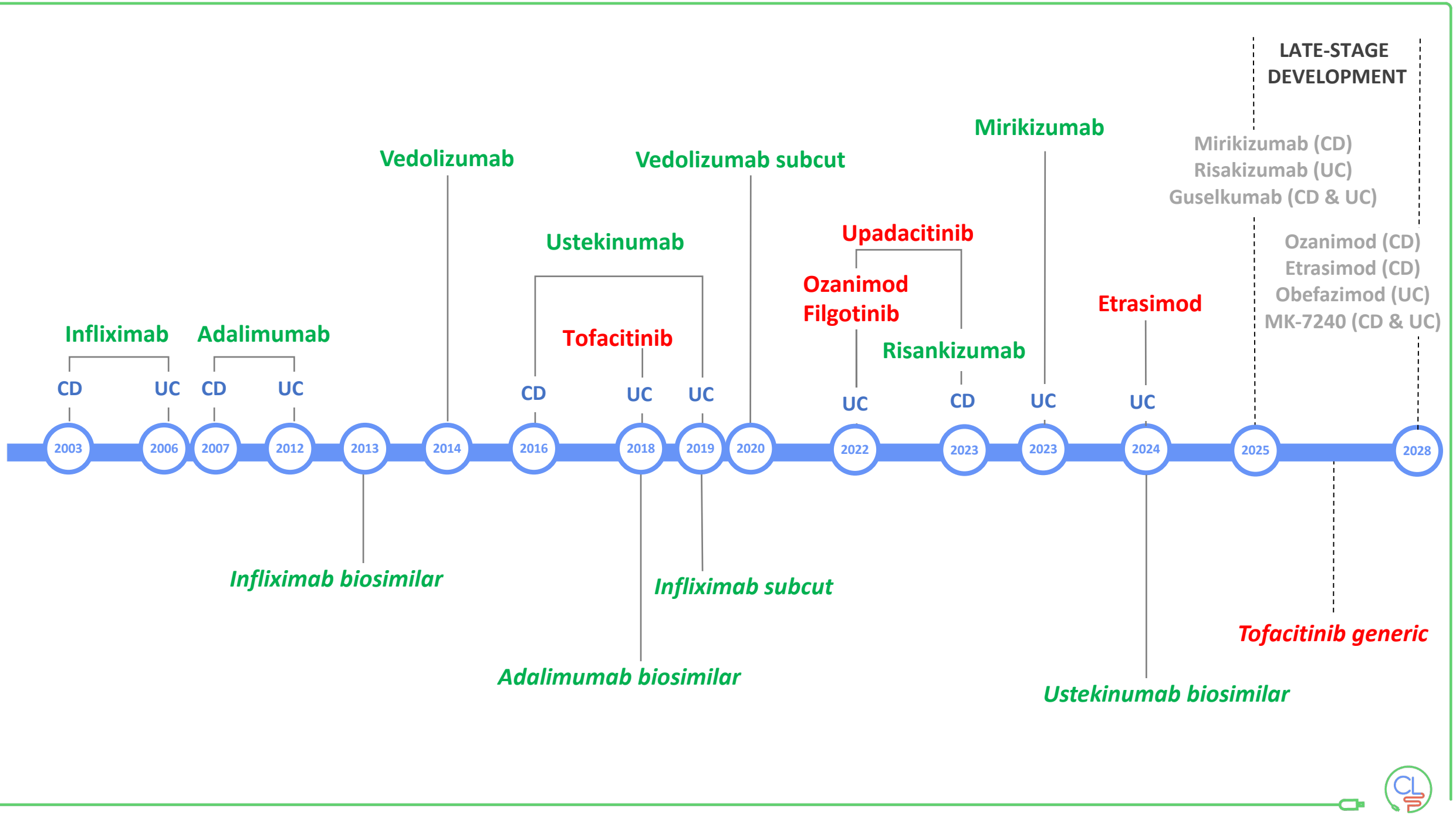
Treatment strategies & drug sequencing with current therapies

- The importance of early effective therapy
- Anti-TNFs versus JAKi and the new biologics

The unmet need after we deploy the new therapies

And the solution?

- **IBD-3.0**


LATE-STAGE DEVELOPMENT
Mirikizumab (CD)
Risakizumab (UC)
Guselkumab (CD & UC)
Ozanimod (CD)
Etrasimod (CD)
Obefazimod (UC)
MK-7240 (CD & UC)
Infliximab
Adalimumab
Vedolizumab
Ustekinumab
Vedolizumab subcut
Tofacitinib
Upadacitinib
Ozanimod
Filgotinib
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Infliximab subcut
Adalimumab biosimilar
Ustekinumab biosimilar
Tofacitinib generic

# IBD-1.0

Drugs are ineffective

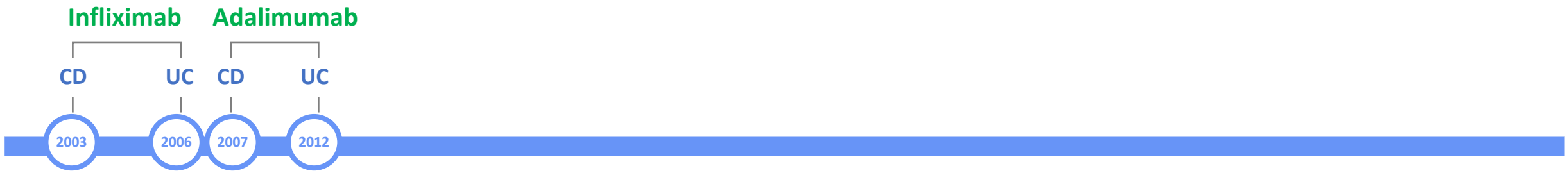
Steroids are prescribed liberally

Patients have a poor quality of life

Treatment targets are non-existent

2003 2007

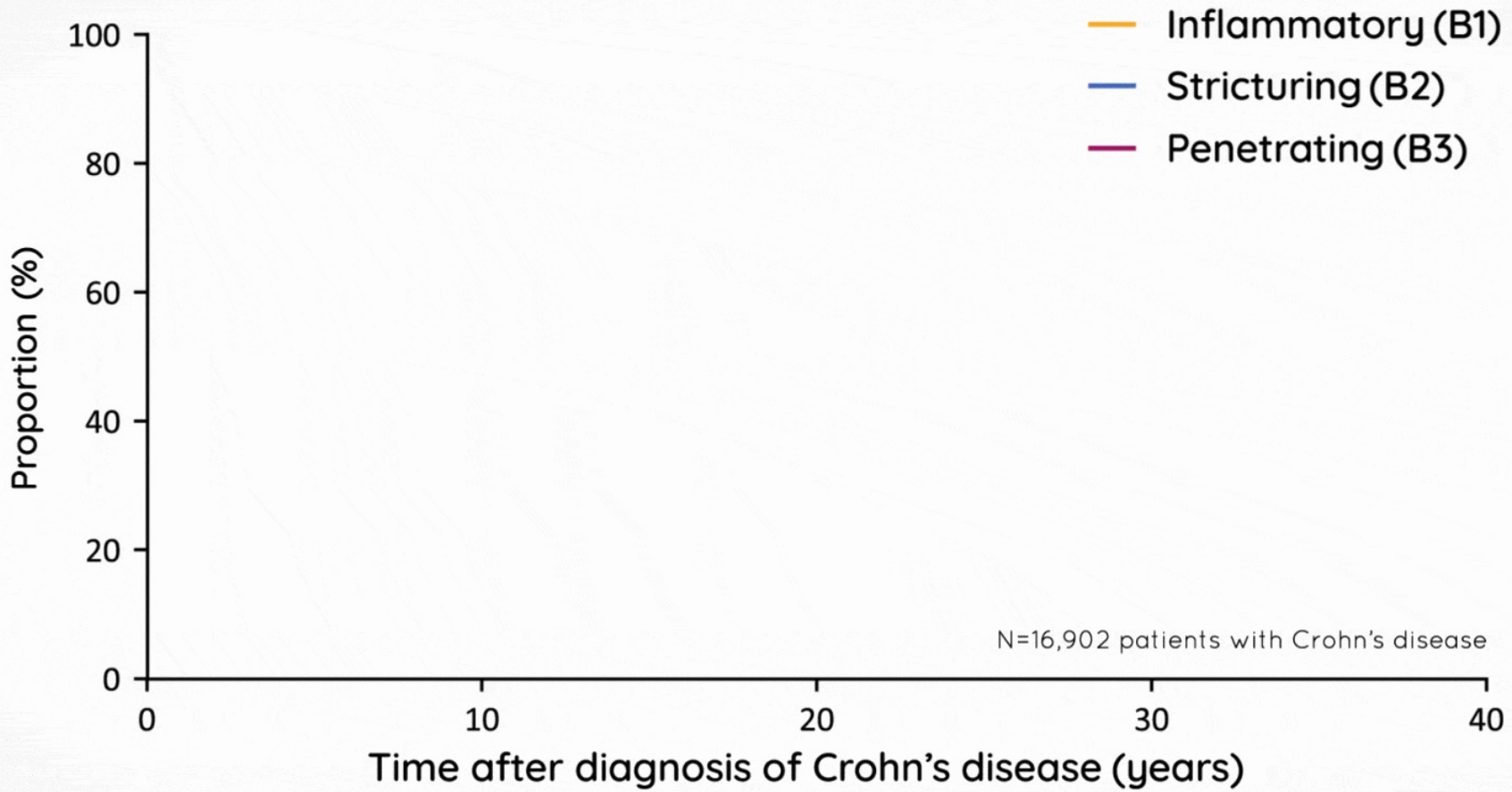
# IBD-1.1




New therapies are expensive

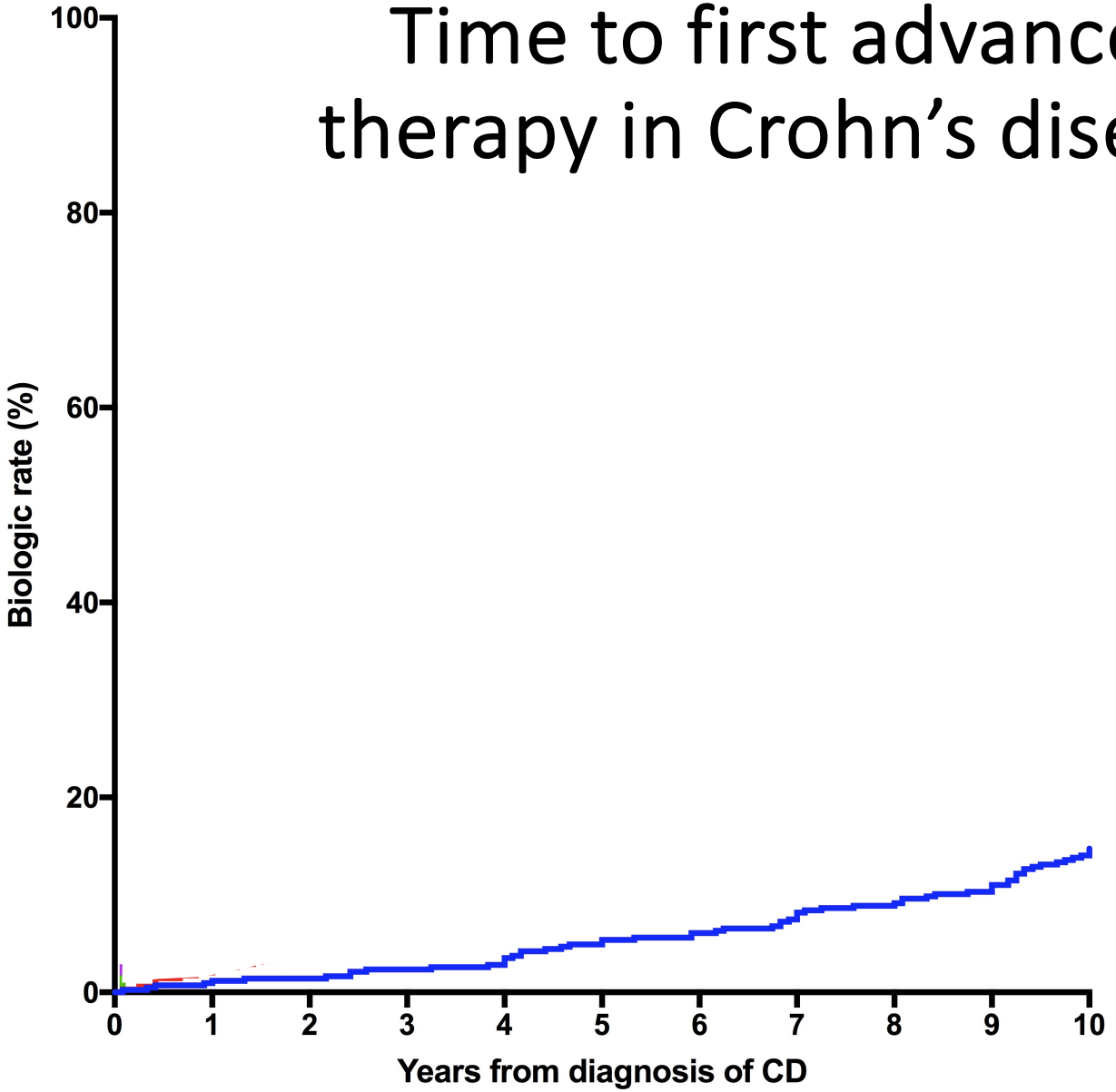
WE have no clue how to use them properly

Surgery, stomas, hospitalisations, gut failure are common




Cleynen I, et al. Lancet 2016;387:156 – 167

# Time to first advanced therapy in Crohn's disease




Jenkinson P et al *Journal Crohn's Colitis* 2020

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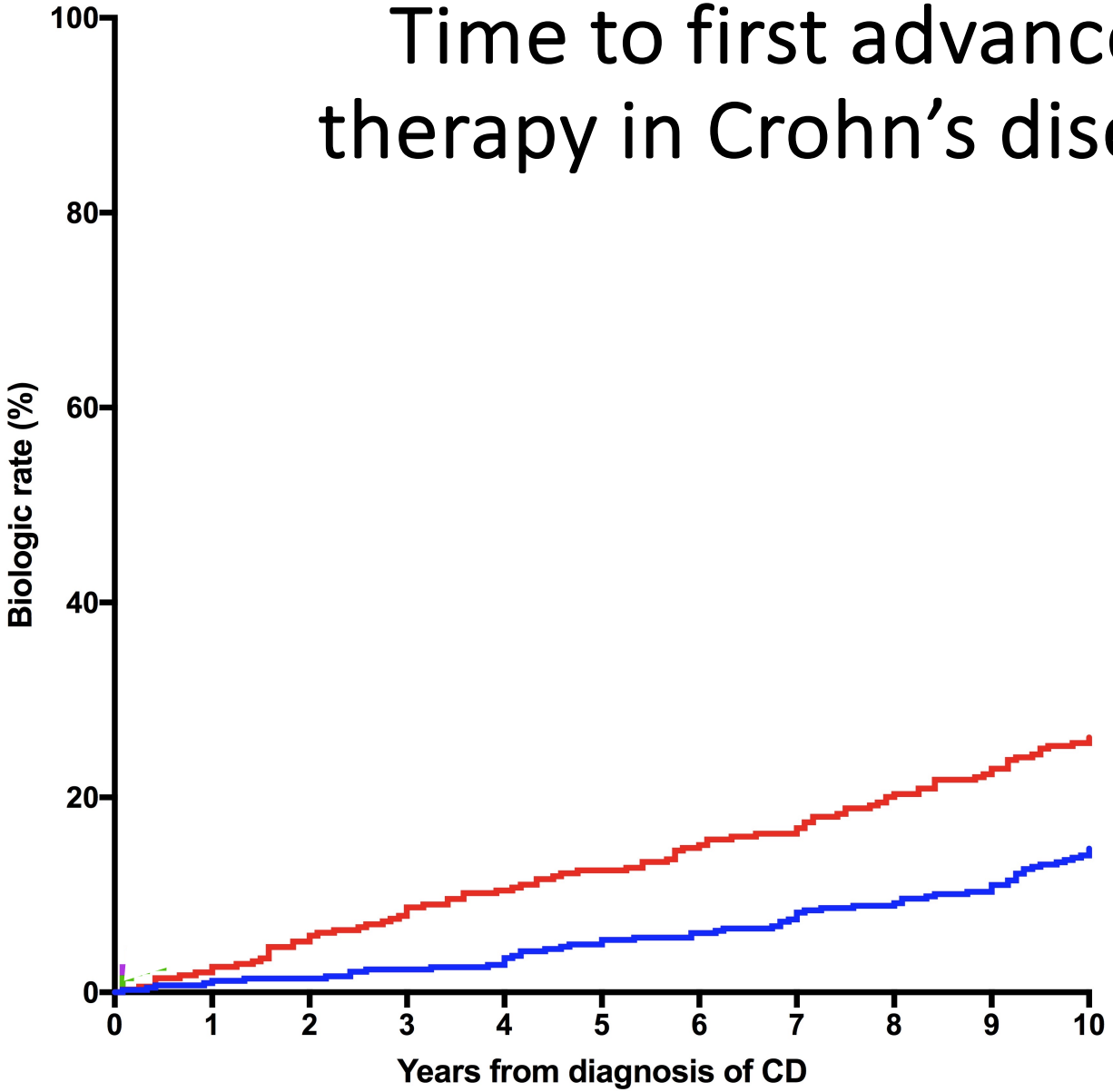


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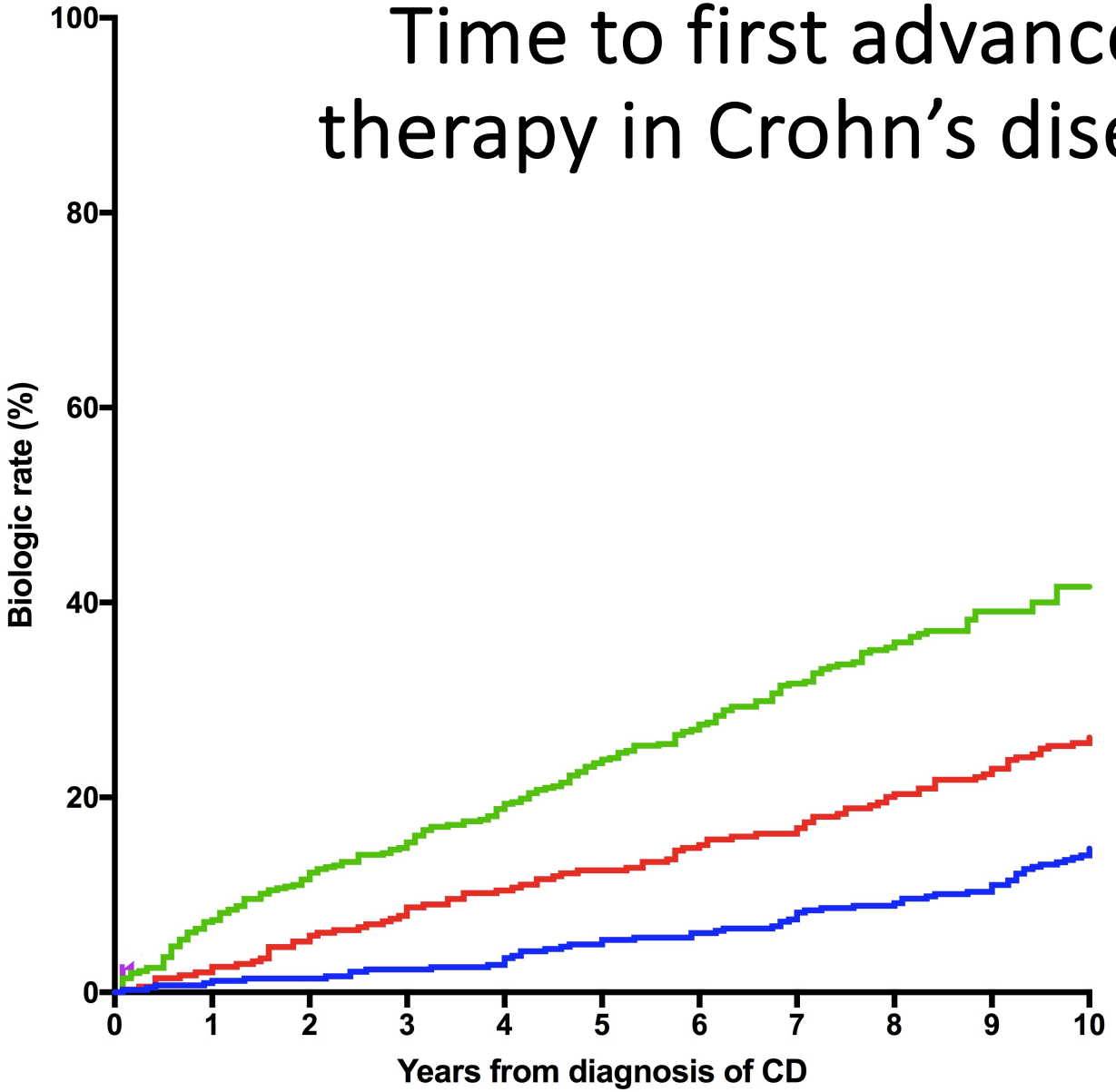
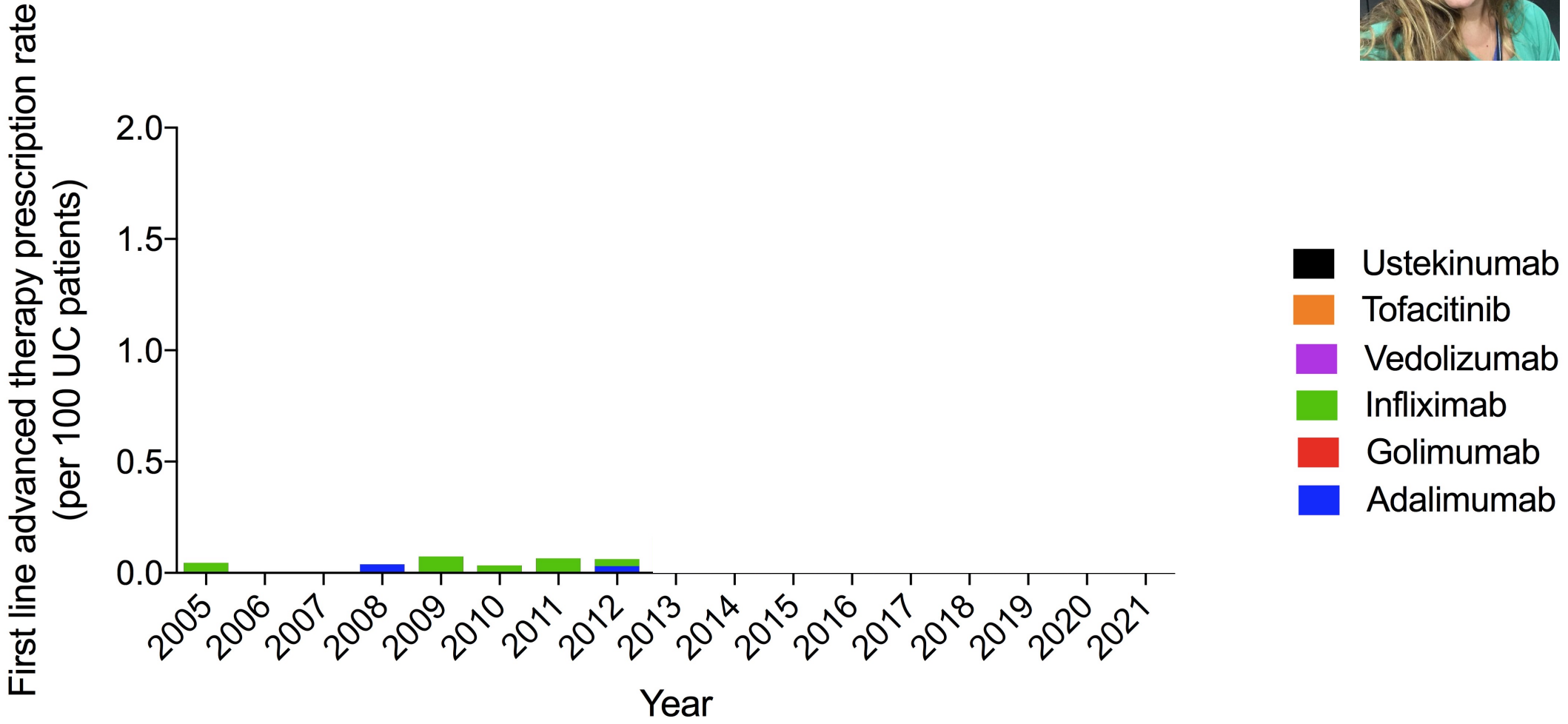



Jenkinson P et al *Journal Crohn's Colitis* 2020

# Lothian IBD Registry UPDATE: UC
# FIRST-LINE ADVANCED THEARPY

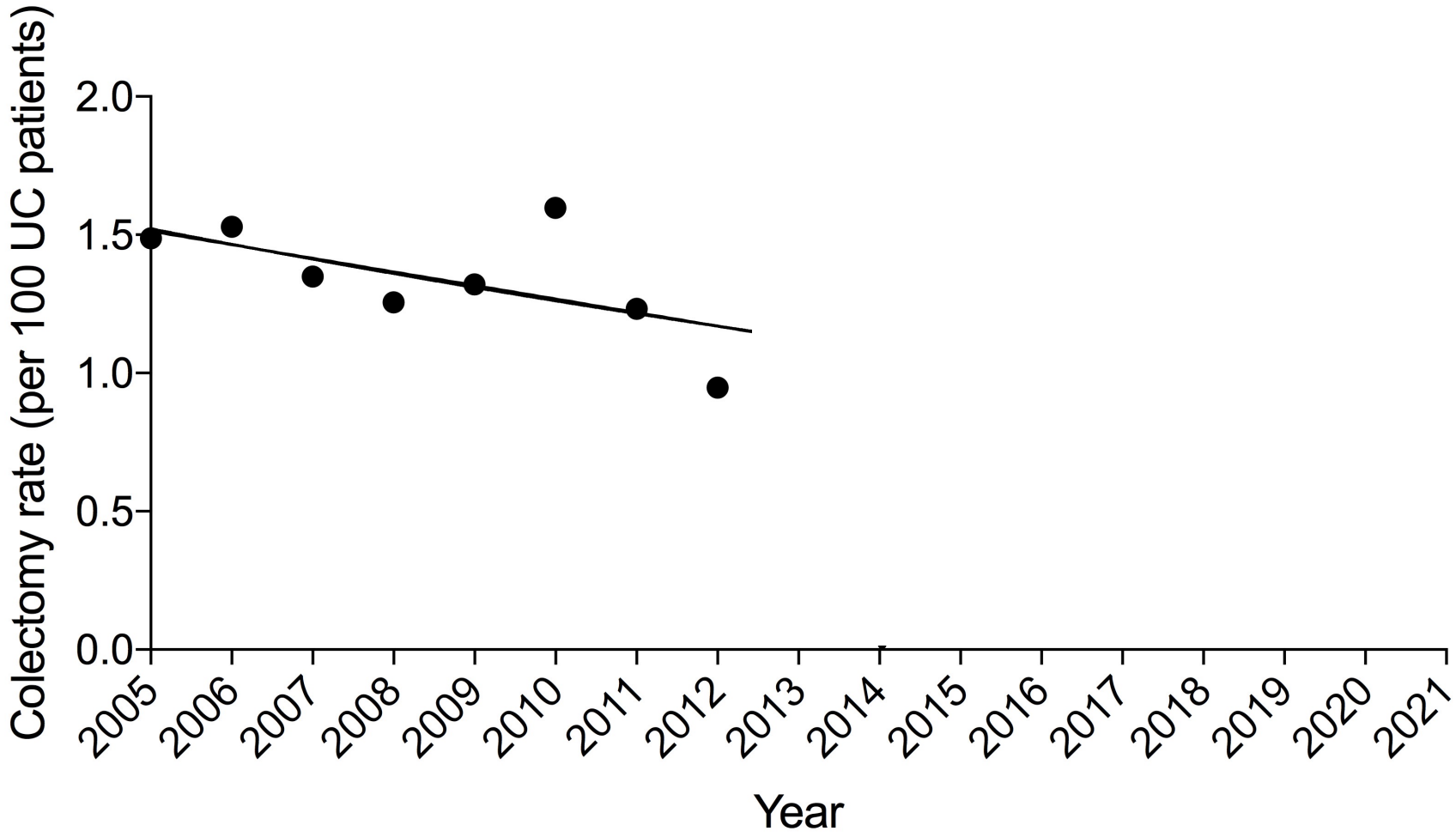




Jenkinson P *et al* ECCO 2022 https://www.ecco-ibd.eu/publications/congress-abstracts/item/p489-temporal-trends-of-colectomy-for-ulcerative-colitis-in-the-multi-drug-era-a-population-based-cohort-study.html Accessed June 2022

Based on clinician's own data

# Lothian IBD Registry UPDATE

Colectomy for UC: temporal trends




Jenkinson P et al ECCO 2022

# How does IBD impact on a person's life?

## Physical aspects

- diarrhoea, urgency, blood in stool and pain
- joint pains, eye problems, skin rashes and mouth ulcers
- night sweats and fevers; nausea and vomiting, loss of appetite and weight loss

## Psychological aspects

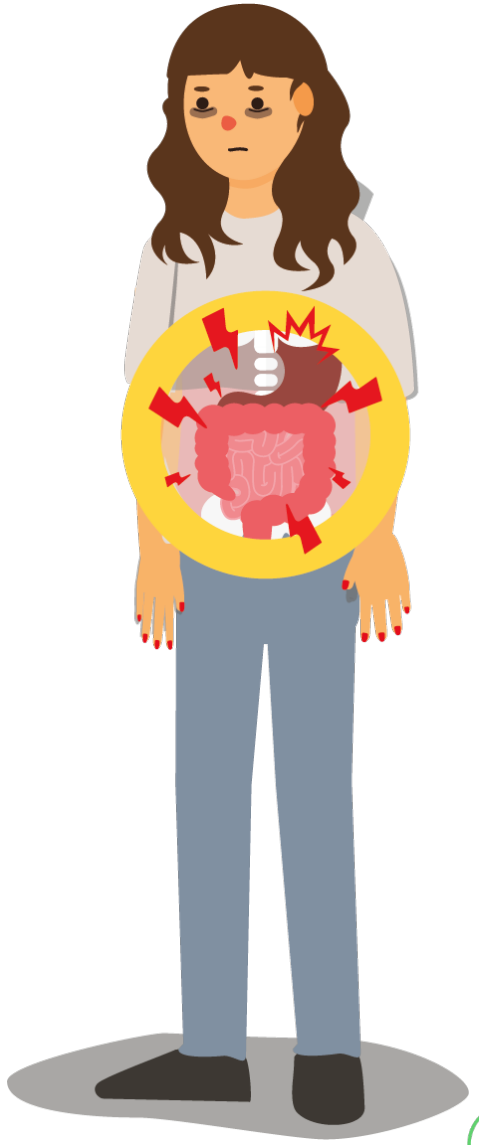
- fatigue and mental exhaustion; anxiety and depression

## Long-term complications of the disease

- hospitalisations for flares; surgical interventions; stoma formation

## Everyday life

- spending more time in the bathroom
- impact on studies and work - including absence and choice of job
- relationships and sex life, family planning and pregnancy
- food choices may be restricted to manage / avoid flares



# IBD-2.0

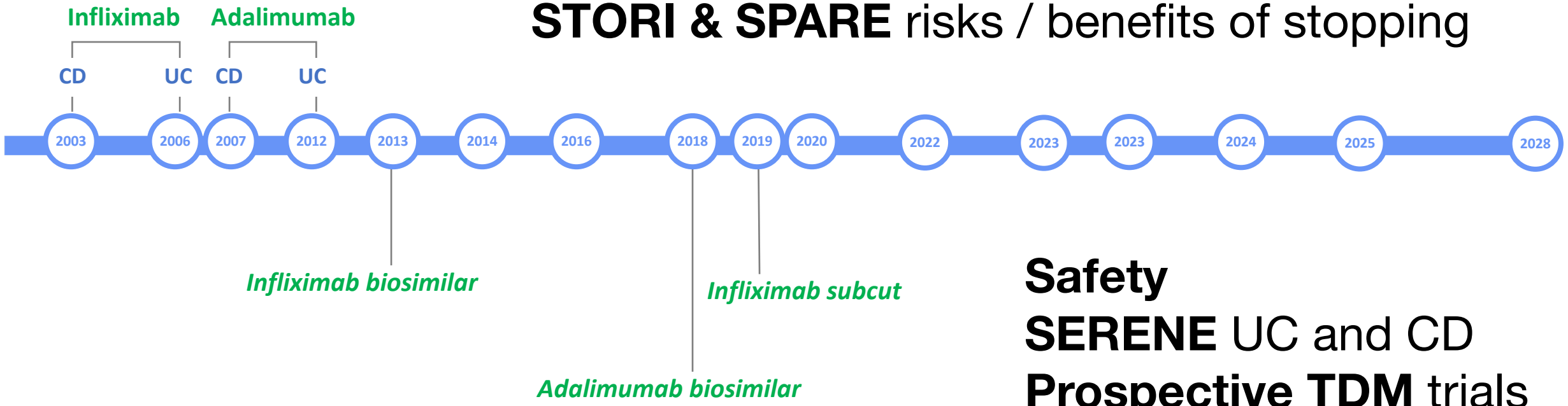
**SONIC** Combo better than mono

**ASUC** Infliximab as rescue therapy

**Biosimilars** IFX & ADA – costs plumet

**Early** effective therapy in Crohn's disease

**STORI & SPARE** risks / benefits of stopping

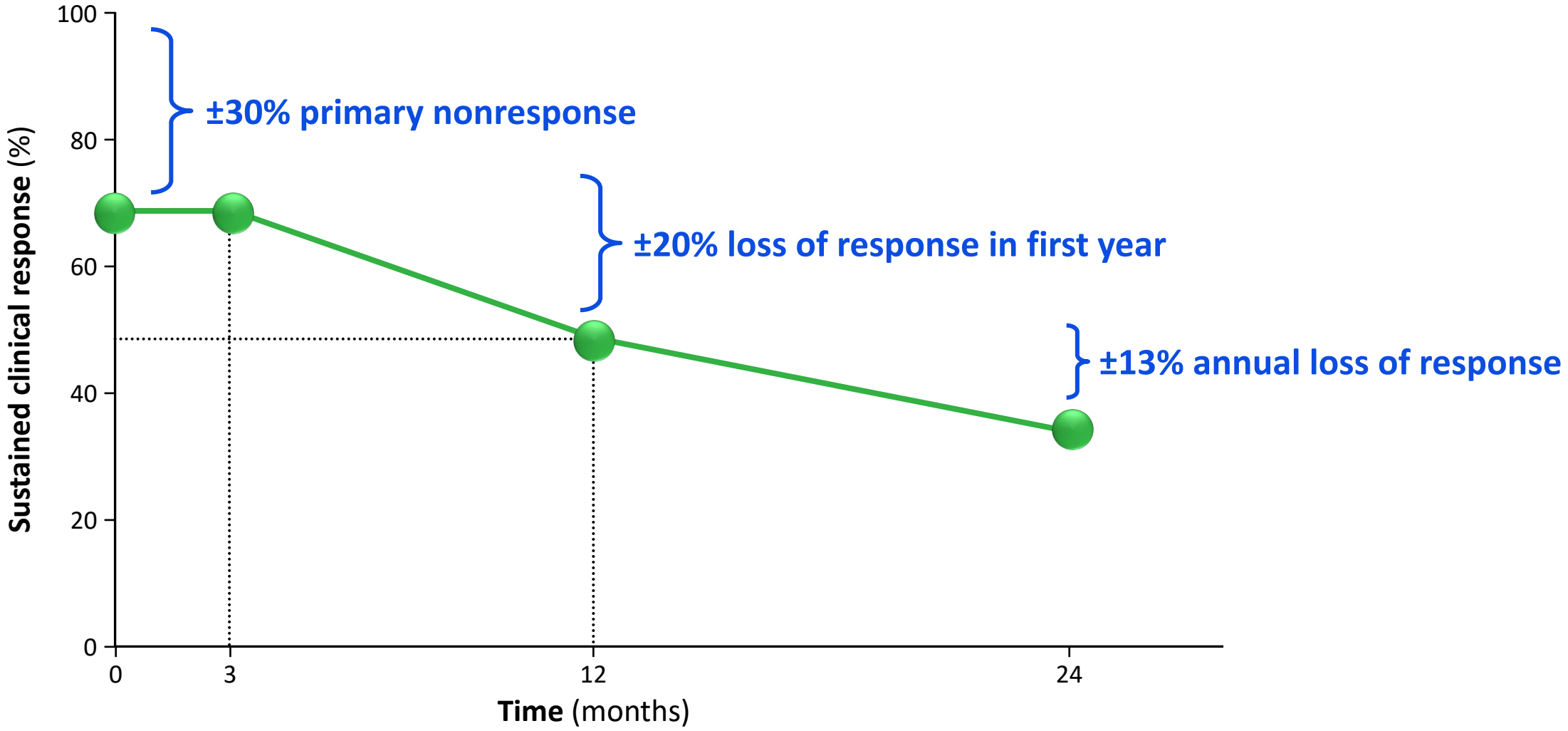



**Safety**

**SERENE** UC and CD

**Prospective TDM** trials

# The problem with TNF drugs




TNF, tumour necrosis factor.
Adapted from Roda G et al. *Clin Transl Gastroenterol* 2016;7:e135.

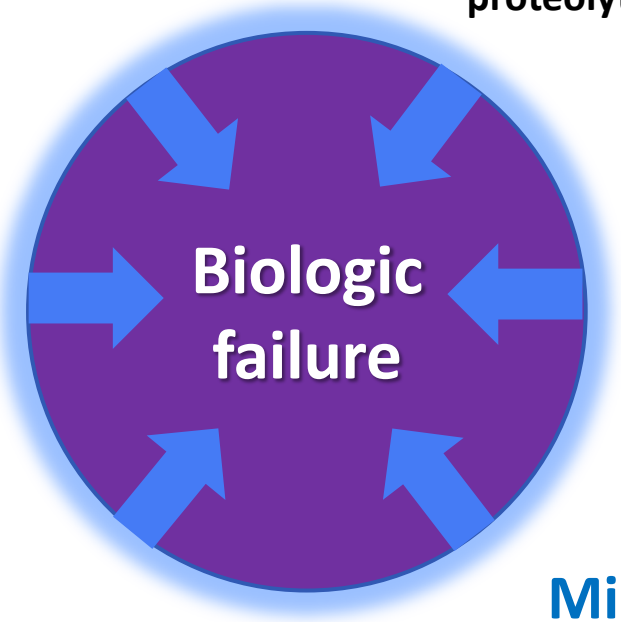
# Multiple mechanisms for biologic failure

## Molecular Resistance

**Immune cell inflitrate CD4+ IL-23R+ TNFR2 T cells, IL-23+ macrophages, OSM**

## Pharmacokinetic factors

**Serum and tissue drug level, ADAs, loss in stool, FcR-mediated endocytosis, proteolytic degradation**




## Clinical Phenotype

**Age, duration of disease, BMI, smoking, severity, complications,**

## Mechanistic Failure

**Low / absent drug target expression – mTNF, TNFR2, α4β7**

## Genomic Factors

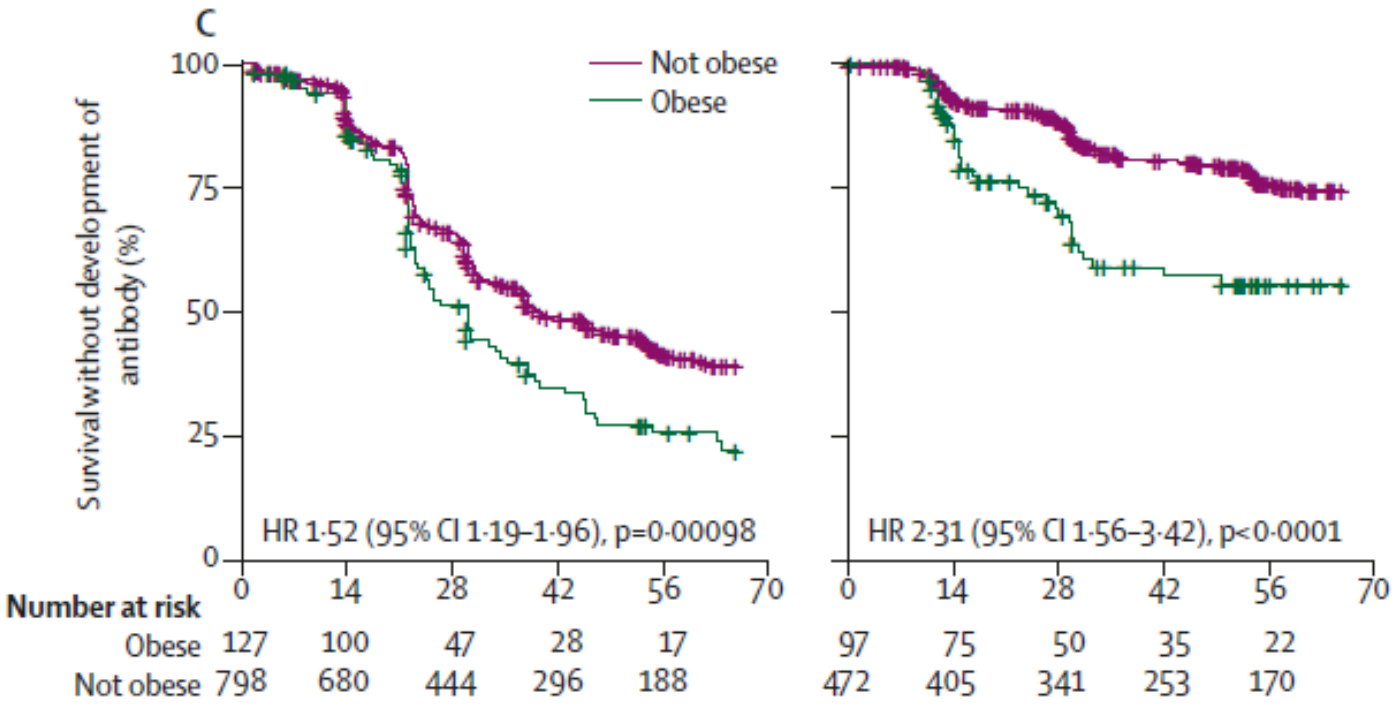
**FCGR3A, TREM1, HLA-DQA1*05,**

## Microbiome

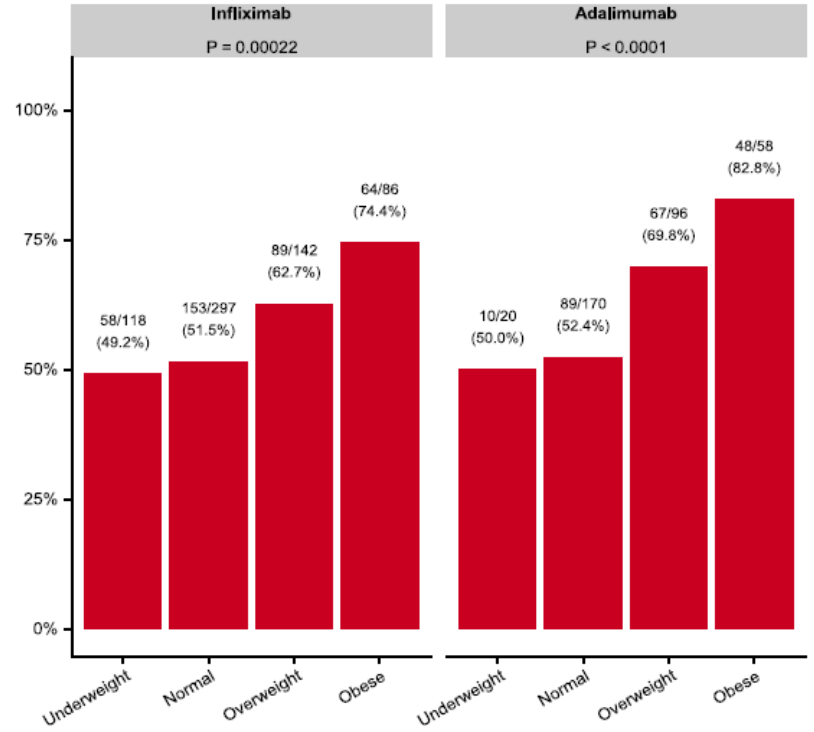
**Faecalibacterium, Clostridiales, Burkholderiales, Bacteroides**

Modified from Atreya R, Neurath MF. *Lancet Gastroenterol Hepatol* 2018;3:790–802.

# Obesity, immunogenicity & non-remission at week 54

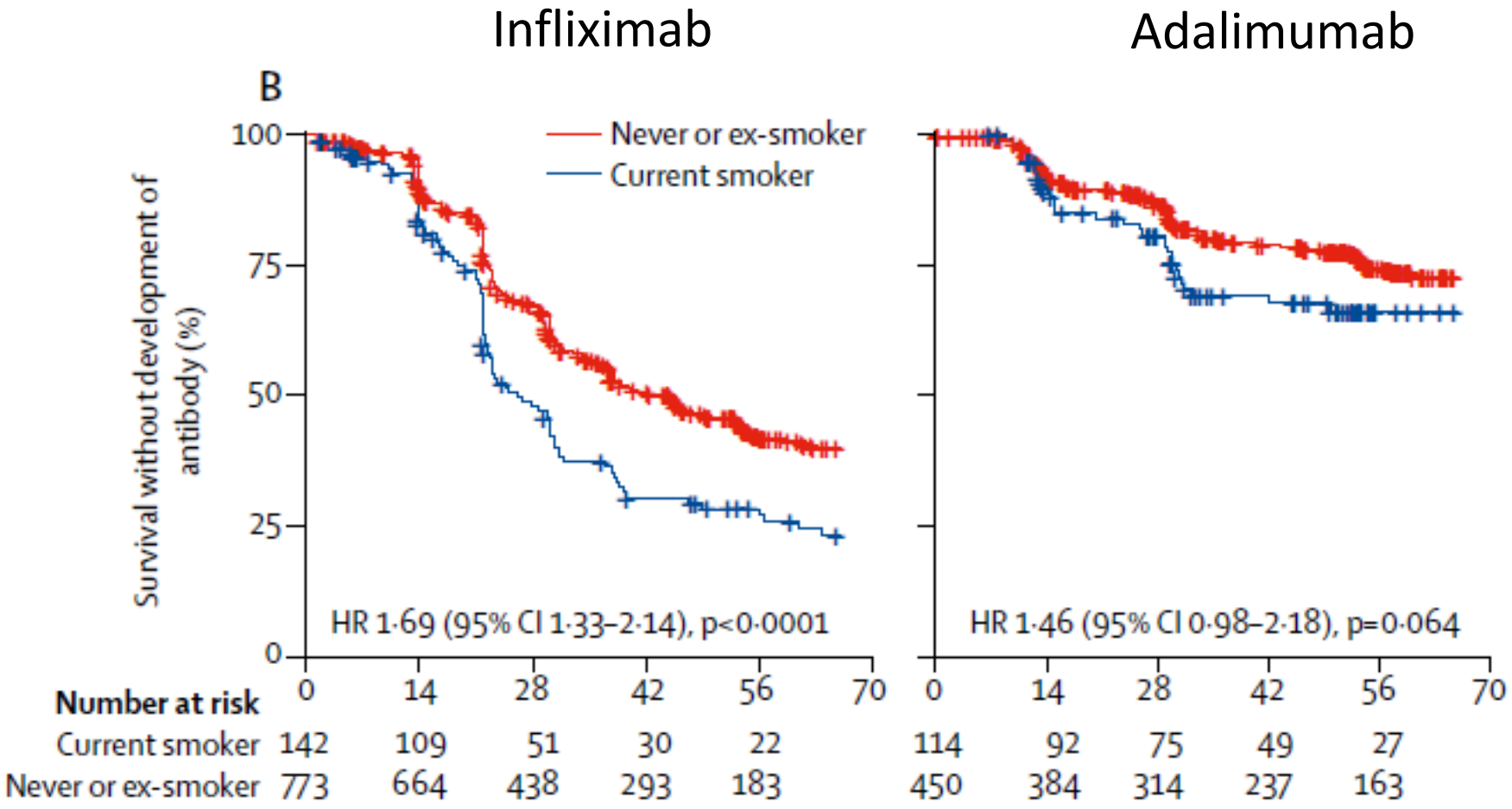



## Non-remission at week 54




Kennedy NA et al Lancet Gastroenterol Hepatol. 2019 May;4(5):341-353. doi: 10.1016/S2468-1253(19)30012-3. Epub 2019 Feb 27.

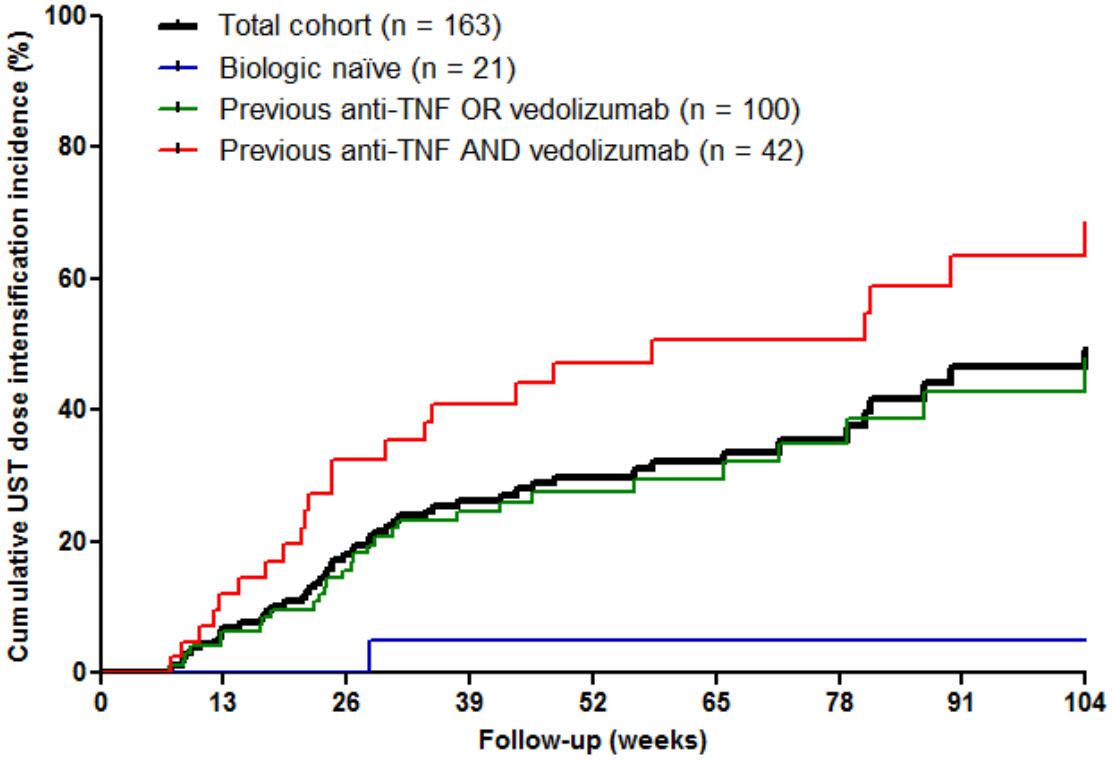
# Smoking and risk of immunogenicity



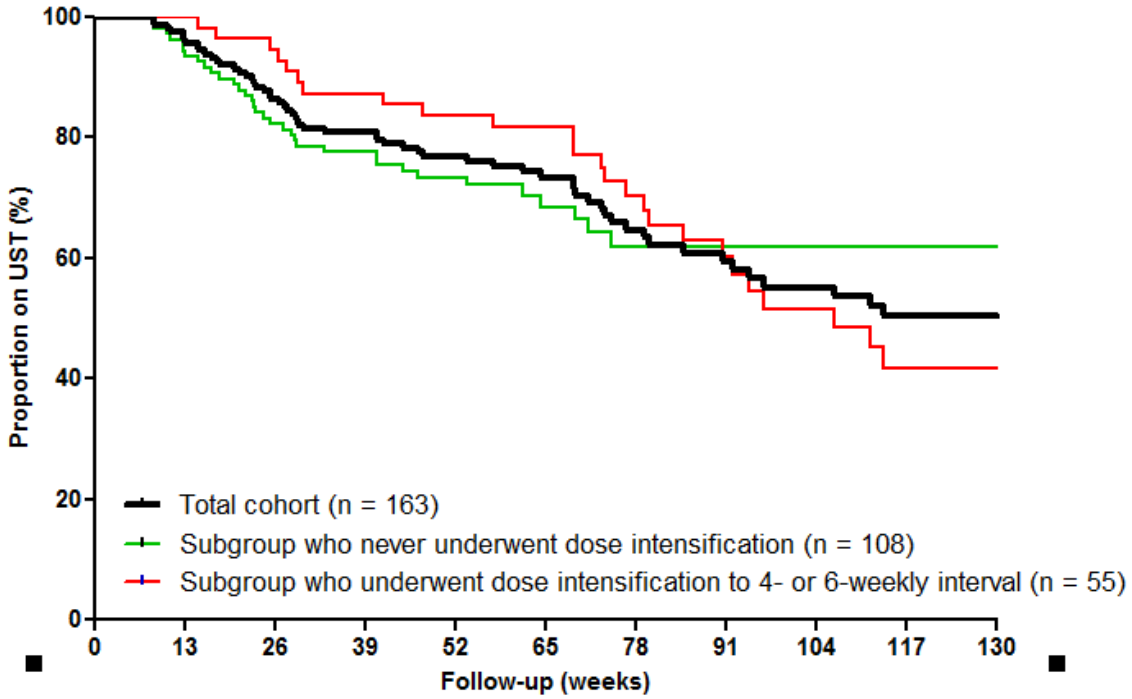

Kennedy NA et al Lancet Gastroenterol Hepatol. 2019 May;4(5):341-353. doi: 10.1016/S2468-1253(19)30012-3. Epub 2019 Feb 27.

# Edinburgh IBD Unit USTE experience

## Dose intensification

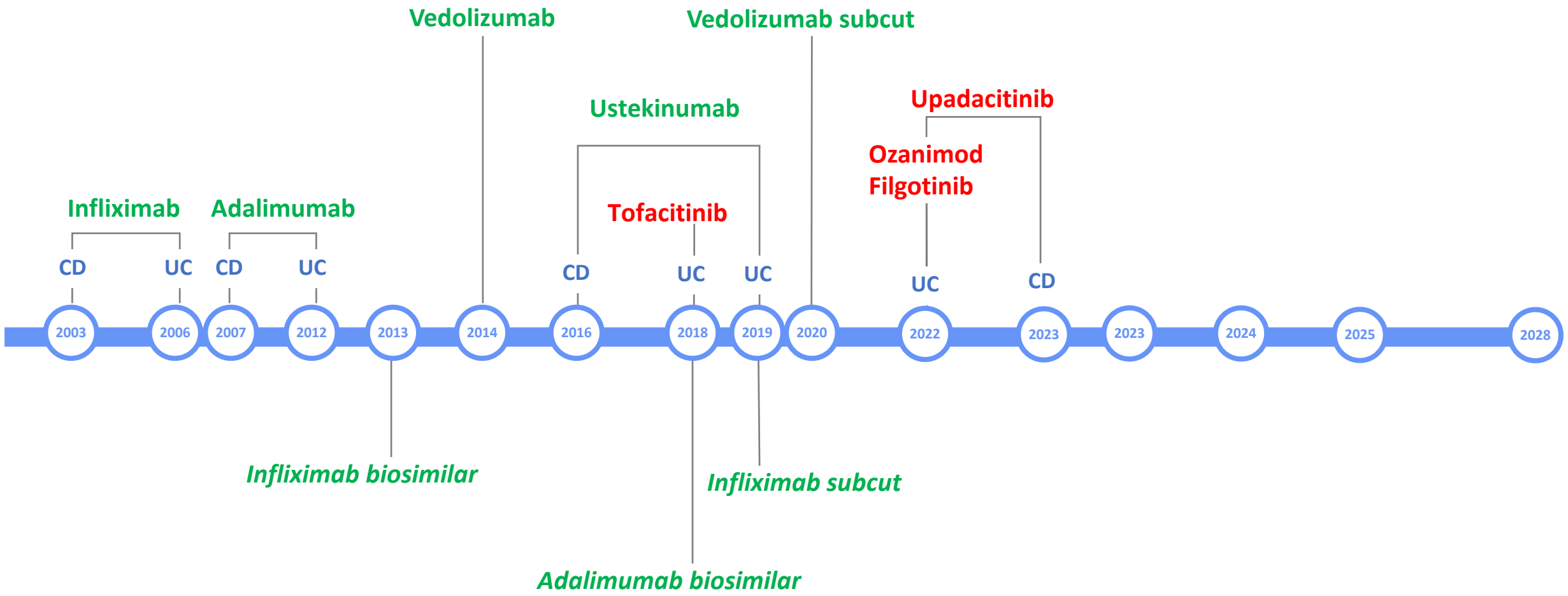



## Drug persistence




Derikix L et al ECCO 2022

# IBD-2.1


Vedolizumab
Vedolizumab subcut
Ustekinumab
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Ozanimod
Filgotinib
Infliximab
Adalimumab
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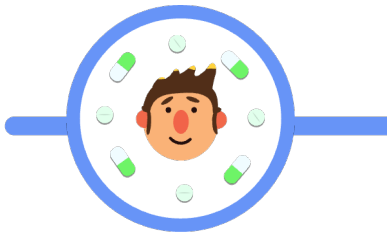
Infliximab biosimilar
Infliximab subcut
Adalimumab biosimilar

# IBD-2.2

Symptomatic response

**Active IBD**

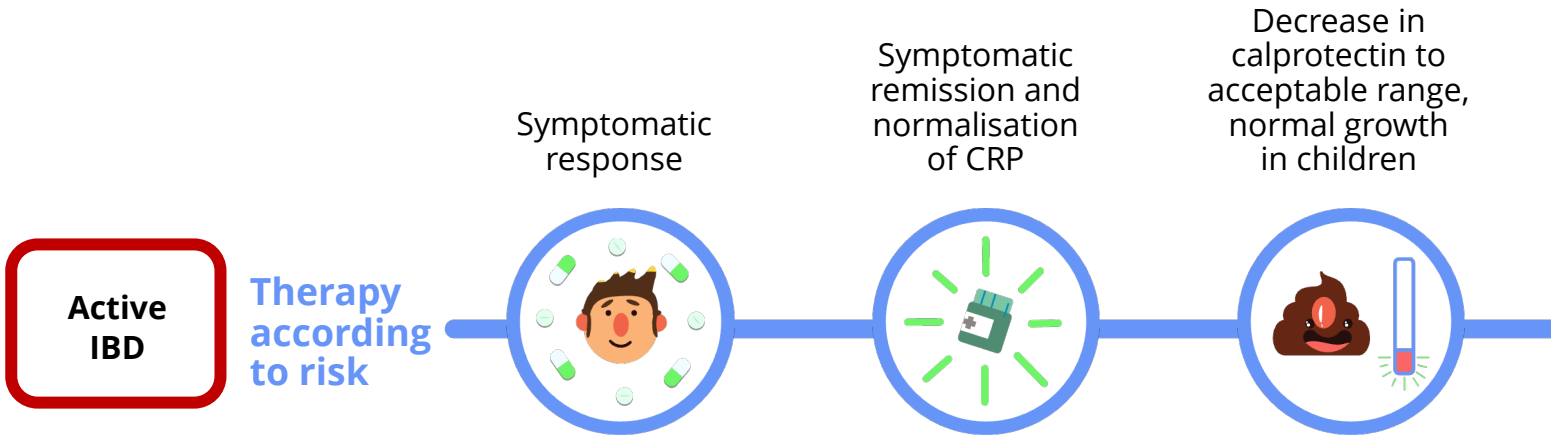
**Therapy according to risk**



Short-term targets →

Turner D, et al. *Gastroenterology* 2021

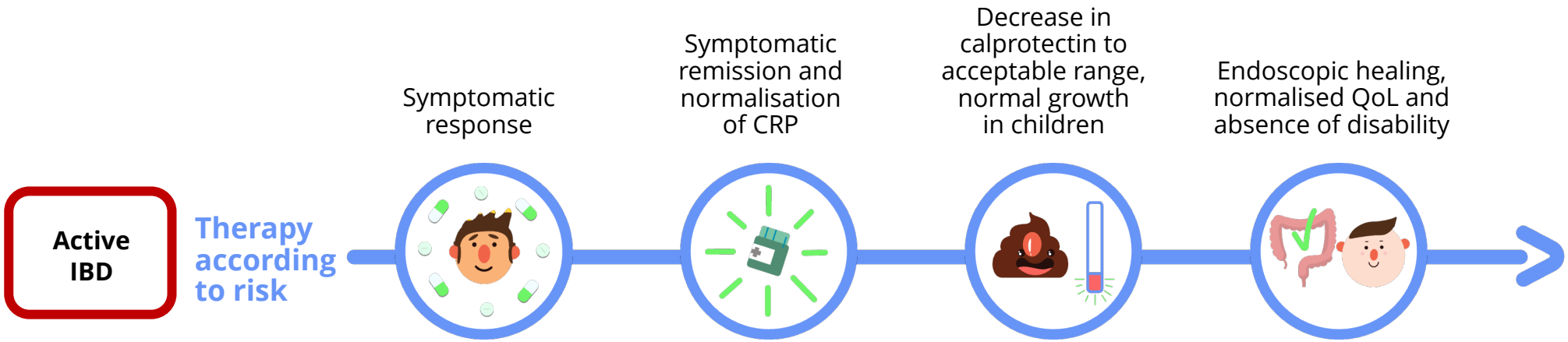
# Treat to target in IBD




Short-term targets → Intermediate targets →

Turner D, et al. *Gastroenterology* 2021

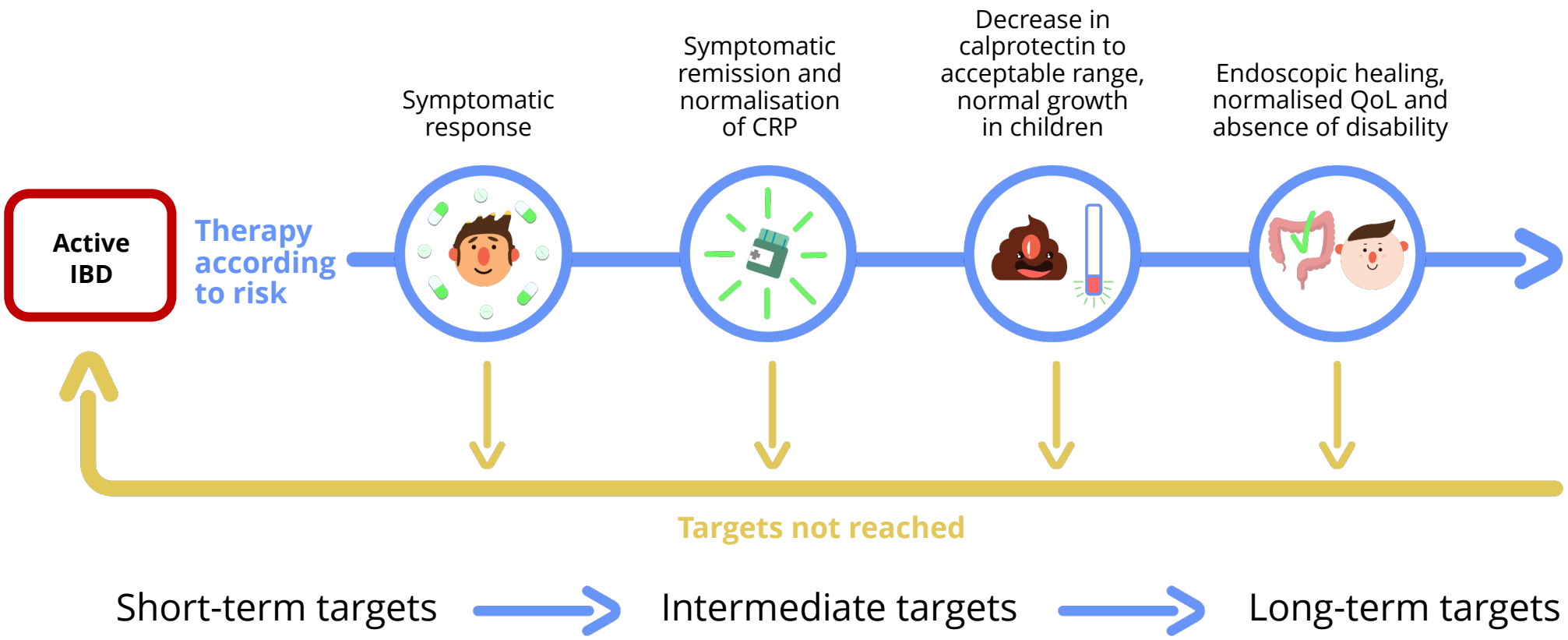
# Treat to target in IBD




Short-term targets → Intermediate targets → Long-term targets

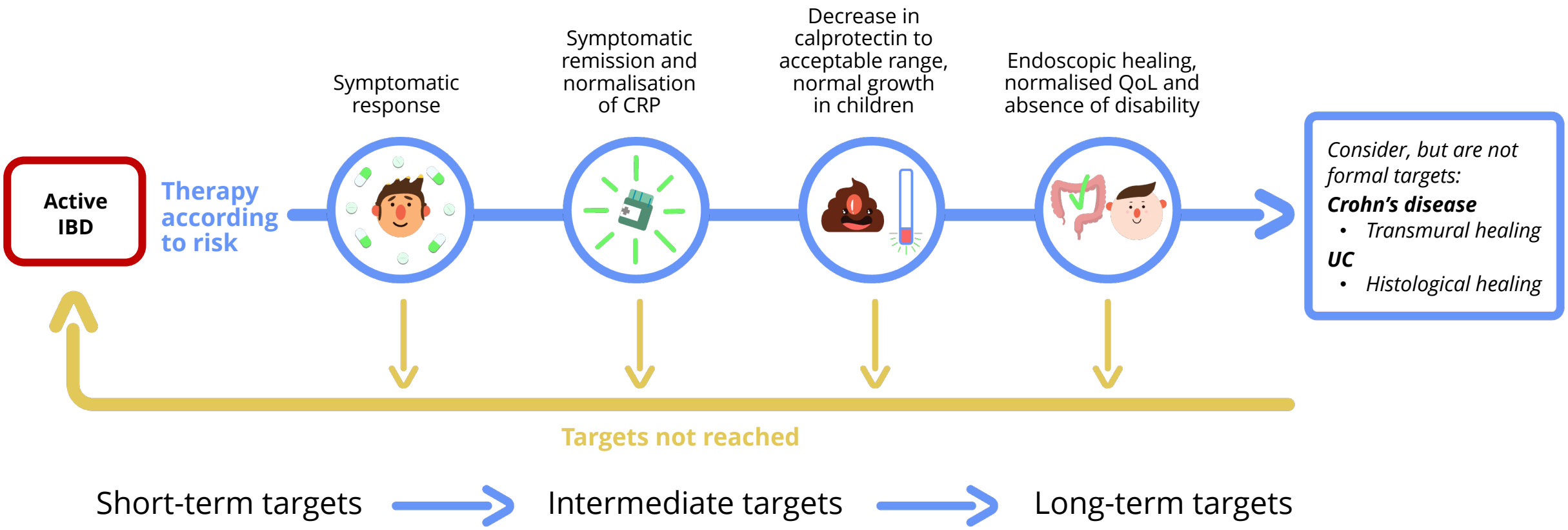
Turner D, et al. *Gastroenterology* 2021

# Treat to target in IBD



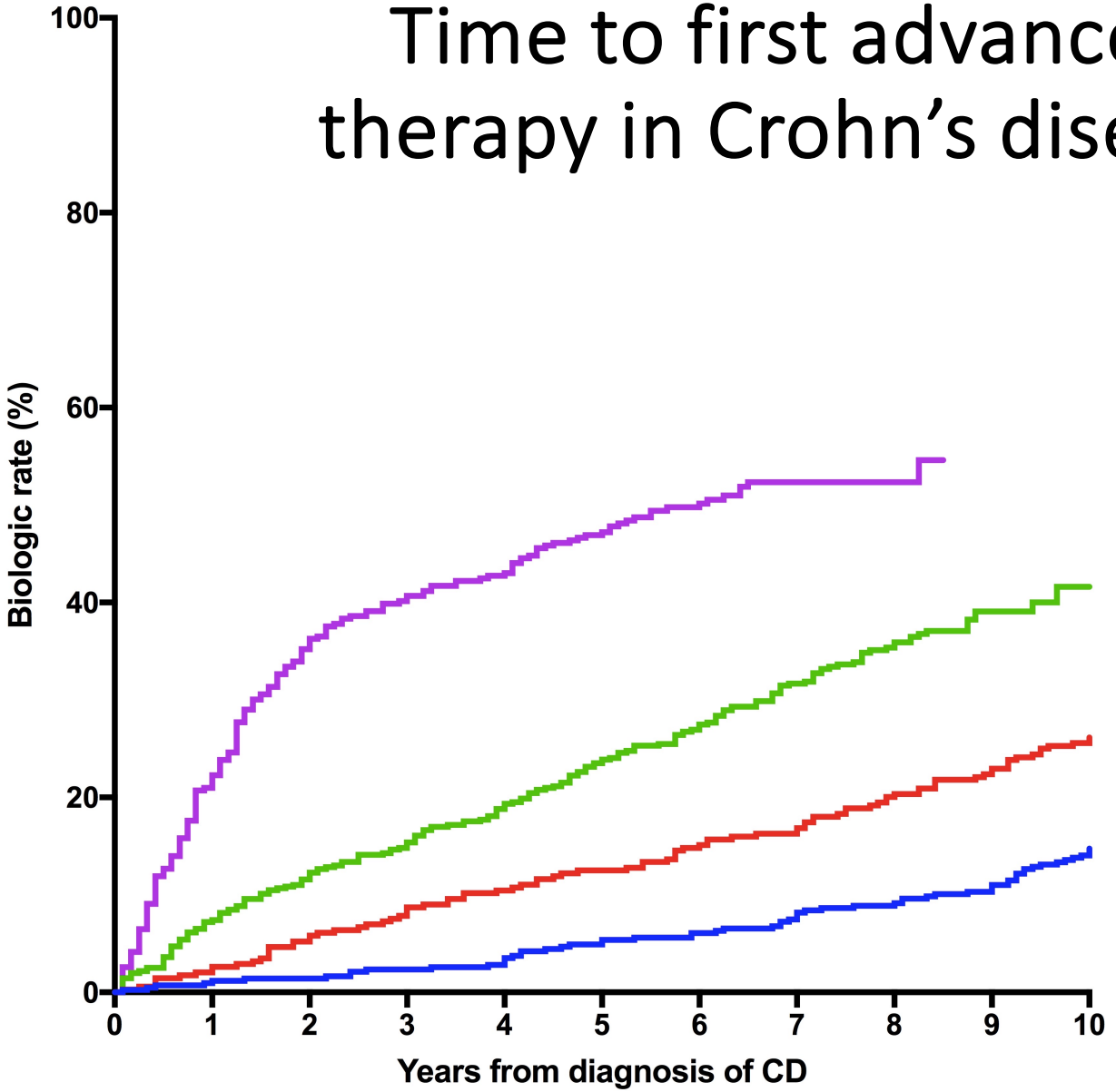

Turner D, et al. *Gastroenterology* 2021

# Treat to target in IBD



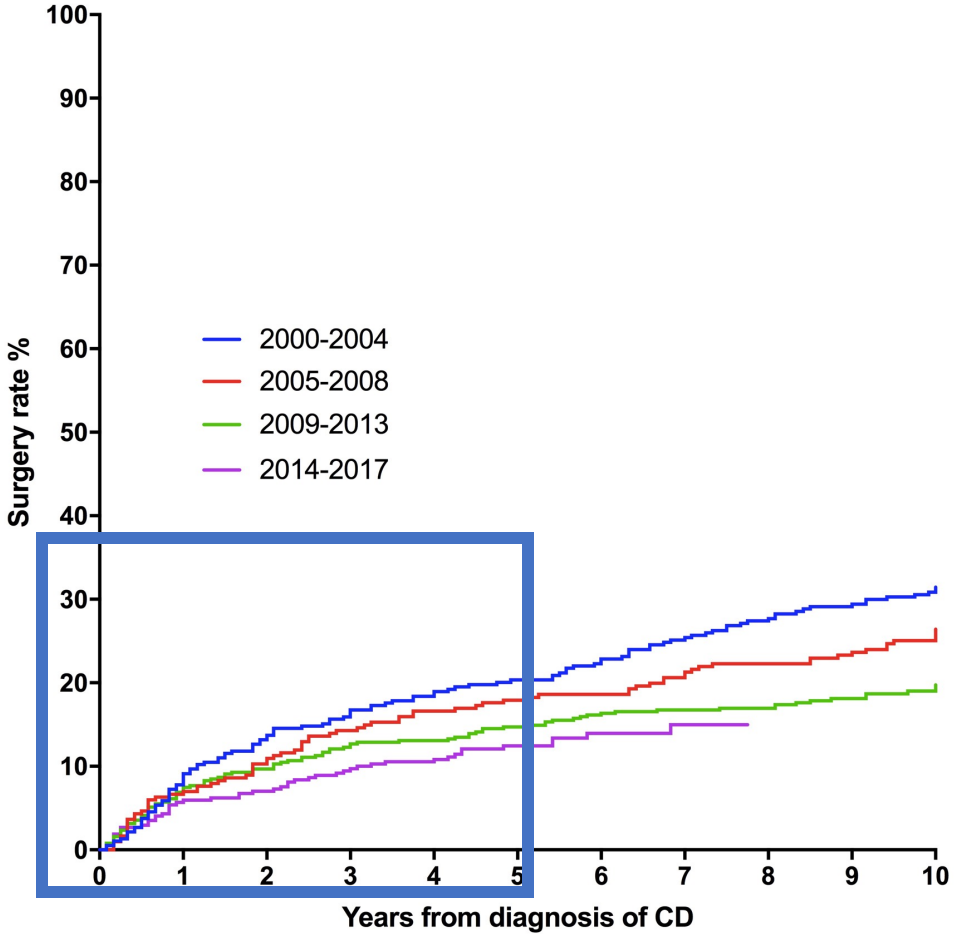

Turner D, et al. *Gastroenterology* 2021

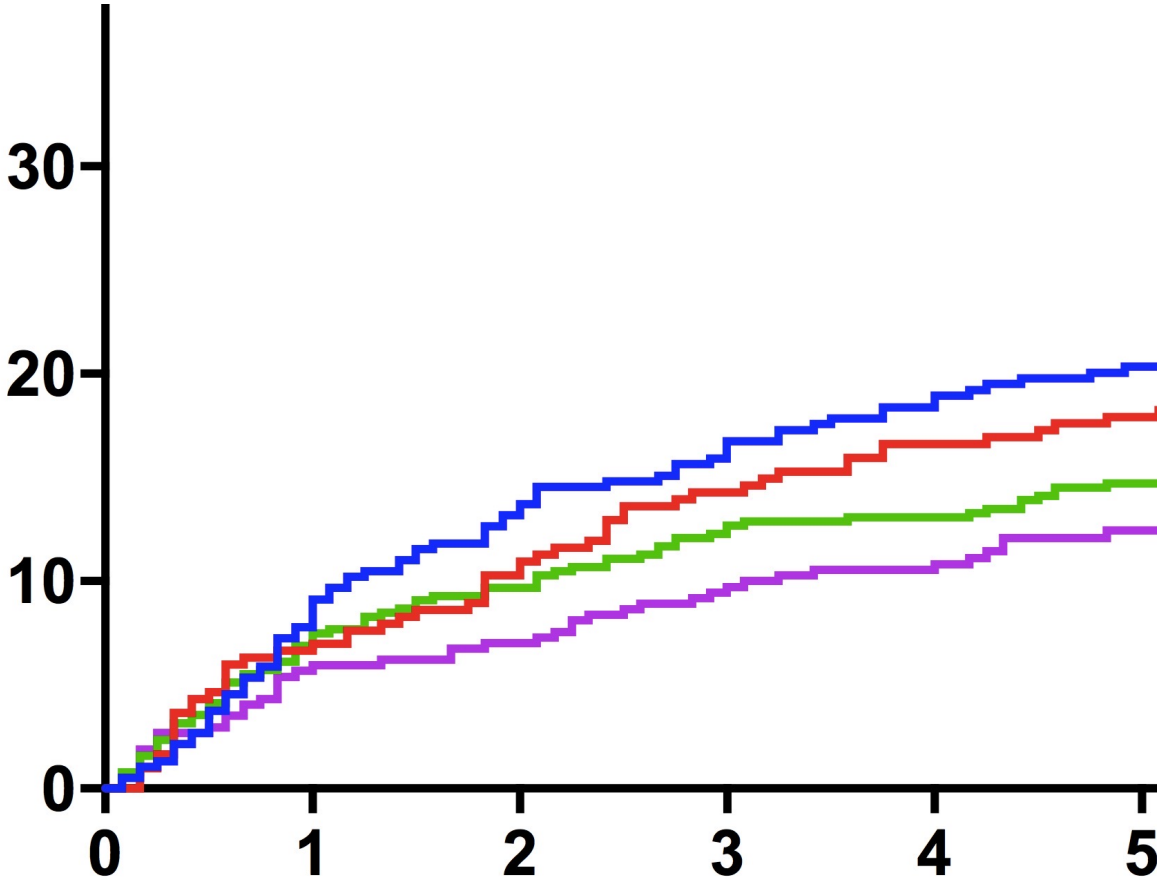
# Time to first advanced therapy in Crohn's disease




Jenkinson P et al *Journal Crohn's Colitis* 2020

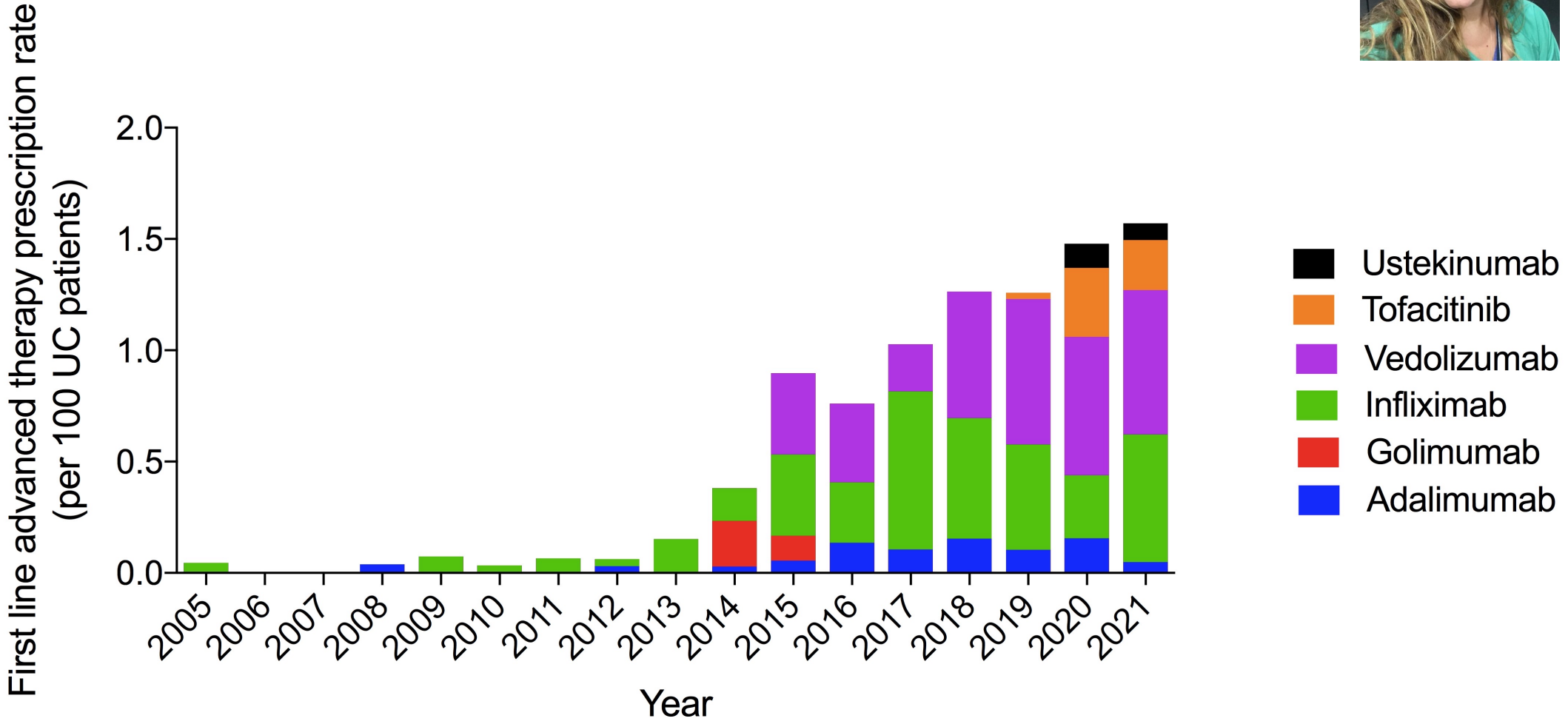
# Time to first resectional surgery in Crohn's disease




Jenkinson P et al *Journal Crohn's Colitis* 2020

# Lothian IBD Registry UPDATE: UC
# FIRST-LINE ADVANCED THEARPY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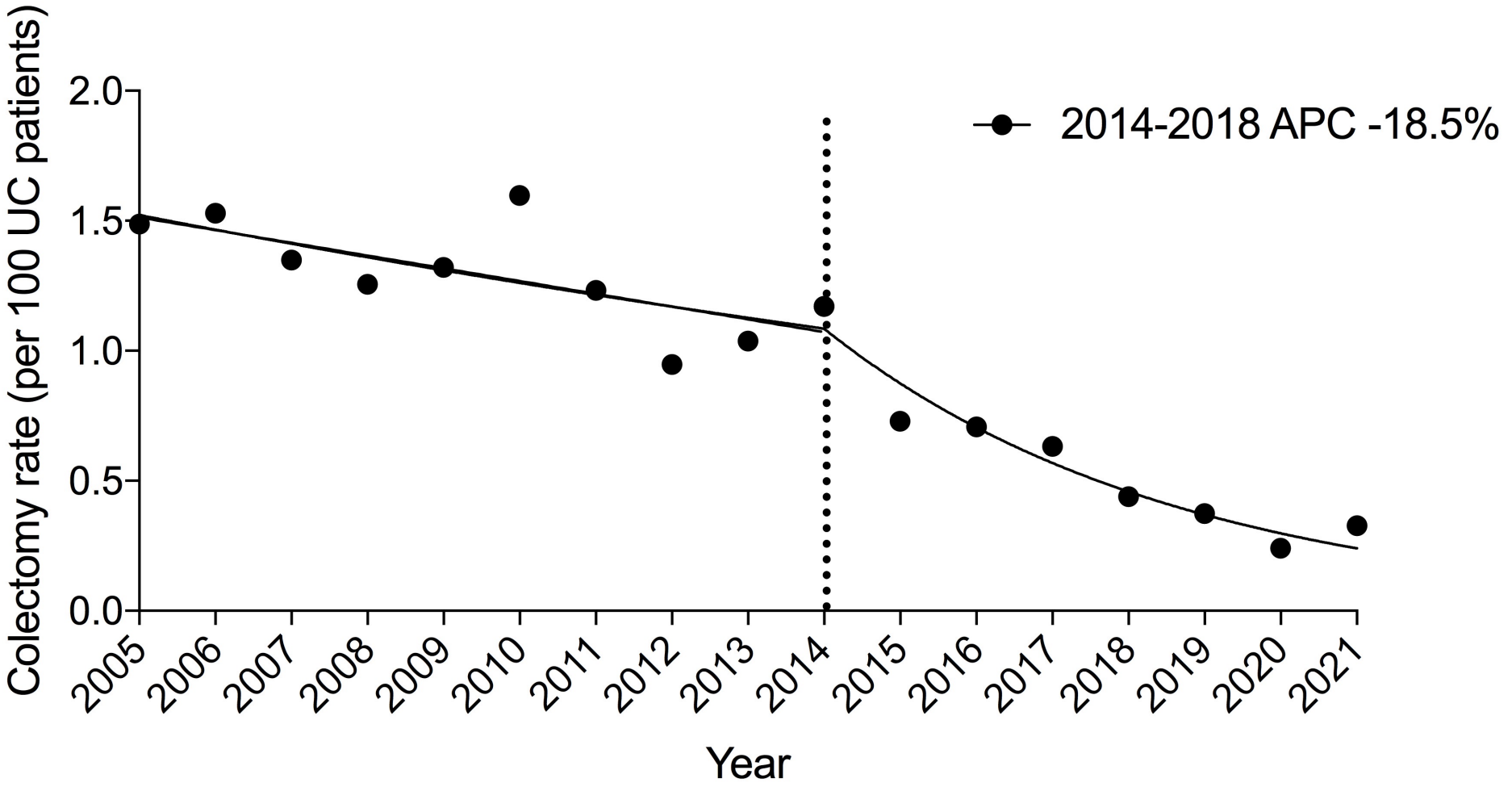
Based on clinician's own data

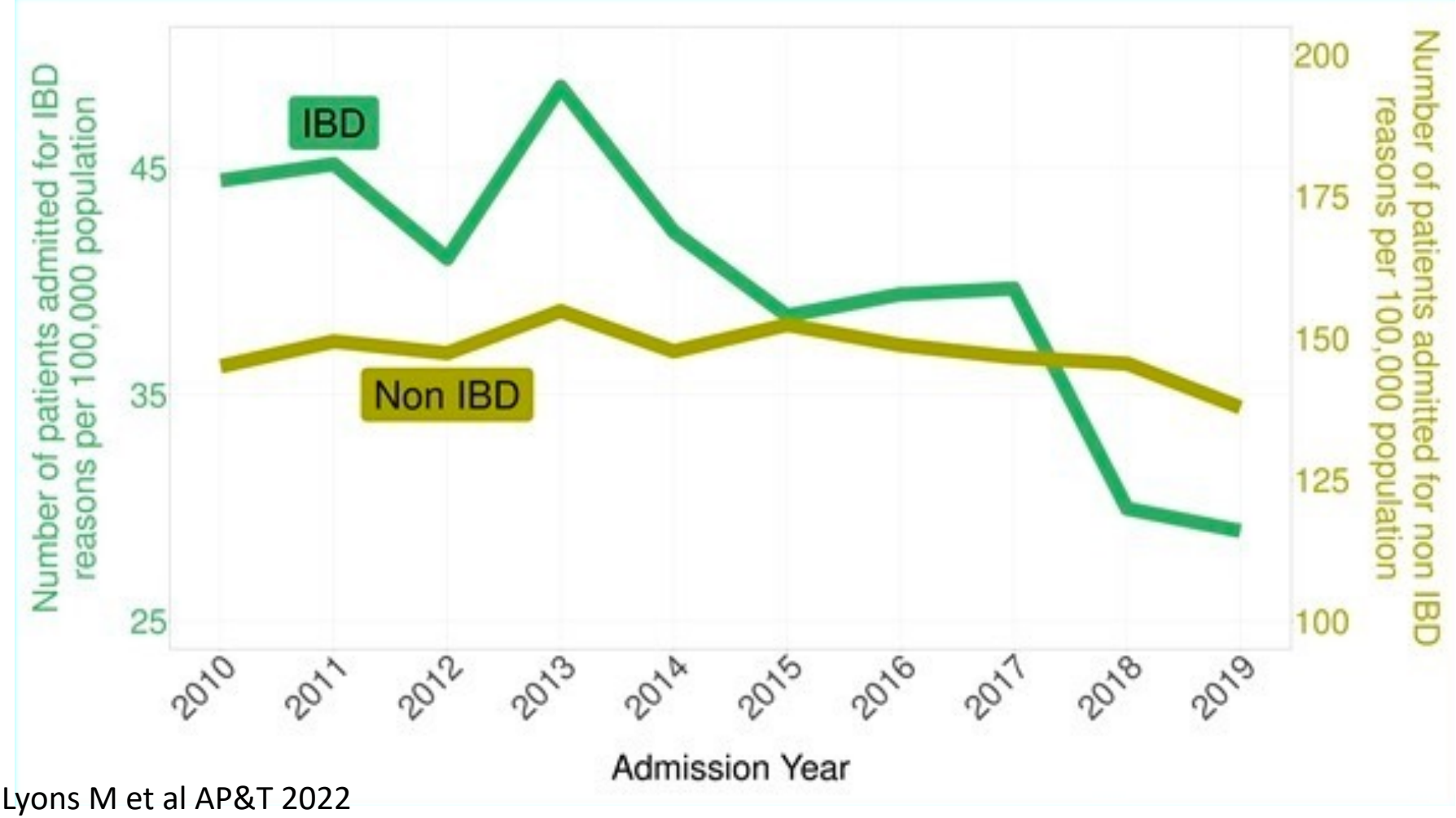
# Lothian IBD Registry UPDATE

## Colectomy for UC: temporal trends



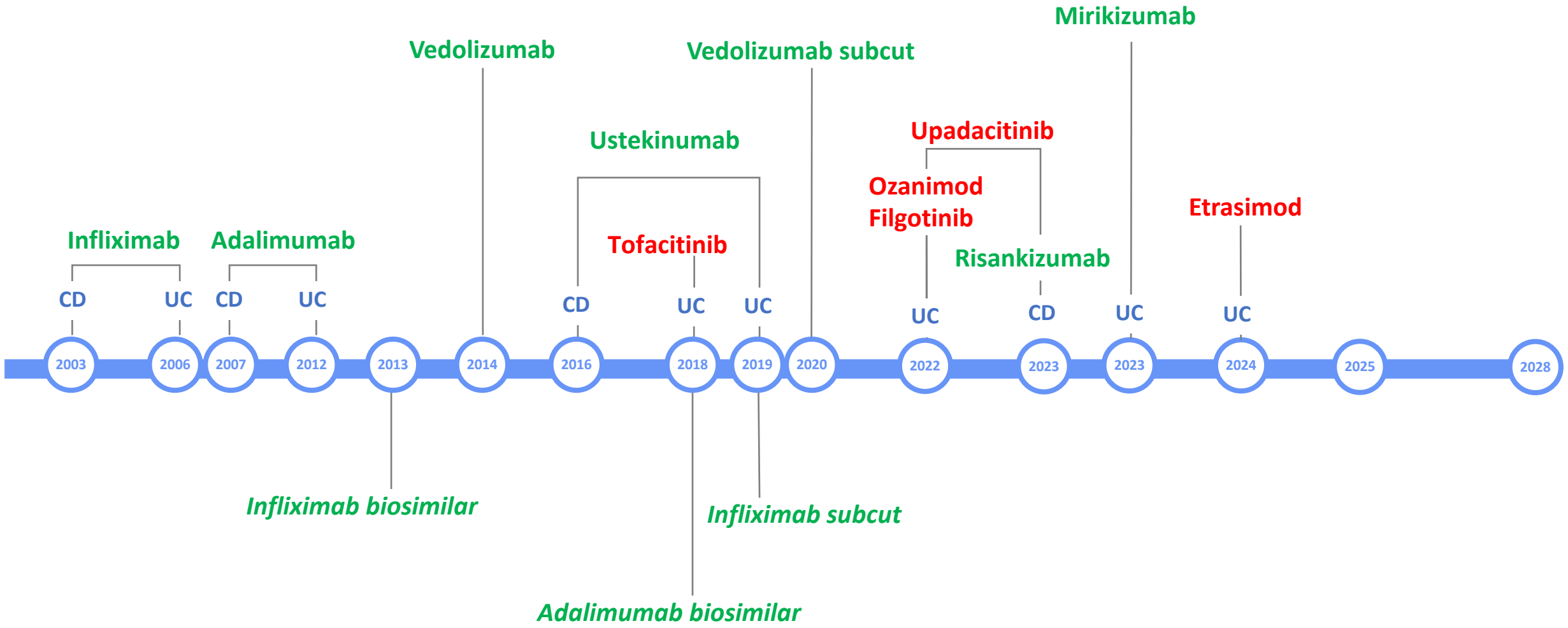

Jenkinson P et al ECCO 2022

# 10-year trends in hospitalisations in the Lothian IBD population




Lyons M et al AP&T 2022

# IBD-2.3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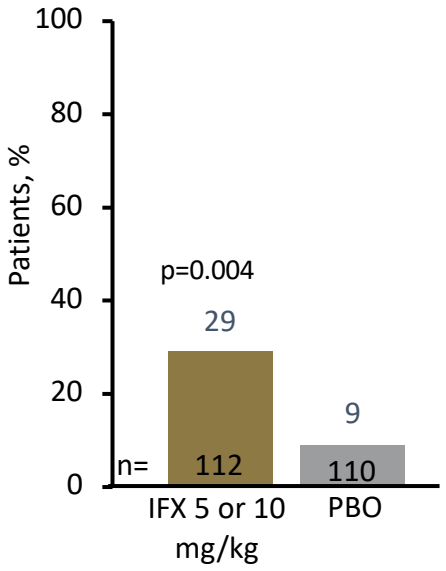
Infliximab biosimilar
Infliximab subcut
Adalimumab biosimilar

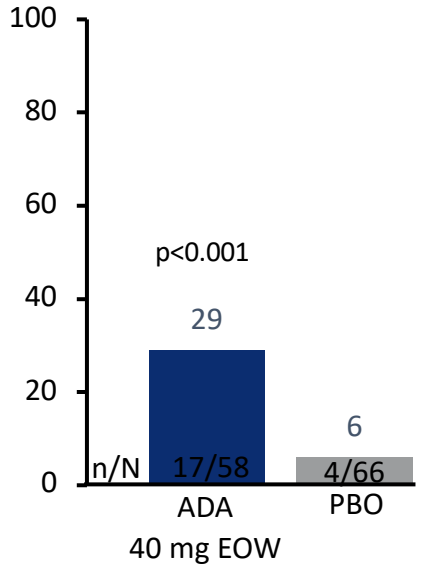
# Steroid-free remission in Crohn's disease trials

## Infliximab[1]
SFR at Week 54



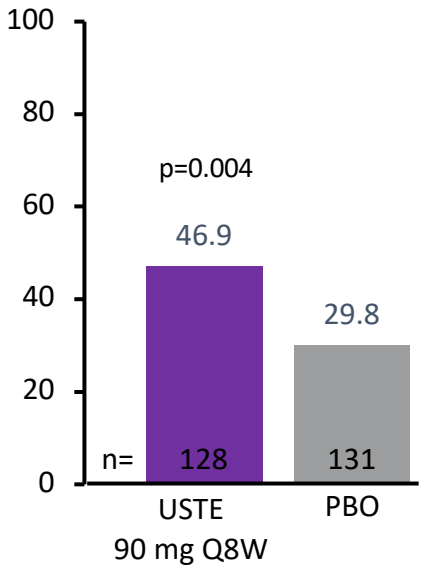

Discontinuation of CS while in clinical remission

## Adalimumab[2]
SFR at Week 56



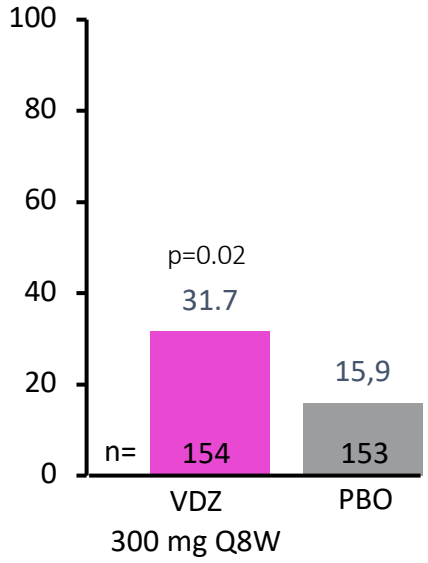

Clinical remission at Week 56 and able to discontinue CS

## Ustekinumab[3]
SFR at Week 44



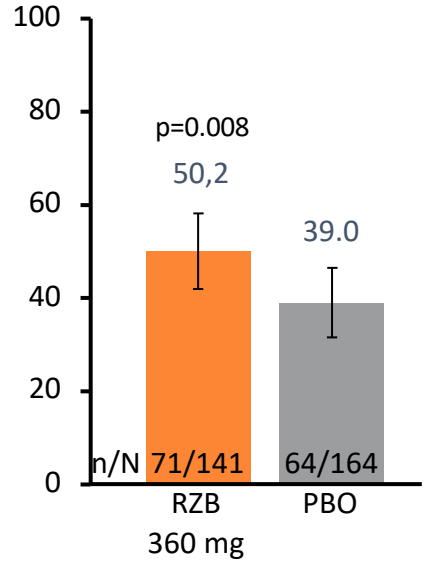

Not defined in publication

## Vedolizumab[4]
SFR at Week 52




Clinical remission at Week 52 without glucocorticoid therapy

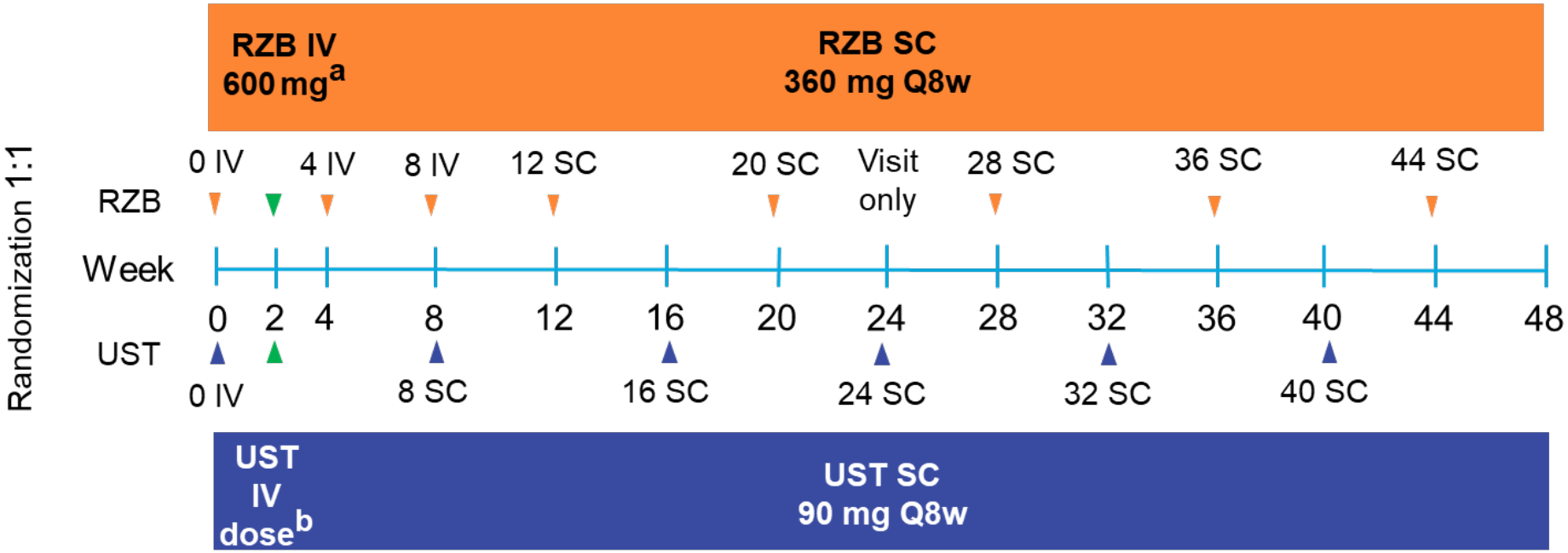
## Risankizumab[5]
SFR at Week 52
*Post-hoc analysis*




Absence of CS use at the time of endpoint assessment

ADA, adalimumab; CS, corticosteroid; EOW, every other week; IFX, infliximab; PBO, placebo; Q8W, every 8 weeks, RZB, risankizumab; SFR, steroid-free remission; USTE, ustekinumab; VDZ, vedolizumab.
Figures adapted from 1. Hanauer SB, et al. *Lancet*. 2002;359;1541–9; 2. Colombel JF, et al. *Gastroenterology*. 2007;132:52–65; 3. Feagan BG, et al. *N Engl J Med*. 2016;375:1946–60;
4. Sandborn WJ, et al. *N Engl J Med.* 2013;369:711–21; 5. Schreiber S, et al. Presented at the 17th Congress of the European Crohn's and Colitis Organisation, Virtual: DOP82.

# SEQUENCE: RZB versus UST in Crohn's disease




▲ Mandatory steroid taper beginning at week 2

**Stratification Factors:**

- Number of prior anti-TNF failure (1, > 1)
- Corticosteroid use at baseline (yes or no)]

## Key Eligibility Criteria

**Moderate to severe Crohn's disease**

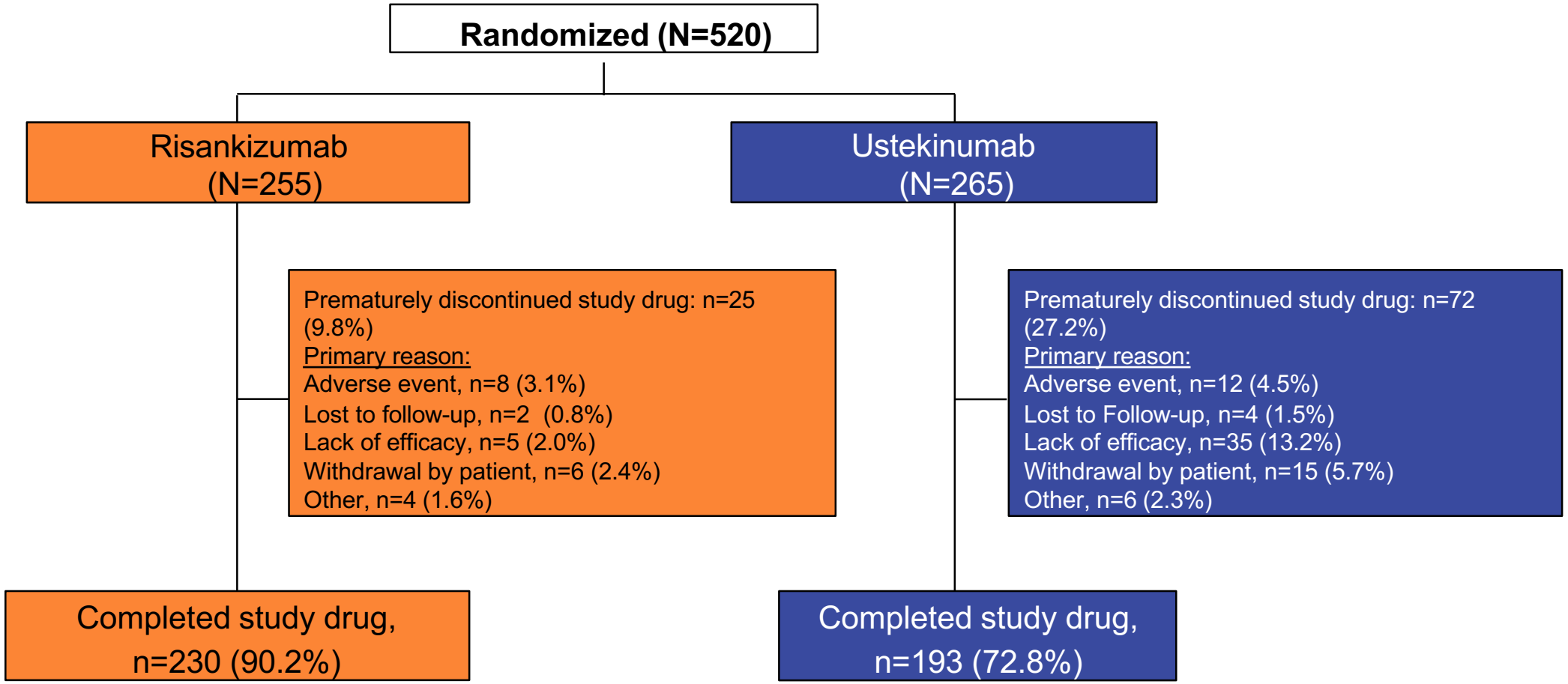
CDAI 220-450

Average daily SF ≥4 and/or average daily APS ≥2

SES-CD ≥6 (≥4 for isolated ileal disease)

**Prior failure of ≥1 anti-TNF therapies**

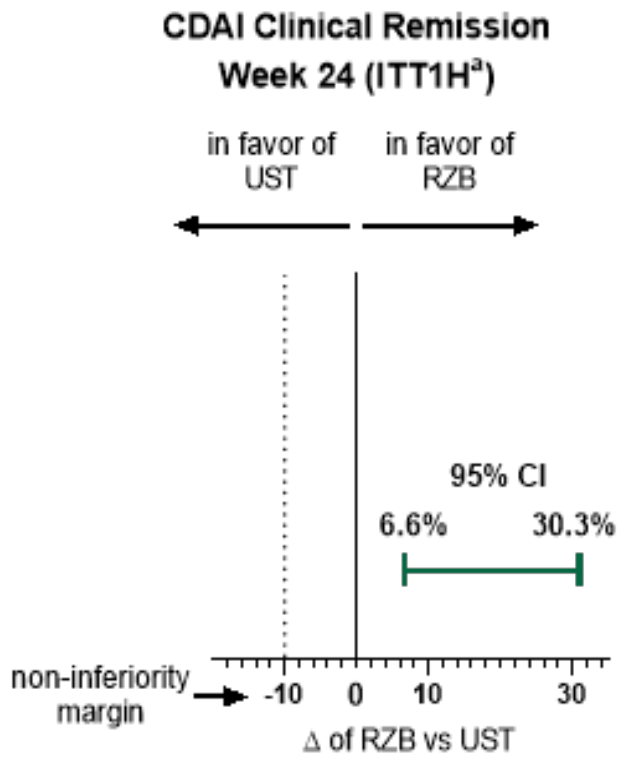
# **SEQUENCE:** Patient disposition (iTT population)

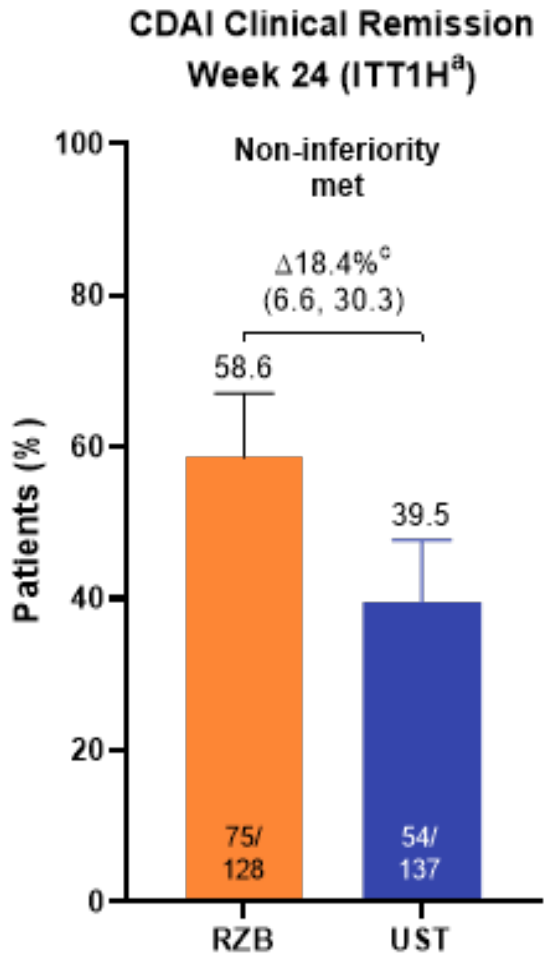


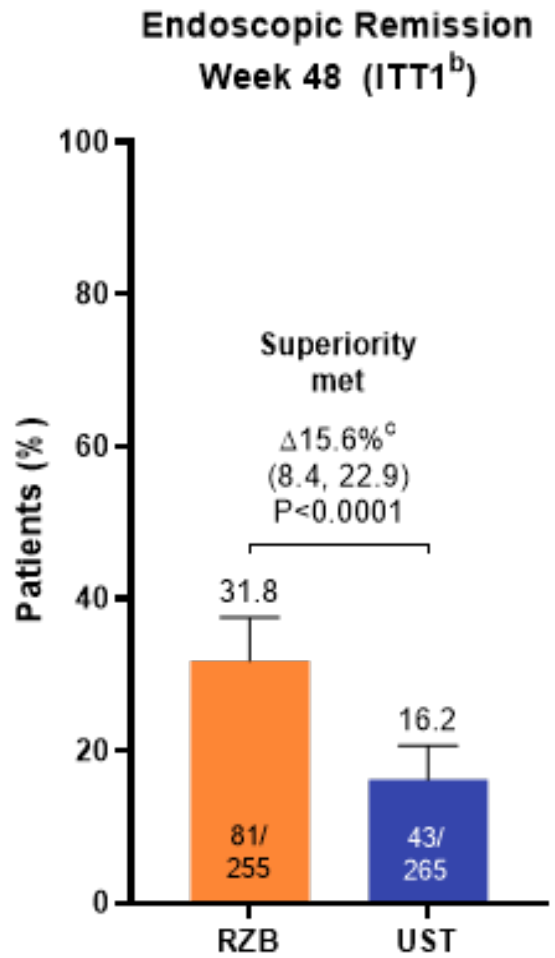

**Mean time to discontinuation of study drug:** RZB182.6 days versus UST 156.3 days

# **SEQUENCE:** primary endpoints

RZB non-inferior to UST for clinical remission at week 24 and
RZB superior to UST for endoscopic remission at week 48



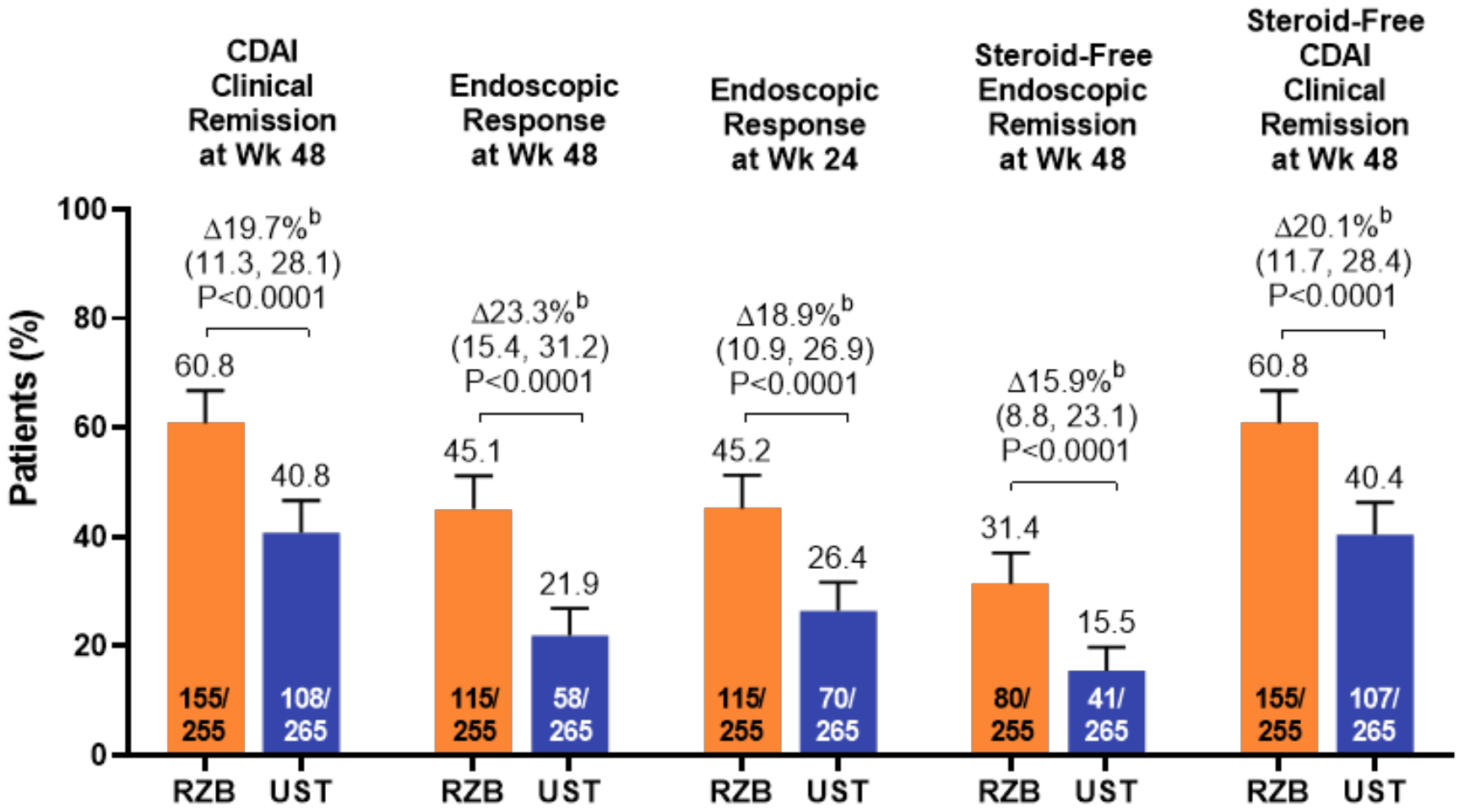



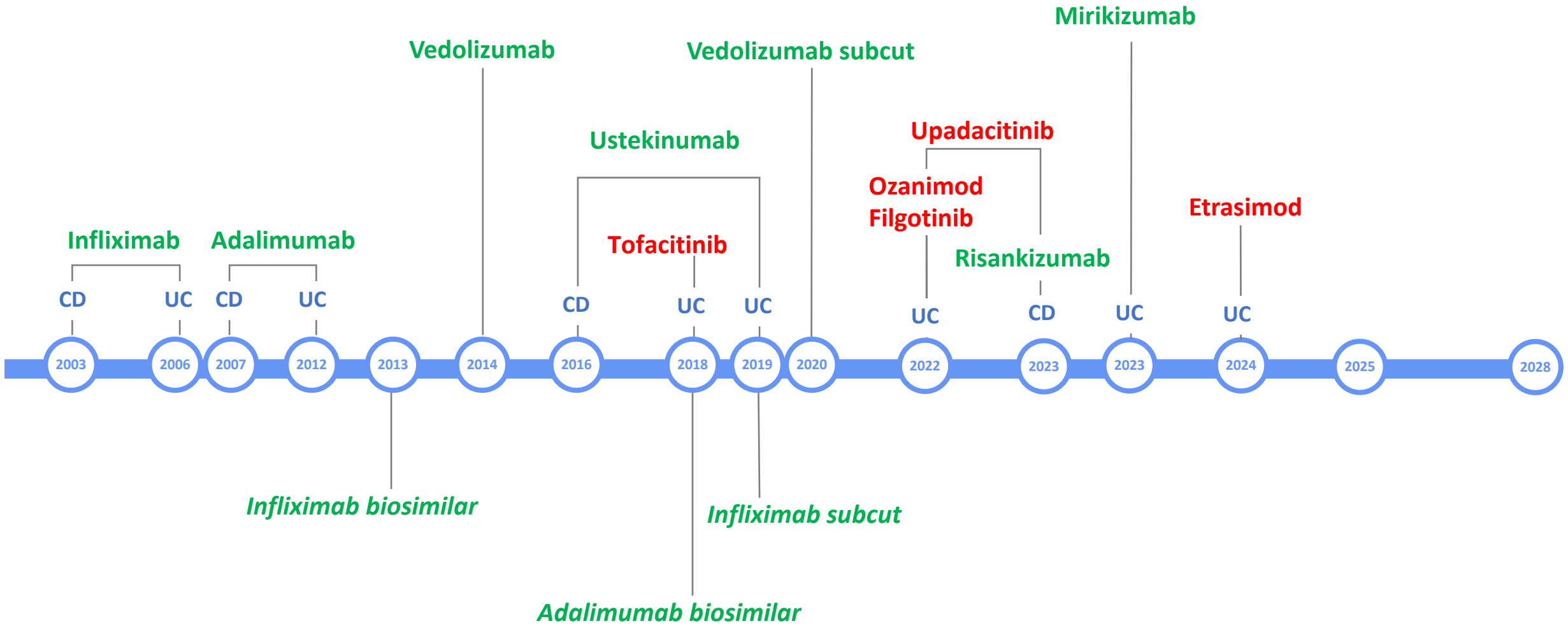

CDAI clinical remission: CDAI < 150
Endoscopic remission: SES-CD ≤ 4 and at least a 2-point reduction versus BL and no subscore > 1

# **SEQUENCE:** ranked secondary endpoints (ITT)

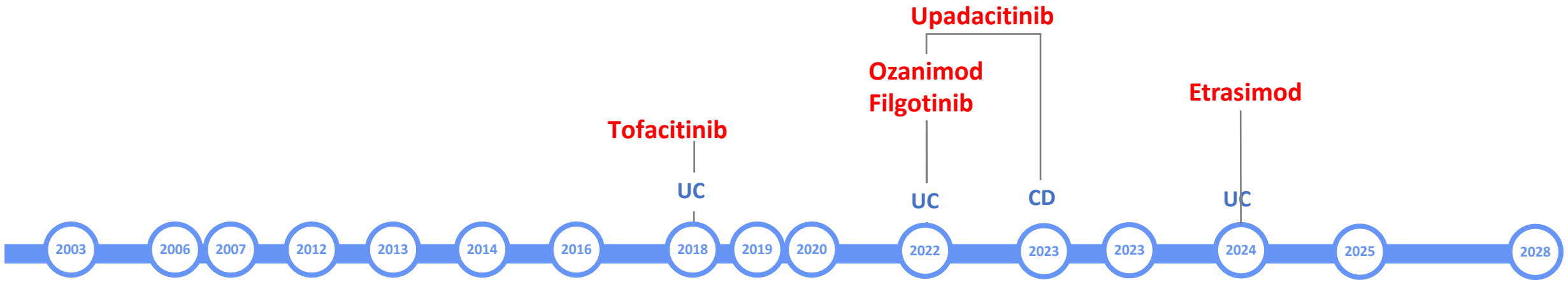
RZB demonstrated superiority to UST for all secondary endpoints



# IBD-2.3

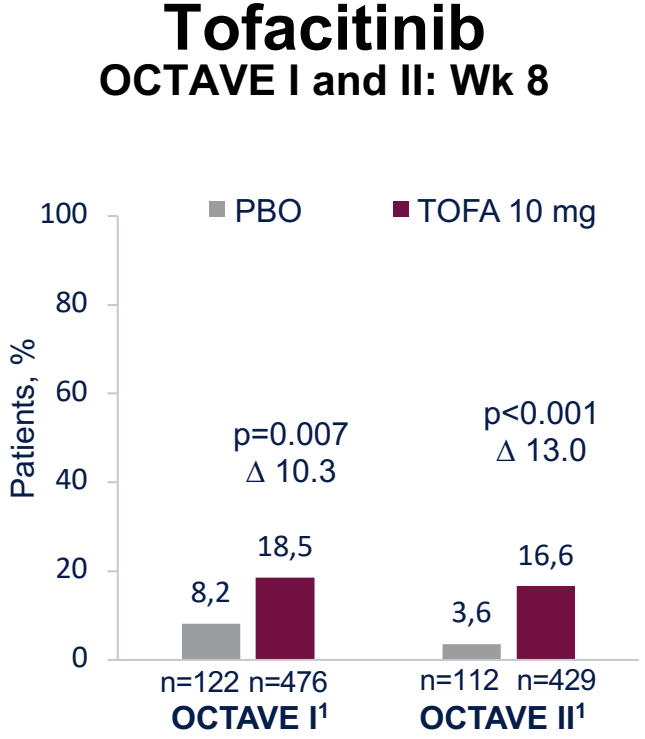

Mirikizumab
Vedolizumab
Vedolizumab subcut
Upadacitinib
Ustekinumab
Ozanimod
Filgotinib
Etrasimod
Infliximab
Adalimumab
Tofacitinib
Risankizumab
CD
UC
CD
UC
CD
UC
UC
CD
UC
UC
2003
2006
2007
2012
2013
2014
2016
2018
2019
2020
2022
2023
2023
2024
2025
2028
Infliximab biosimilar
Infliximab subcut
Adalimumab biosimilar

# IBD-2.4


Upadacitinib
Ozanimod
Filgotinib
Etrasimod
Tofacitinib
UC
UC
CD
UC
2003
2006
2007
2012
2013
2014
2016
2018
2019
2020
2022
2023
2023
2024
2025
2028

# **JAK inhibitors in UC:** clinical remission after induction

***Note: This is not a head-to-head comparison of different therapies***

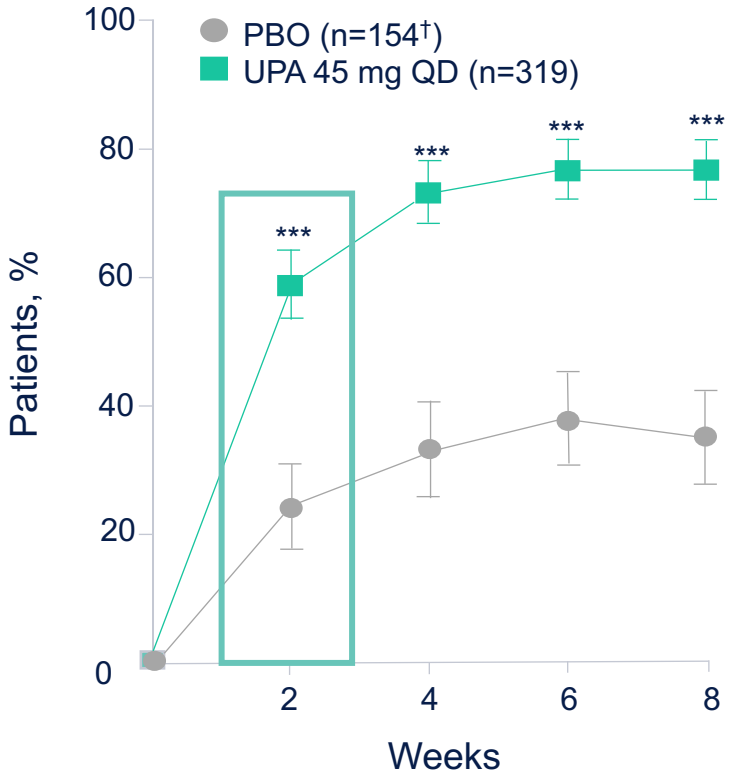


# **UPA in UC:** clinical response rates during induction

Clinical response at Week 2 is one of the ranked secondary endpoints

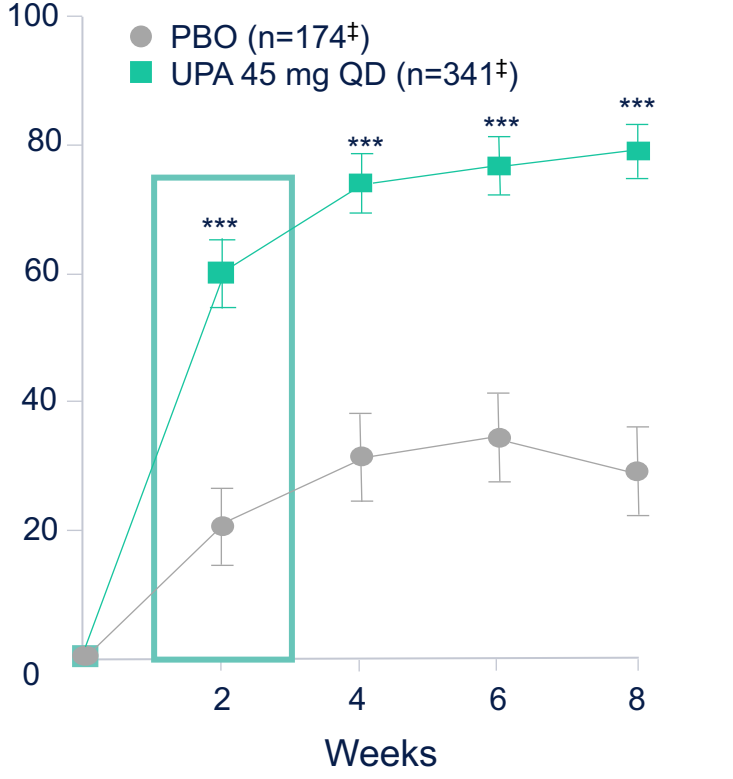
U-ACHIEVE M14-234

**Clinical response (per partial adapted Mayo Score) over time[1]**

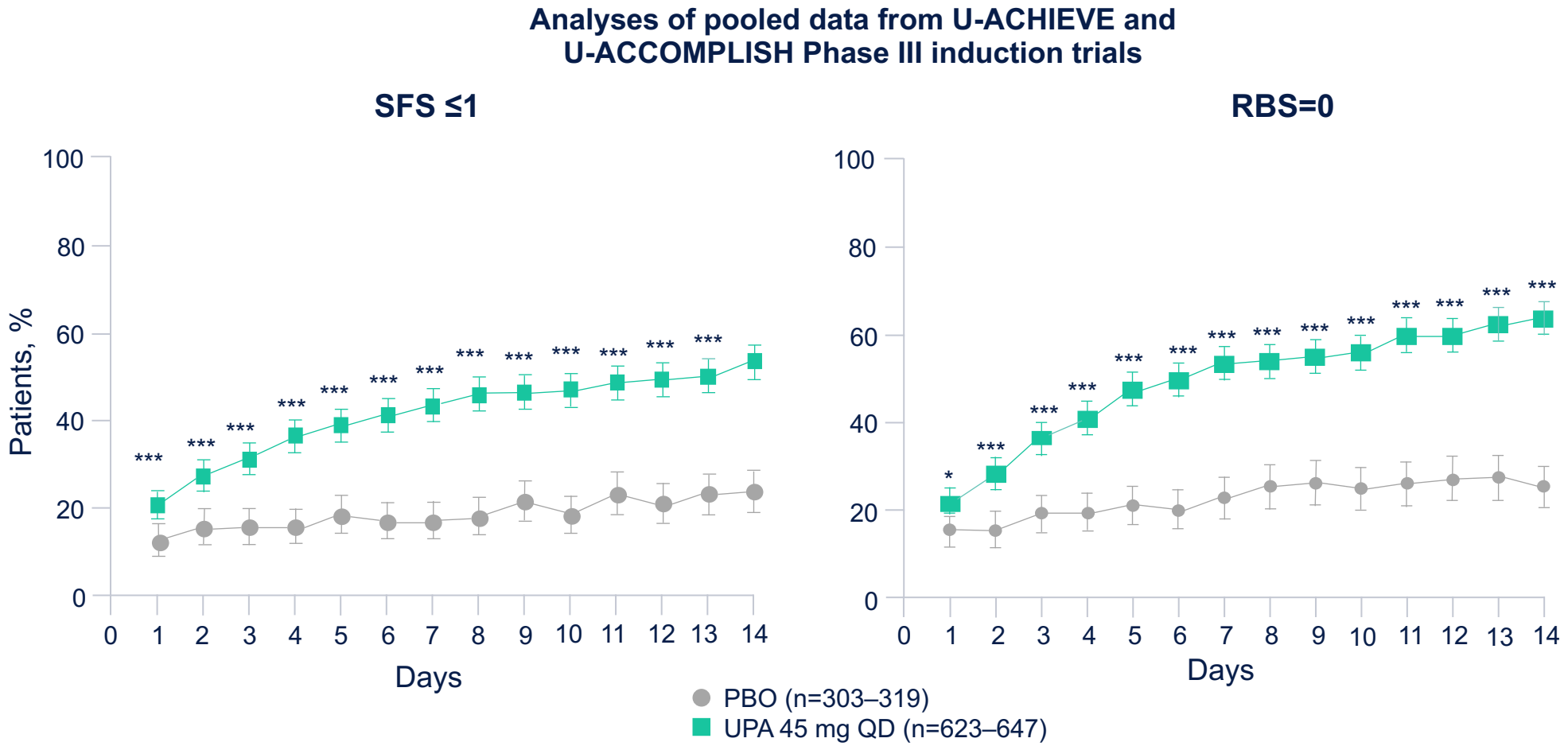



U-ACCOMPLISH M14-675

**Clinical response (per partial adapted Mayo Score) over time[2]**



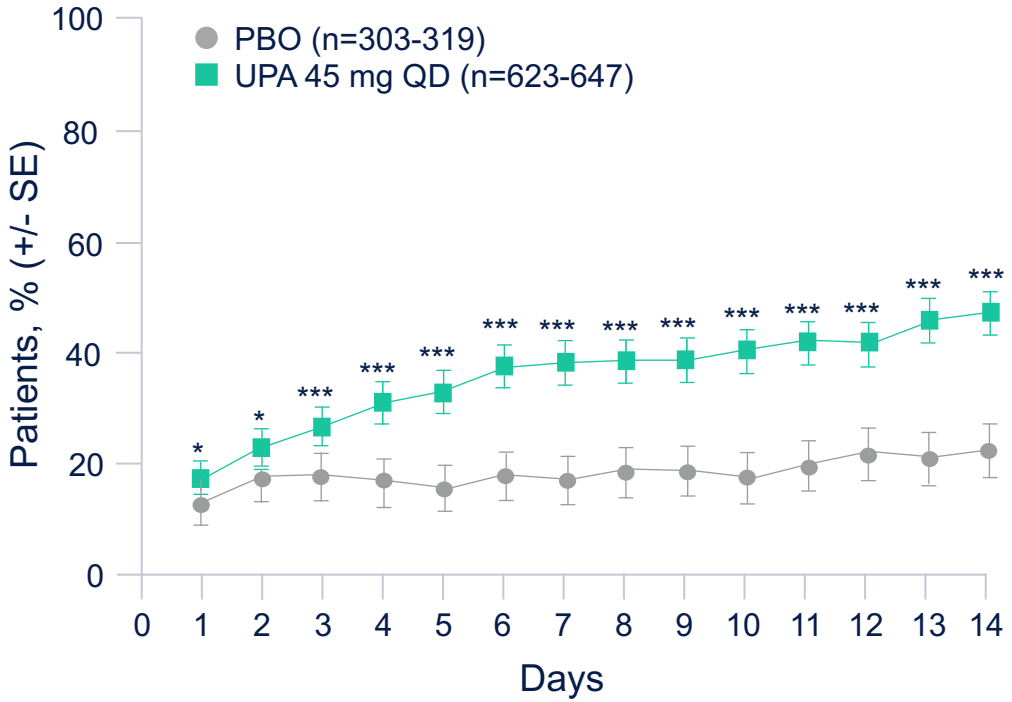
# **UPA in UC:** symptom improvement in first days



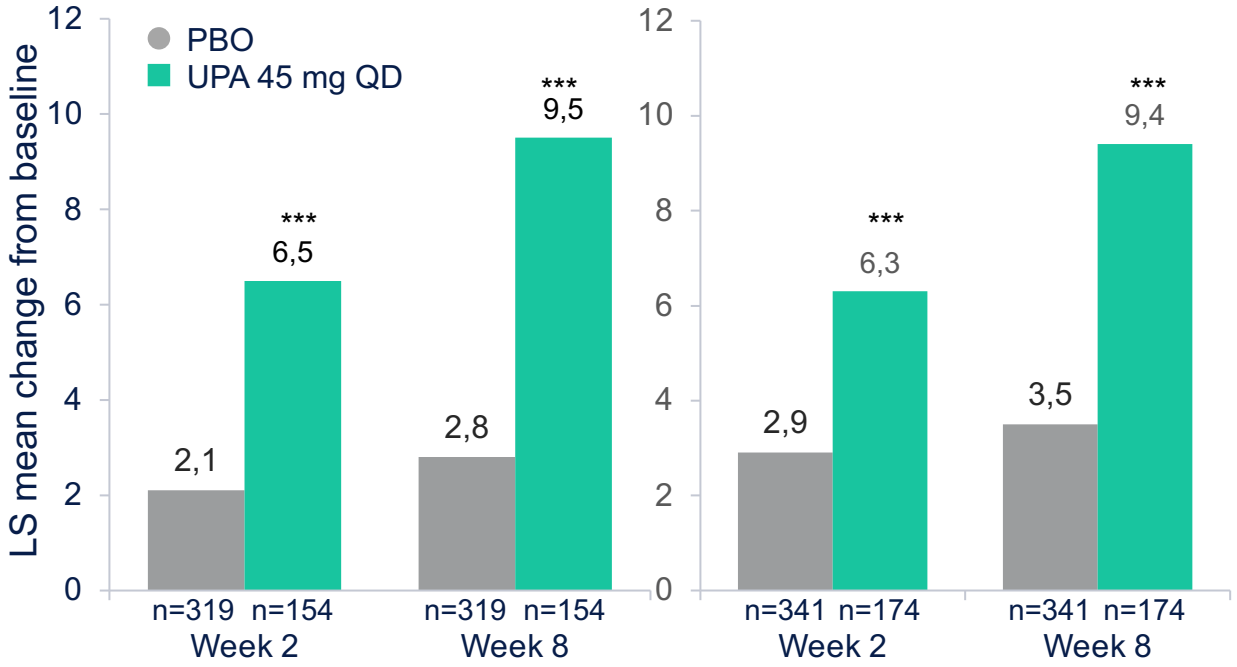
# **UPA in UC:** bowel urgency and fatigue during induction

**Analyses of pooled data from U-ACHIEVE and U-ACCOMPLISH Phase III induction trials**

## Absence of bowel urgency[1†]

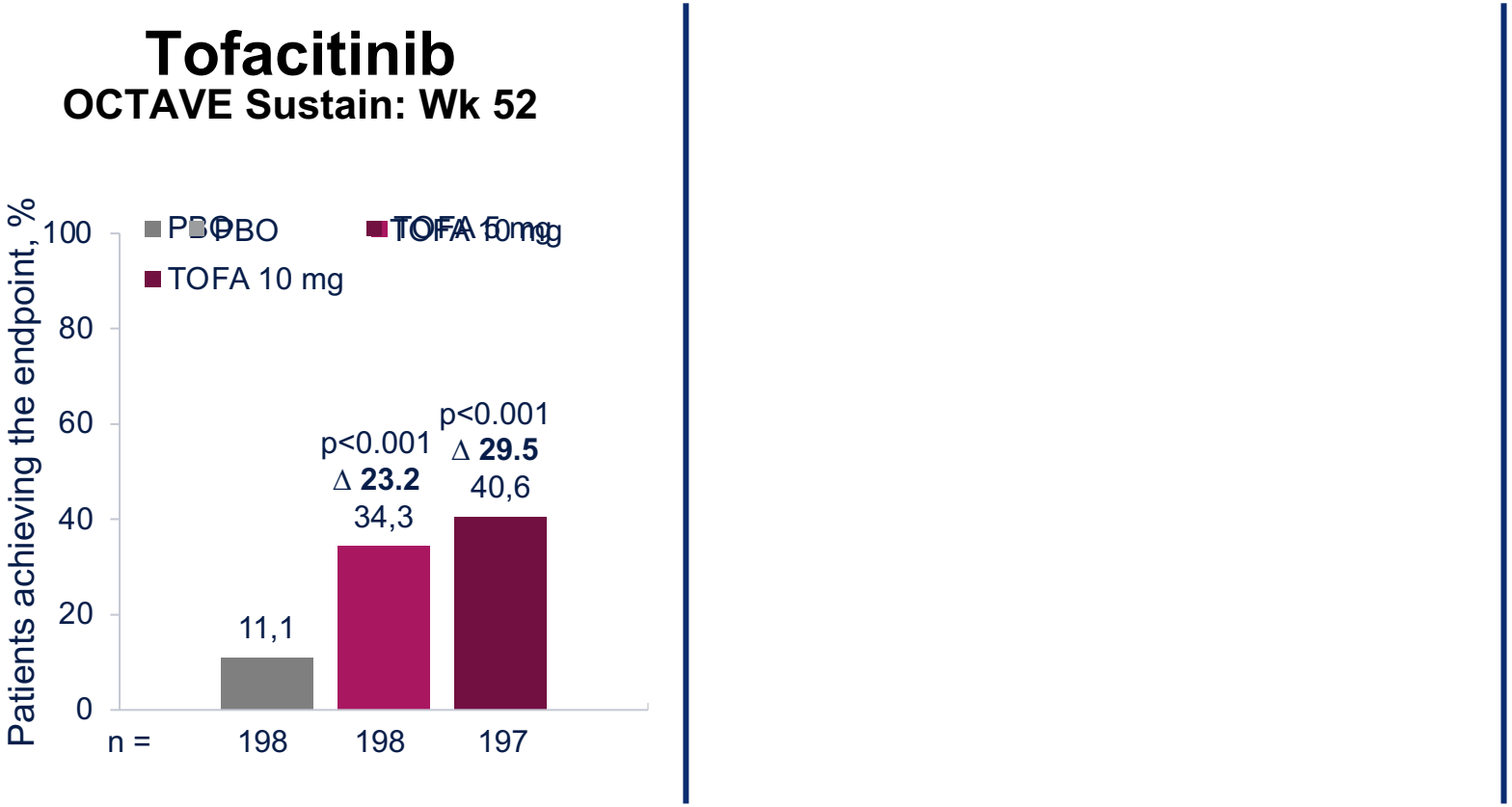



## Change from baseline in FACIT-F[2]



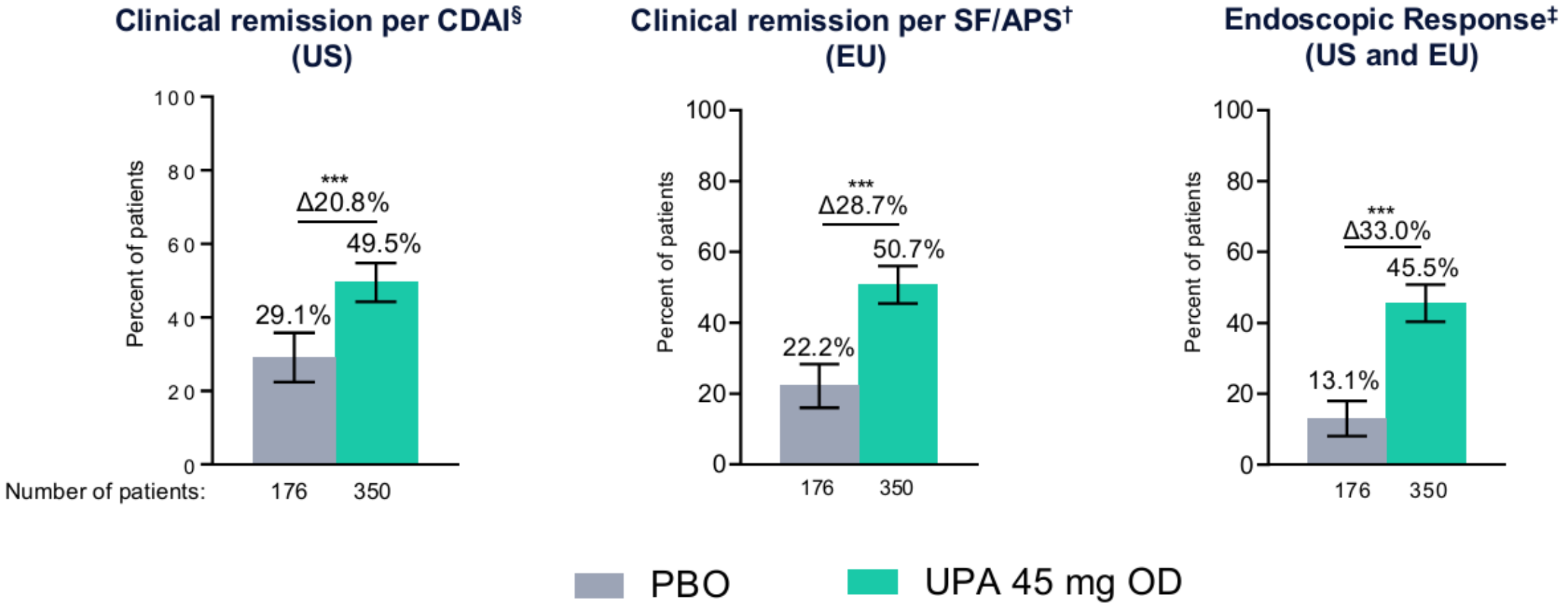
# **JAK inhibitors in UC:** clinical remission at 1 year

***Note: This is not a head-to-head comparison of different therapies***



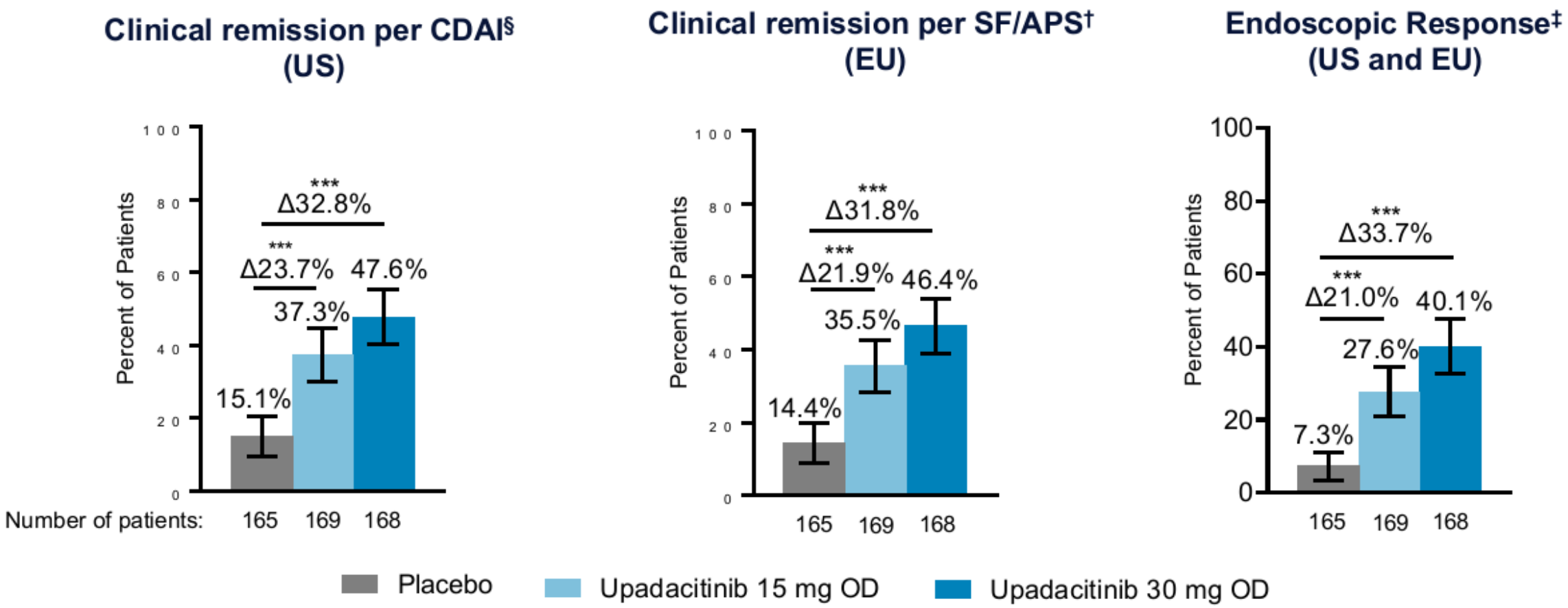
# **UPA in Crohn's**: co-primary data week 12

U-EXCEL CD M14-433

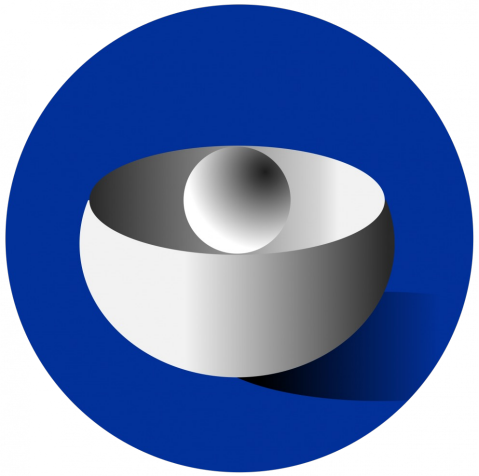


# **UPA in Crohn's**: co-primary maintenance data

U-ENDURE CD M14-430



# PRAC Article 20



CHMP has endorsed the recommendations by the PRAC to miminise the risk of Serious side effects from JAK inhibitors used to treat multiple immune mediated diseases

These medicines (*) should only be used in the following patients where no other treatment options area available

- Aged 65 years or over
- Increased risk of major adverse cardiovascular outcomes
- Those who smoke or who have done for a long time in the past
- Use with caution in those with risk factors for clots in the lungs or deep veins (other than to those above)
- Doses should be decreased in those who are at risk for MACE, DVT or cancer where possible

*** EMA concluded that the identified risk applies to all JAK inhibitors approved for the treatment of chronic inflammatory disorders**

# ECCO Standpoint on JAK inhibitors


European Crohn's and Colitis Organisation

About ECCO Congresses & Events Membership

ECCO Standpoint on JAK inhibitors in IBD

S. DANESE, F. MAGRO, A. HART, J. VAN DER WOUDE, A. ARMUZZI, B. SIEGMUND, L. PEYRIN-BIROULET

In a recent randomized trial by Ytterberg and colleagues, called Oral Surveillance, patients with rheumatoid arthritis (RA) aged > 50 years and with at least an additional cardiovascular (CV) risk factor at baseline, treated with tofacitinib 5 or 10 mg twice daily experienced a higher proportion of major adverse cardiovascular events (MACE) and cancer compared with the control group (adalimumab or etanercept) [1].

These new data might have crucial implications in ulcerative colitis (UC) where tofacitinib, filgotinib and upadacitinib are approved.

Inflammatory bowel diseases and RA have different pathogenesis, as demonstrated by the different efficacy of drugs (e.g. etanercept, anti-IL17, antiCTLA-4, anti-CD20) or by the different risk of developing malignancies such as lymphoma [2,3].

Extrapolating the RA findings to other therapeutic areas may also not be appropriate as prevalence of risk factors is different across different indications. UC patients are very different from RA ones from an epidemiological standpoint and very different is the prevalence of specific risk factors, such as older age and smoking status, identified from an Oral Surveillance post hoc analysis as the most relevant to define the differential risk of tofacitinib vs TNF inhibitors [4]. UC patients are much younger [5] than RA patients and have a lower incidence of comorbidities, such as hypertension and diabetes; in addition to this, their active smoking habit is also very low (10-15%) [6], thus defining a lower baseline CV) risk [7,8].

Whilst specific thrombotic and cardiovascular risk assessment would require dedicated head-to-head studies in UC patients with similar characteristics to those of the surveillance trial, to date no increased risk of MACE or malignancy was identified in the overall tofacitinib-treated UC population up to 7.0 years of follow-up, suggesting a reliable safety profile [9,10].

In addition, the 3 different JAK inhibitors (JAKi), such as tofacitinib, filgotinib and upadacitinib, are very different [11] in terms of selectivity, dose, cytokine inhibition, efficacy and safety profile, including clinical experience in real world data. All JAKi have demonstrated efficacy in patients before and after biologics, needing most of the time higher doses in patients previously exposed to biologics. In conclusion, for all the reasons above and because the prevalence of risk factors is not the same for individual patients having UC, we believe that IBD specialists should have the possibility to use the proper treatment based on patient profile and individual benefit-risk profile based on the risk factors identified by the surveillance study, including age, smoking status and presence of other baseline CV , VTE or cancer risks [12].

Such a similar positioning has been also recently embraced by EULAR[13].

Positioning of JAKi should be kept before or after biologics.

When extrapolating findings from ORAL surveillance it is important to consider both differences in epidemiology and risk factors in UC vs RA patients

The **pathogenesis** of IBD and RA are different

Patients with IBD are often **younger** than those with RA

Patients with IBD are less likely to have **comorbidities** such as hypertension and diabetes

Patients with IBD have a lower **active smoking habit** is also very low (10-15%) and a lower baseline CV risk

No increased risk of **MACE or malignancy** was identified in the overall tofacitinib-treated UC population up to **7.8 years** of follow-up

- All 3 JAKi differ in terms of selectivity, dose, cytokine inhibition, efficacy & safety profile
- Treatment decisions should be determined by patient profile, benefit-risk profile
- Positioning of JAKi's should be kept before or after biologics

# **Network Meta-analysis of advanced therapies in UC:** induction of clinical remission and endoscopic improvement[1]

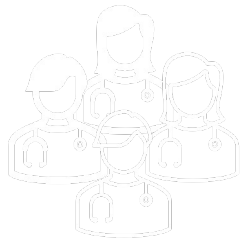
| Upadacitinib | 2.70 (1.18-6.20) | 4.49 (2.18-9.24) | 6.15 (2.98-12.72) | 2.84 (1.28-6.31) | 4.91 (2.59-9.31) | 2.92 (1.31-6.51) | 3.56 (1.84-6.91) | 3.00 (1.32-6.82) | 4.64 (2.47-8.71) | 2.70 (1.18-6.20) | 9.54 (5.45-16.69) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 3.01 (1.59-5.67) | Ozanimod | 1.65 (0.77-3.55) | 2.27 (1.05-4.89) | 1.05 (0.45-2.41) | 1.81 (0.91-3.60) | 1.07 (0.46-2.49) | 1.31 (0.65-2.67) | 1.10 (0.47-2.61) | 1.71 (0.87-3.37) | 0.93 (0.47-1.85) | 3.52 (1.91-6.49) |
| 2.91 (1.19-7.10) | 0.97 (0.39-2.39) | Filgotinib 200 mg | 1.37 (0.71-2.62) | 0.63 (0.30-1.31) | 1.09 (0.63-1.89) | 0.65 (0.31-1.35) | 0.79 (0.44-1.41) | 0.66 (0.31-1.42) | 1.03 (0.60-1.77) | 0.56 (0.32-0.97) | 2.12 (1.34-3.35) |
| 5.96 (2.35-15.14) | 1.98 (0.77-5.09) | 2.04 (0.66-6.33) | Filgotinib 100 mg | 0.46 (0.22-0.95) | 0.79 (0.45-1.39) | 0.47 (0.22-0.99) | 0.57 (0.32-1.03) | 0.48 (0.22-1.03) | 0.75 (0.43-1.30) | 0.41 (0.23-0.71) | 1.54 (0.97-2.45) |
| 3.05 (1.68-5.51) | 1.01 (0.55-1.86) | 1.04 (0.43-2.50) | 0.51 (0.20-1.27) | Tofacitinib | 1.72 (0.90-3.29) | 1.02 (0.45-2.30) | 1.25 (0.64-2.45) | 1.05 (0.46-2.41) | 1.63 (0.86-3.08) | 0.89 (0.46-1.69) | 3.35 (1.90-5.91) |
| 4.71 (2.83-7.83) | 1.56 (0.92-2.66) | 1.61 (0.71-3.65) | 0.78 (0.33-1.86) | 1.54 (0.96-2.48) | Etrolizumab | 0.59 (0.31-1.14) | 0.72 (0.48-1.08) | 0.61 (0.31-1.21) | 0.94 (0.69-1.29) | 0.51 (0.36-0.72) | 1.94 (1.42-2.64) |
| 3.45 (1.90-6.24) | 1.14 (0.62-2.11) | 1.18 (0.49-2.83) | 0.57 (0.23-1.44) | 1.13 (0.64-1.99) | 0.73 (0.45-1.18) | Ustekinumab | 1.22 (0.62-2.39) | 1.02 (0.44-2.35) | 1.59 (0.83-3.02) | 0.86 (0.45-1.66) | 3.26 (1.83-5.79) |
| 4.71 (2.68-8.28) | 1.56 (0.87-2.81) | 1.61 (0.68-3.79) | 0.79 (0.32-1.93) | 1.54 (0.90-2.63) | 1.00 (0.64-1.55) | 1.36 (0.79-2.33) | Vedolizumab | 0.84 (0.41-1.68) | 1.30 (0.96-1.74) | 0.71 (0.45-1.10) | 2.67 (1.87-3.80) |
| 4.52 (2.55-8.01) | 1.50 (0.83-2.72) | 1.54 (0.65-3.65) | 0.75 (0.30-1.86) | 1.48 (0.86-2.55) | 0.95 (0.61-1.51) | 1.31 (0.76-2.26) | 0.95 (0.57-1.60) | Golimumab | 1.54 (0.79-3.01) | 0.84 (0.43-1.65) | 3.17 (1.74-5.79) |
| 5.41 (3.30-8.86) | 1.79 (1.07-3.01) | 1.85 (0.82-4.15) | 0.90 (0.38-2.12) | 1.77 (1.11-2.81) | 1.14 (0.88-1.49) | 1.56 (0.98-2.48) | 1.15 (0.75-1.75) | 1.19 (0.77-1.84) | Adalimumab | 0.54 (0.37-0.79) | 2.05 (1.54-2.73) |
| 2.75 (1.66-4.55) | 0.91 (0.54-1.54) | 0.94 (0.41-2.14) | 0.46 (0.19-1.09) | 0.90 (0.56-1.44) | 0.58 (0.43-0.78) | 0.79 (0.49-1.27) | 0.58 (0.37-0.91) | 0.60 (0.39-0.95) | 0.51 (0.37-0.69) | Infliximab | 3.76 (2.77-5.12) |
| 8.23 (5.32-12.75) | 2.74 (1.72-4.34) | 2.82 (1.30-6.12) | 1.38 (0.60-3.14) | 2.71 (1.81-4.02) | 1.74 (1.34-2.26) | 1.74 (1.34-2.26) | 1.74 (1.22-2.49) | 1.82 (1.25-2.63) | 1.52 (1.21-1.92) | 3.00 (2.33-3.82) | Placebo |

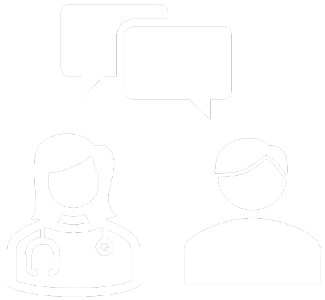
Clinical remission

Endoscopic improvement

**1.** Lasa JS, et al. *Lancet Gastroenterol Hepatol.* 2022;7(2):161-170.

# But are things actually getting better?









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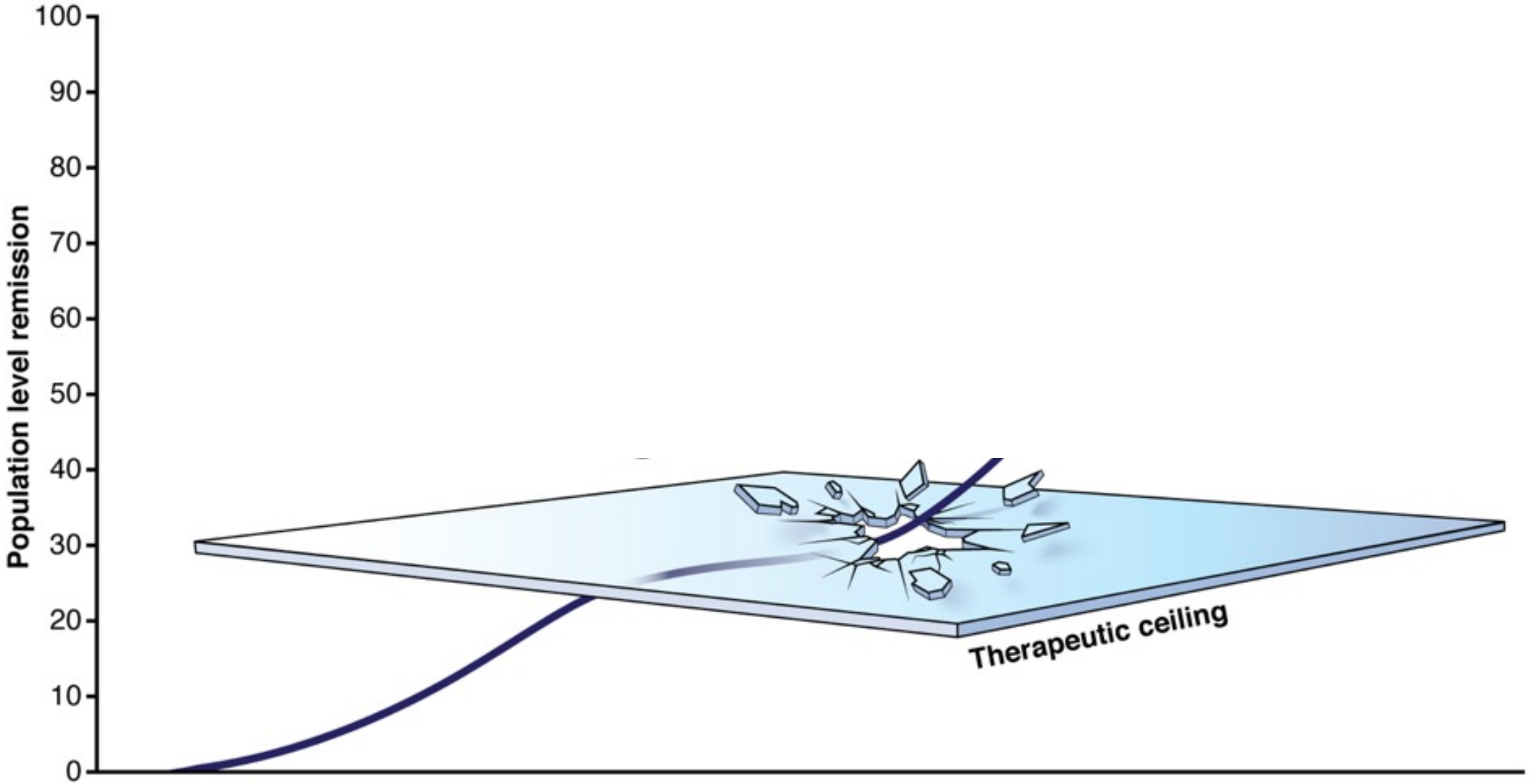
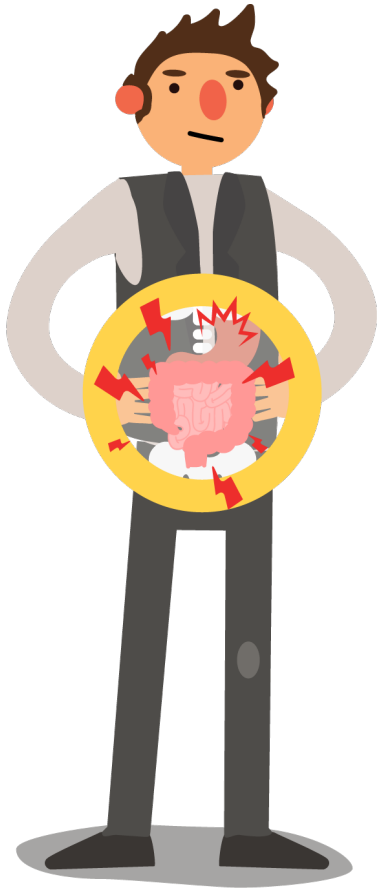
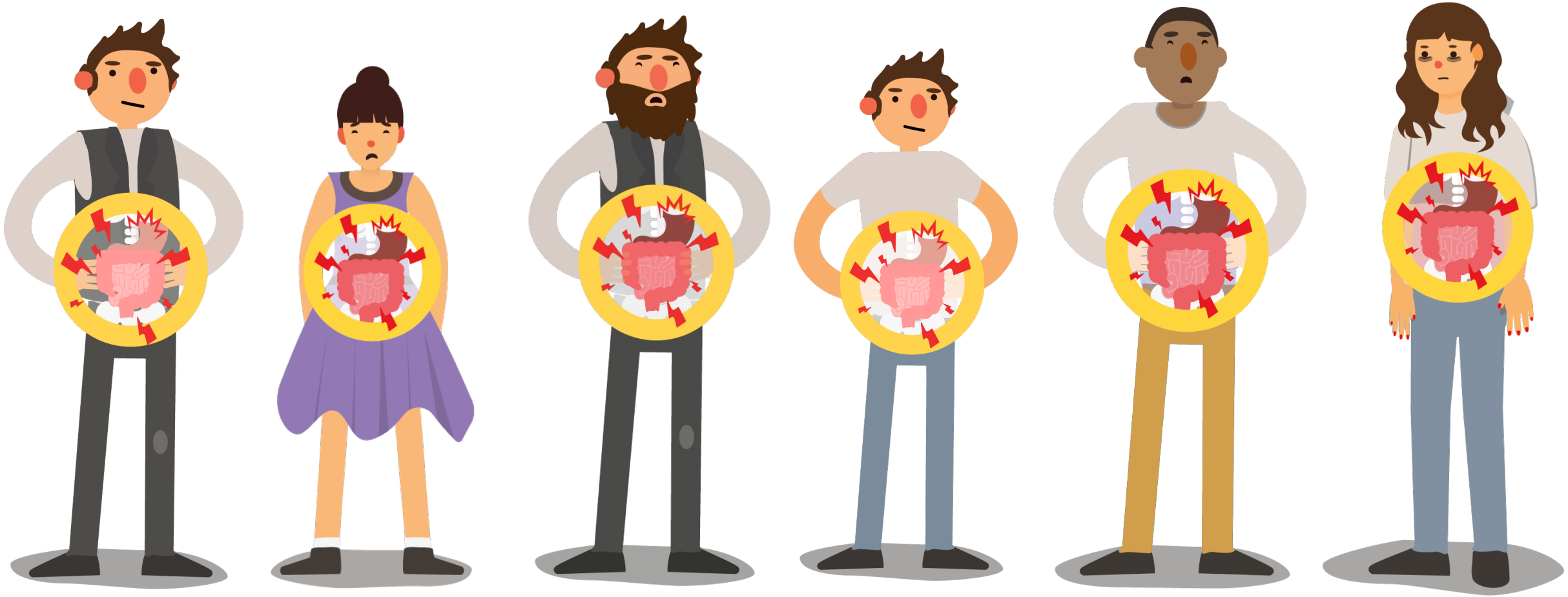


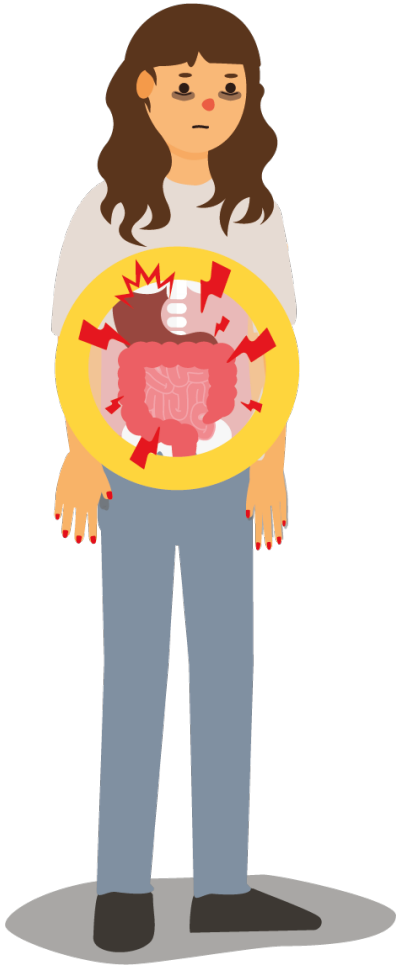

Raine and Danese *Gastro* 2022



# Right **drug,** right **person,** right **time**



# We still have a major PREDICTION problem



## **Stratification** of patients

**DISEASE BEHAVIOUR**

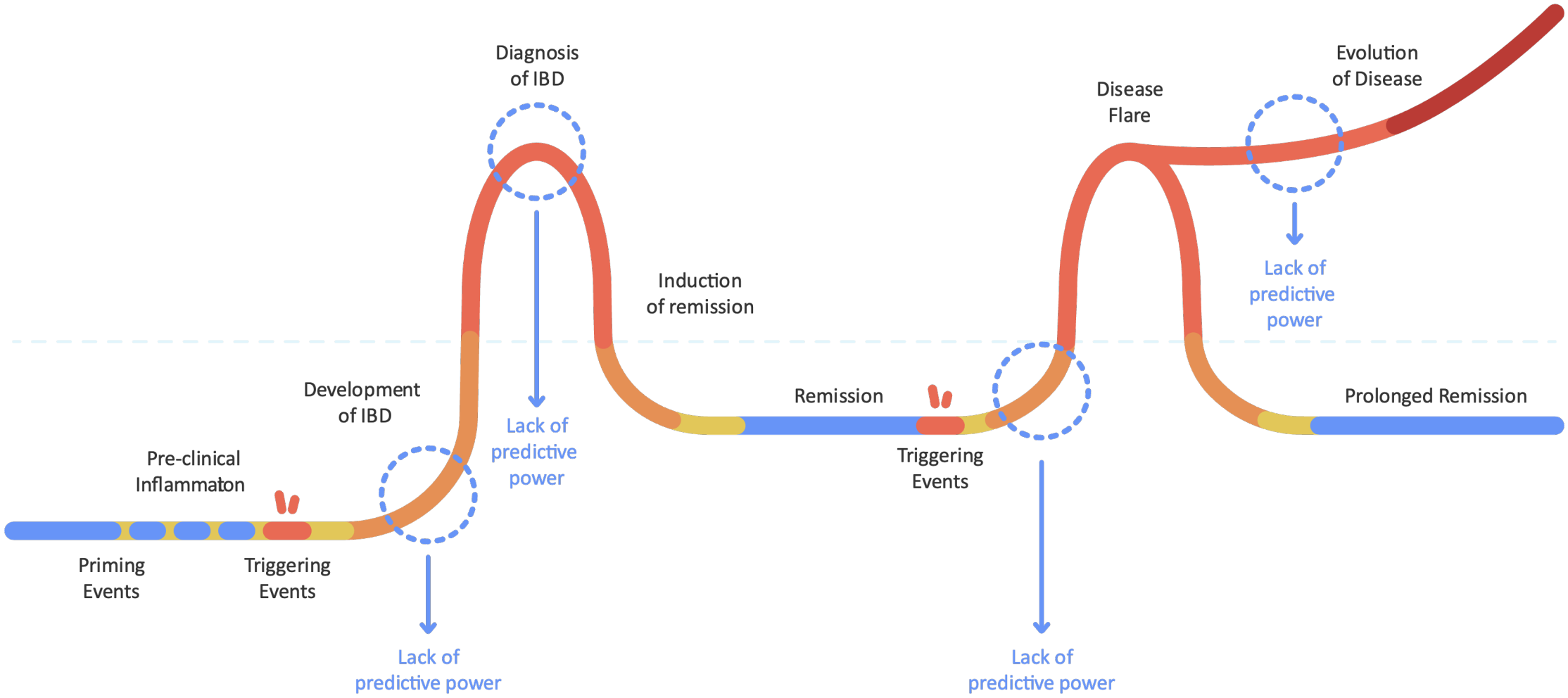
- Aggressive vs quiescent disease

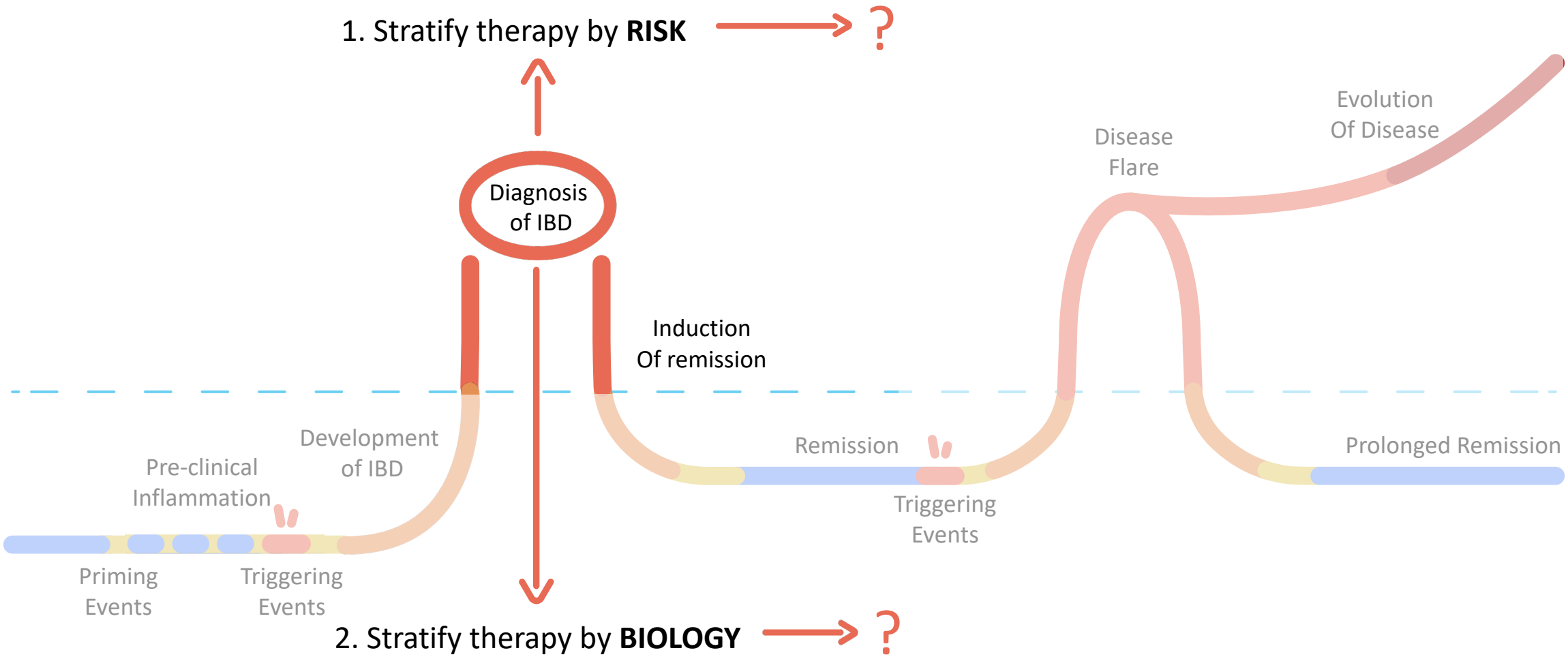
**DRUG RESPONSE**

- Predicting treatment response

**COMPLICATIONS**

- Who gets complications of drugs / disease

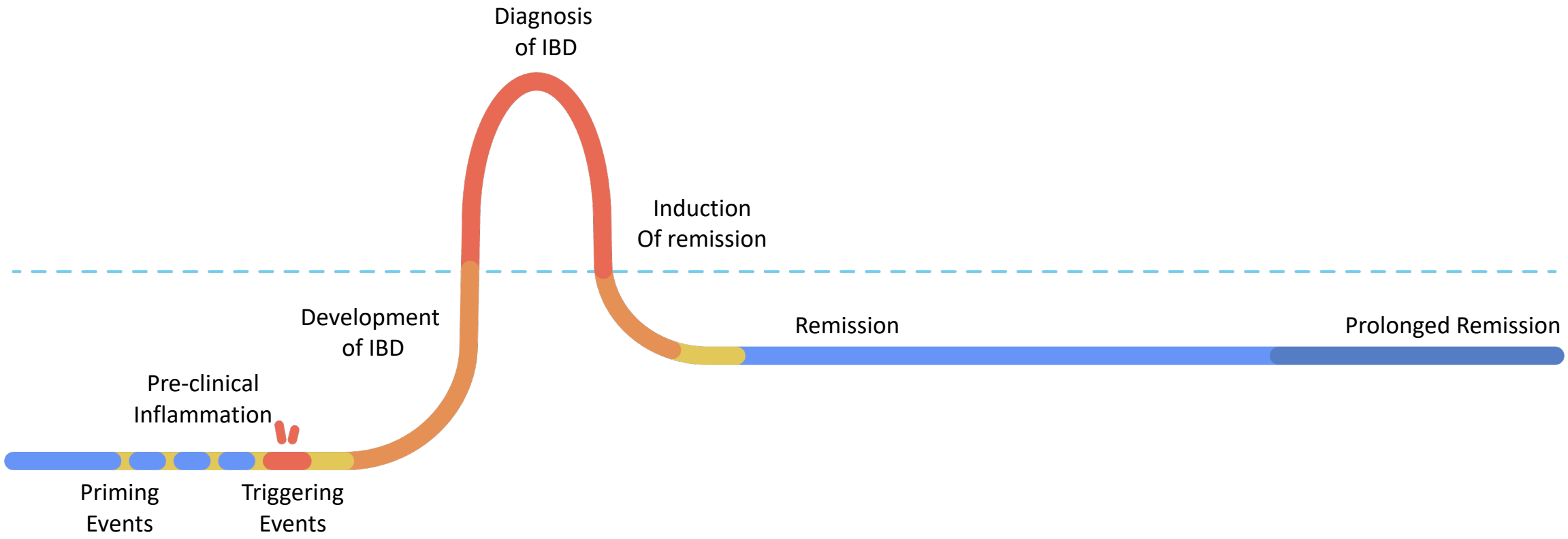

Diagnosis
of IBD
Evolution
of Disease
Disease
Flare
Induction
of remission
Lack of
predictive
power
Lack of
predictive
power
Development
of IBD
Remission
Prolonged Remission
Pre-clinical
Inflammaton
Triggering
Events
Priming
Events
Triggering
Events
Lack of
predictive power
Lack of
predictive power


1. Stratify therapy by **RISK** ?
Diagnosis of IBD
Induction Of remission
Development of IBD
Pre-clinical Inflammation
Priming Events
Triggering Events
Remission
Triggering Events
Disease Flare
Evolution Of Disease
Prolonged Remission
2. Stratify therapy by **BIOLOGY** ?

# These are the patients we risk over-treating

Approximately one-third of patients with IBD

Predicting who they are at diagnosis is remarkably difficult

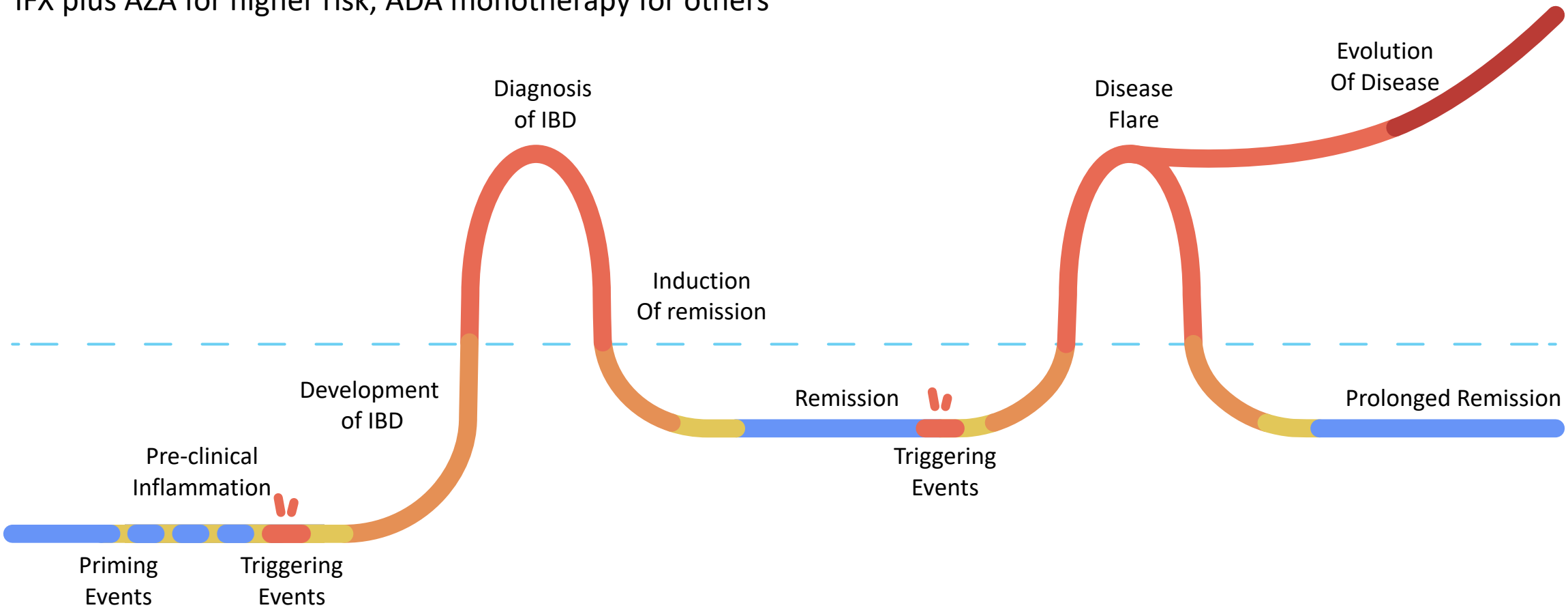


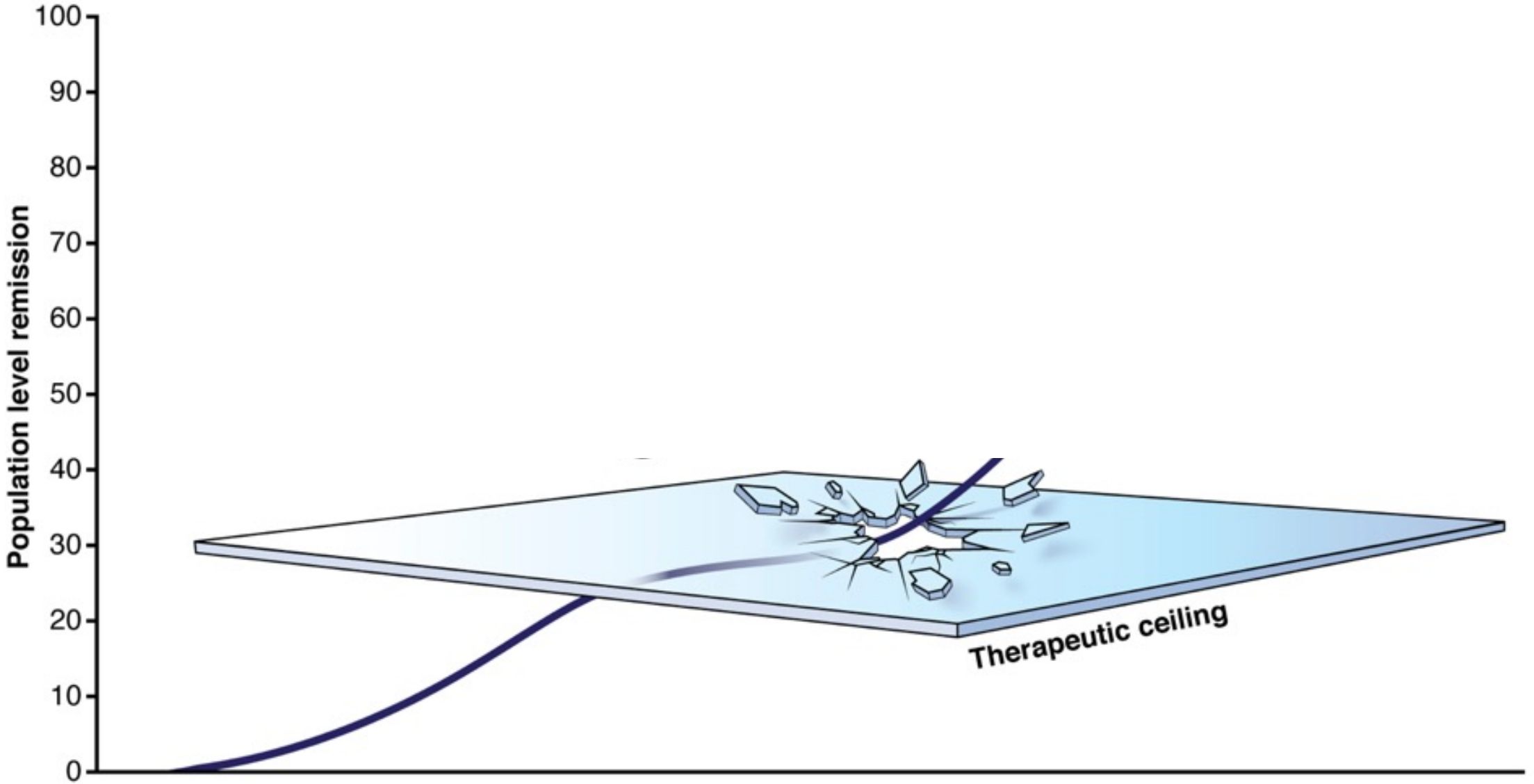
# These are the patients we risk under-treating

At the very least, start a biologic at diagnosis for patients with:

- extensive small bowel disease, peri-anal disease, rectal involvement and deep ulcers

IFX plus AZA for higher risk; ADA monotherapy for others



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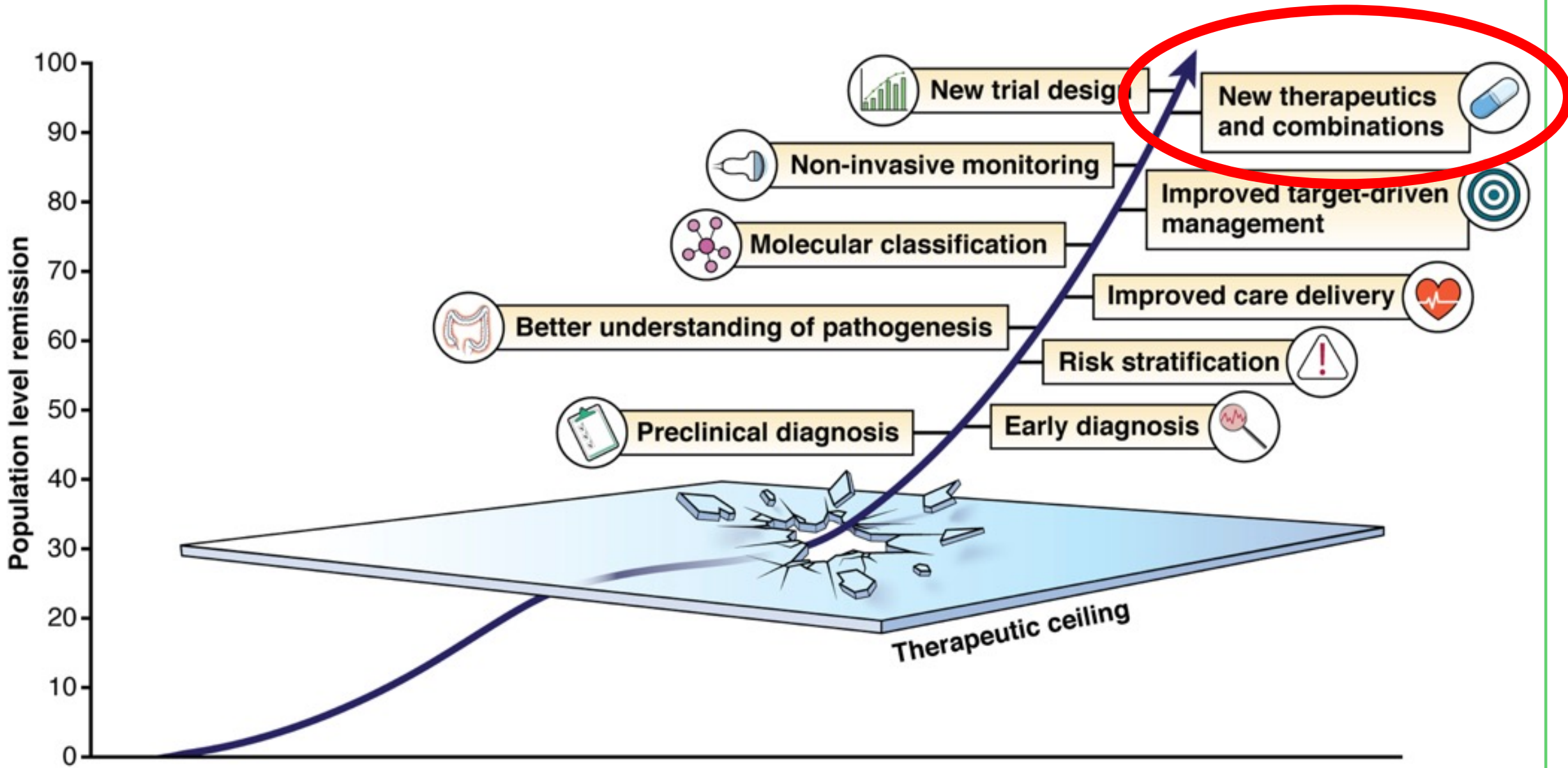
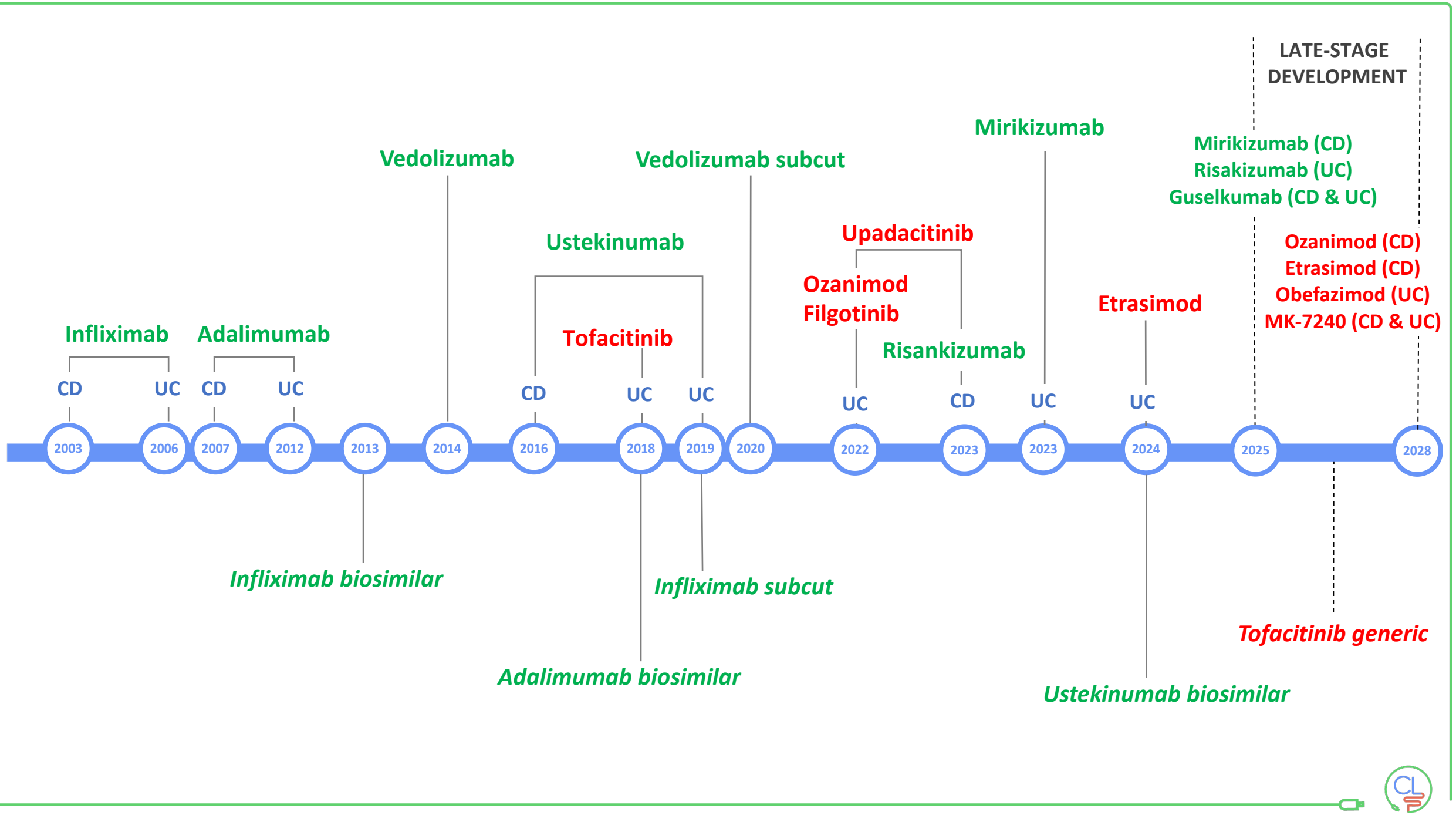



Raine and Danese *Gastro* 2022


LATE-STAGE DEVELOPMENT
Mirikizumab (CD)
Risakizumab (UC)
Guselkumab (CD & UC)
Ozanimod (CD)
Etrasimod (CD)
Obefazimod (UC)
MK-7240 (CD & UC)
Mirikizumab
Vedolizumab
Vedolizumab subcut
Upadacitinib
Ustekinumab
Ozanimod
Filgotinib
Etrasimod
Risankizumab
Infliximab
Adalimumab
Tofacitinib
CD
UC
CD
UC
CD
UC
UC
CD
UC
UC
2003
2006
2007
2012
2013
2014
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2018
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2020
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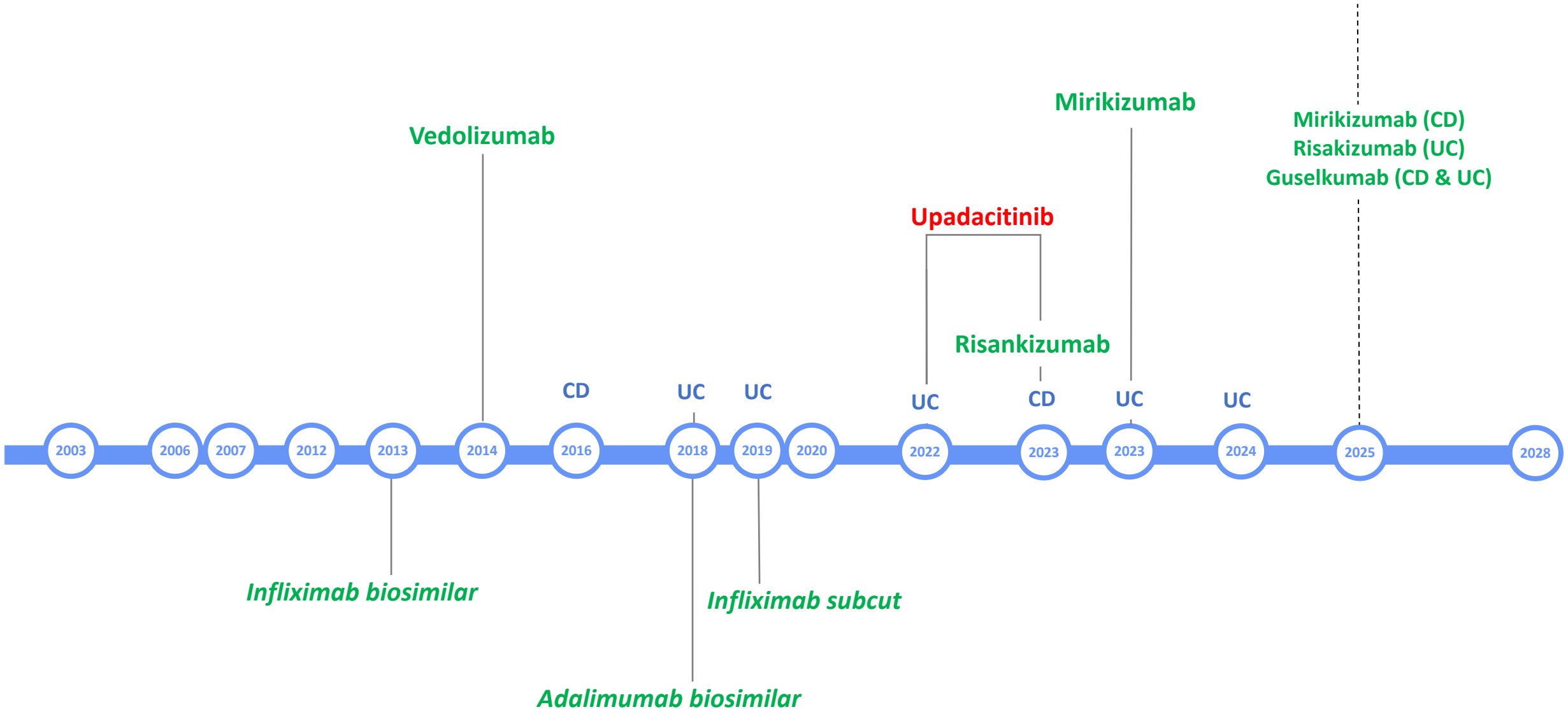
Infliximab biosimilar
Infliximab subcut
Adalimumab biosimilar
Ustekinumab biosimilar
Tofacitinib generic


Vedolizumab
Mirikizumab
Mirikizumab (CD)
Risakizumab (UC)
Guselkumab (CD & UC)
Upadacitinib
Risankizumab
CD
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UC
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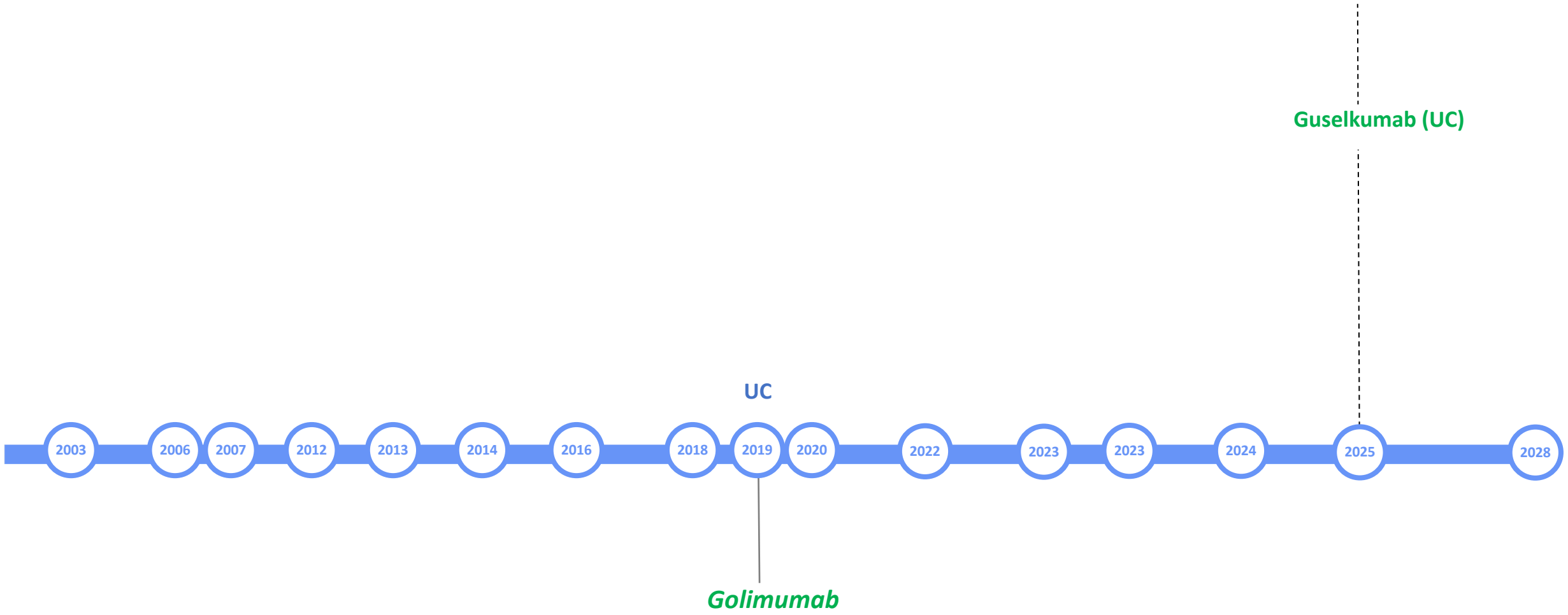
Infliximab biosimilar
Infliximab subcut
Adalimumab biosimilar


Guselkumab (UC)
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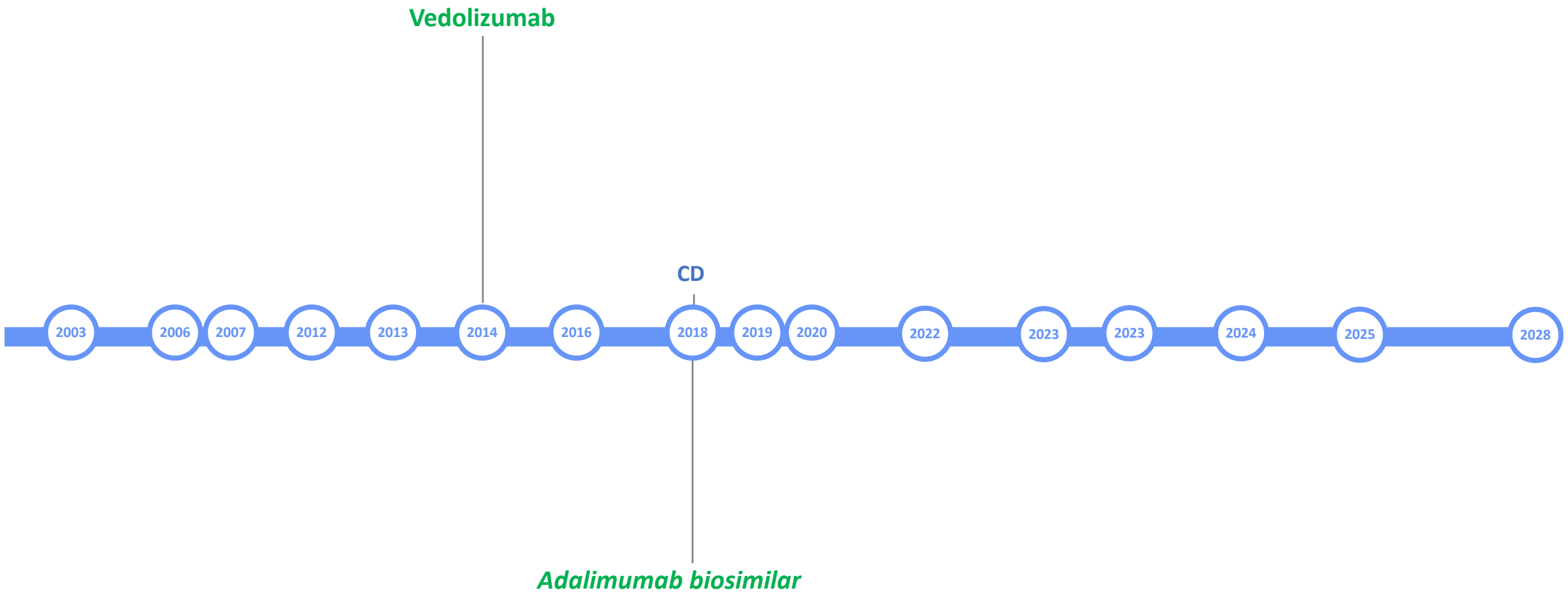
Golimumab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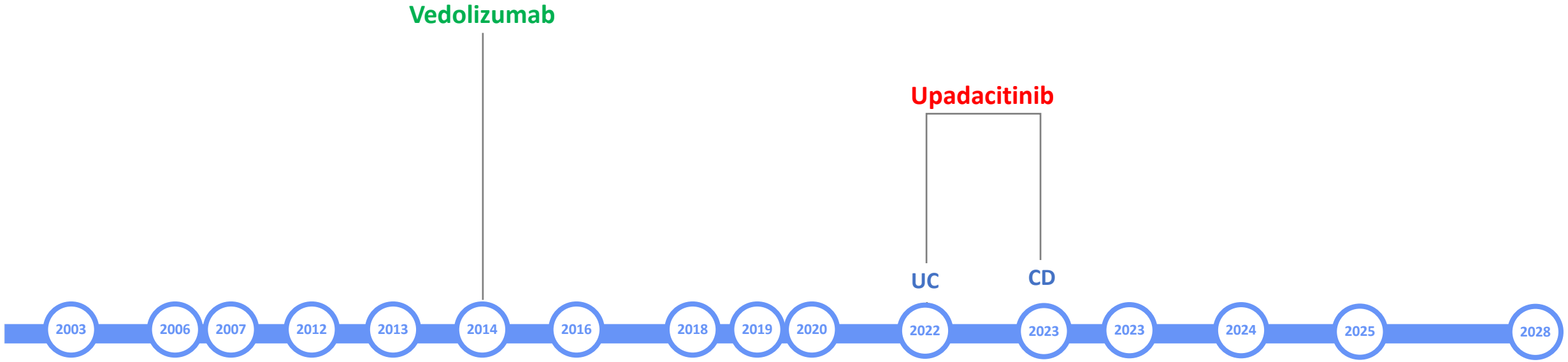
Adalimumab biosimilar


Vedolizumab
Upadacitinib
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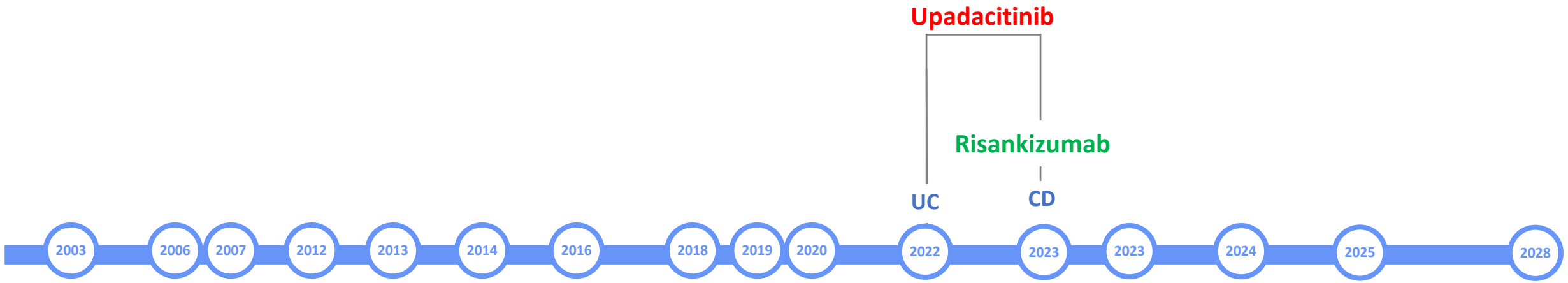
Upadacitinib
Risankizumab
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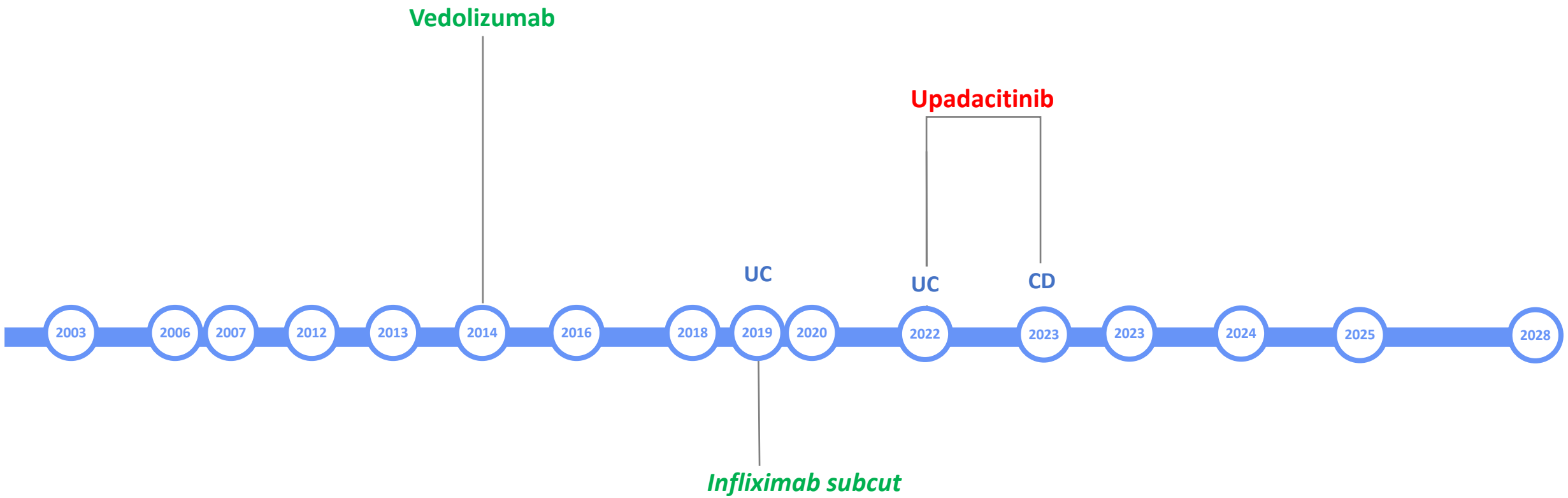
Vedolizumab
Upadacitinib
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Infliximab subcut

# Our decisions are driven by

- Cost
- Guidelines
- Local availability
- Experience / familiarity
- Limited head-to-head data
- The latest network meta—analysis
- Real world evidence with propensity matching
- And the hype from the latest conference / marketing

**WE ARE PERSONALISING MEDICINE**

*BUT … this is **not yet** precision medicine*

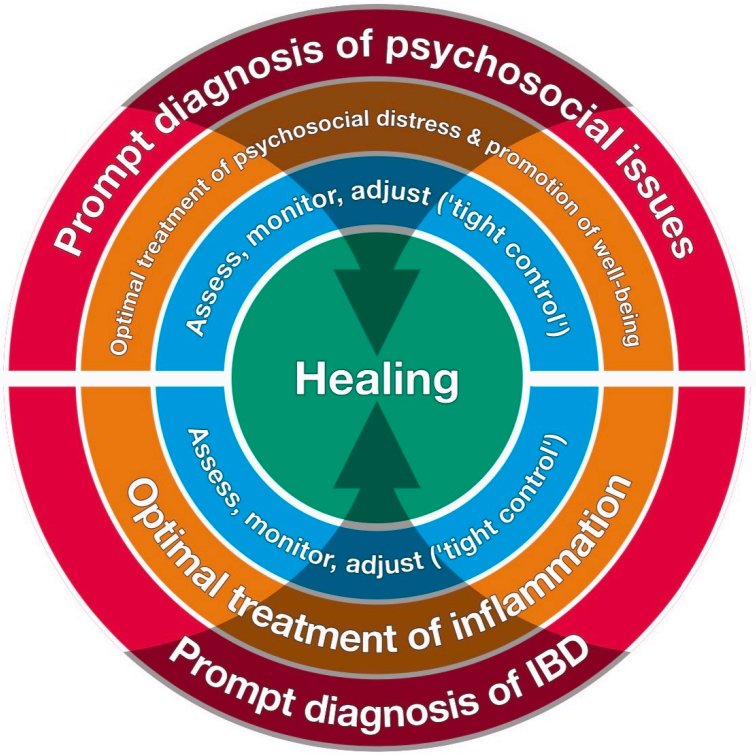
# What are the key decisions / unknowns

**FIRST DRUG in Crohn's** to induce and maintain remission for 5+ years
- anti-TNF (really?) versus USTE versus RISA versus UPA
- versus combo JAKi plus p19 or anti-integrin and maintenance

**AFTER first TNF failure**
- second anti-TNF or RISA or UPA

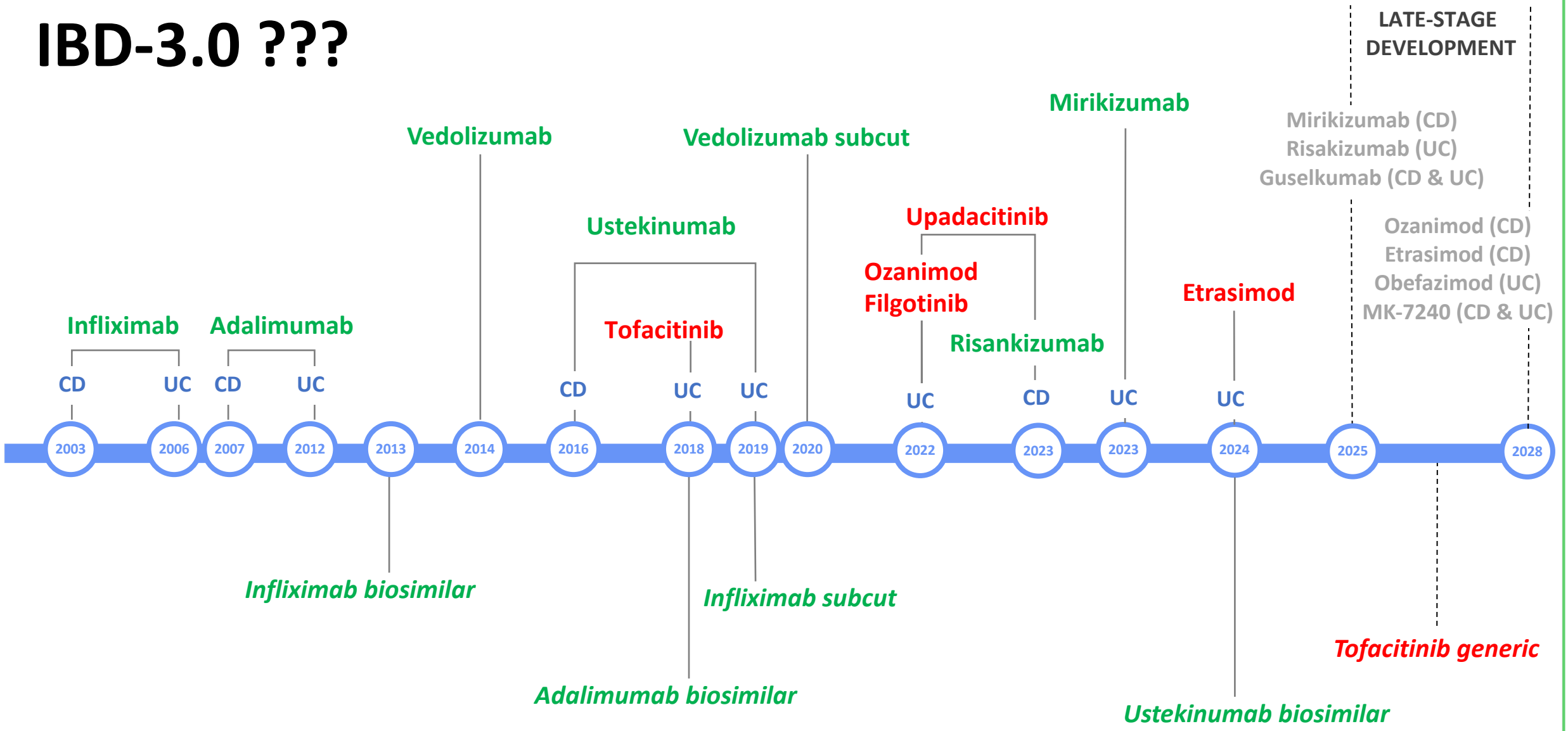
**FIRST DRUG in UC??????????**
- p40 versus p19
- anti-integrin versus S1P modulator
- JAKi versus JAKi

**After JAKi failure** – another JAKi or out of class




- ✓ Treat symptoms
- ✓ Control gut inflammation
- ✓ Minimise steroid exposure
- ✓ Keep patient out of hospital
- ✓ Prevent the disease from progressing
- ✓ Decrease surgery and stoma formation
- ✓ Minimise complications from drugs and disease

# IBD-3.0 ???


LATE-STAGE DEVELOPMENT
Mirikizumab (CD)
Risakizumab (UC)
Guselkumab (CD & UC)
Ozanimod (CD)
Etrasimod (CD)
Obefazimod (UC)
MK-7240 (CD & UC)
Infliximab
CD
UC
Adalimumab
CD
UC
Vedolizumab
Ustekinumab
CD
Tofacitinib
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UC
Vedolizumab subcut
Upadacitinib
Ozanimod
Filgotinib
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Risankizumab
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Mirikizumab
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Etrasimod
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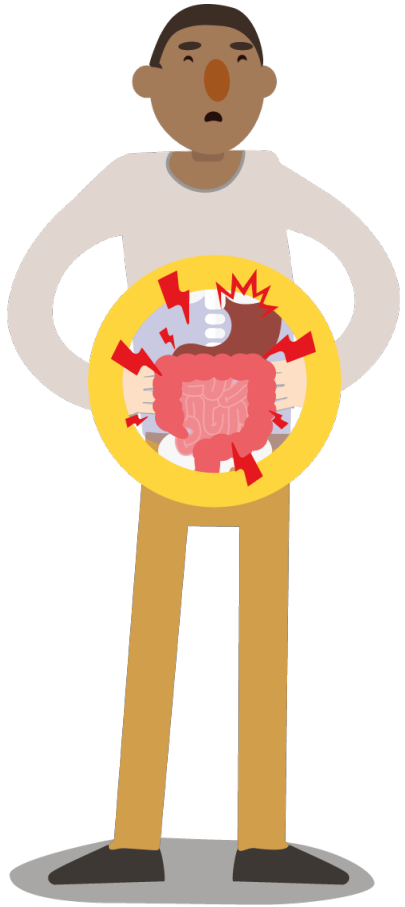
Ustekinumab biosimilar

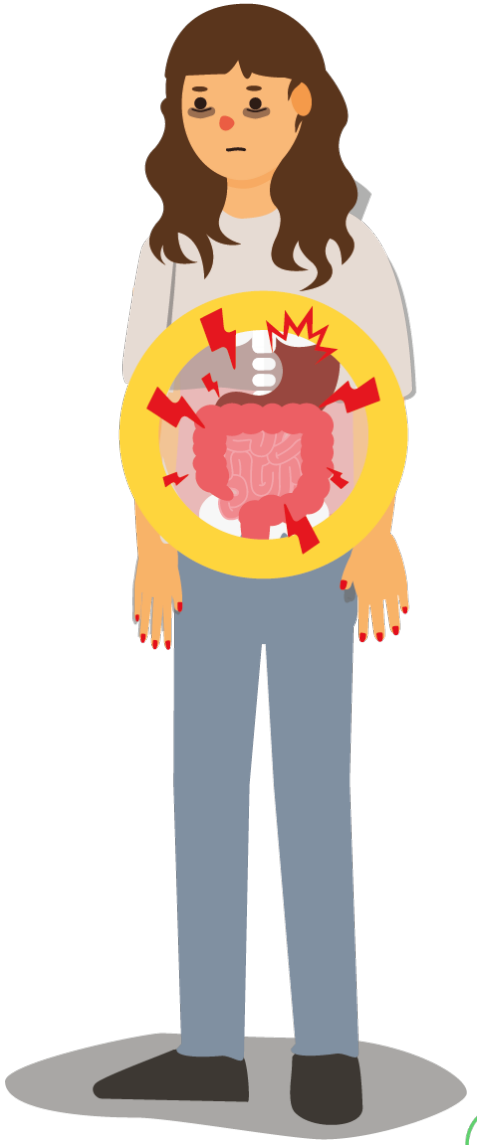
# Where should we focus our efforts?

1. **Building solid evidence**
2. **Fistula** and **stricture** therapy
3. **Microbial** and **dietary** strategies
4. **Rational combinations** of therapies
5. **Special populations:** children especially
6. **Delivery of high-quality care** to all patients
7. **Biomarker discovery** to enable precision medicine
8. **Psychological** and **holistic** approaches to enhance care
9. **Frictionless** and **passive monitoring** that work for patients



# Is this really a new life for our patients?

*”good progress, but more work to do”*



ATOMIC IBD

UK Research and Innovation

PREdiCCt

CROHN'S & COLITIS UK

THE UNIVERSITY of EDINBURGH