# Using personalized medicine to optimize IBD therapy

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Western University

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# Speaker Disclosures

- Dr. James Gregor
- I have the following relationships with financial interests:
  - Advisory Board/Speakers Bureau: Innomar, NKS, Ferring AbbVie, Janssen, Takeda, Pfizer, Avir, Celltrion, JAMP
  - Funding (Grants/Honoraria): Janssen, Takeda, Pfizer, Celltrion, Organon, Fresinius Kabi
  - Research/Clinical Trials: BMS, AbbVie, Takeda, Janssen
  - Speaker/Consulting Fees: Janssen, Takeda, Pfizer, Avir, Celltrion, Organon
  - Other
    - Current/past employee of: Western University
    - Investments: None
    - Patent in product: None


OAG
GAMIFICATION
Gregor - Game Code:
CABLECAR

# Case

## Background

- 32 year old female referred to the GI clinic from the emergency department
- Diagnosed with ileocolonic Crohn's disease at age 24 (followed elsewhere)
- Cigarette smoker
- No children but may have in future
- South Asian descent, family history negative for IBD

## Treatments

1. Prednisone for 4 months in early disease
2. Adalimumab for 2 years after that – she did well initially but was eventually lost response
3. Treated by a naturopath for several years until now

# Case

## Current symptoms

- 6 weeks
- Right lower quadrant pain
- Diarrhea up to 6 times daily with occasional blood
- Fatigue
- Bilateral knee/ankle pain and swelling
- Anorexia, weight loss 5 kg

## Physical exam

- 167 cm, 55 kg, BMI 19.7
- Few mouth ulcers
- Moderate tenderness with slight fullness at RLQ
- Tenderness knees and ankles bilaterally
- No perianal disease

# Case

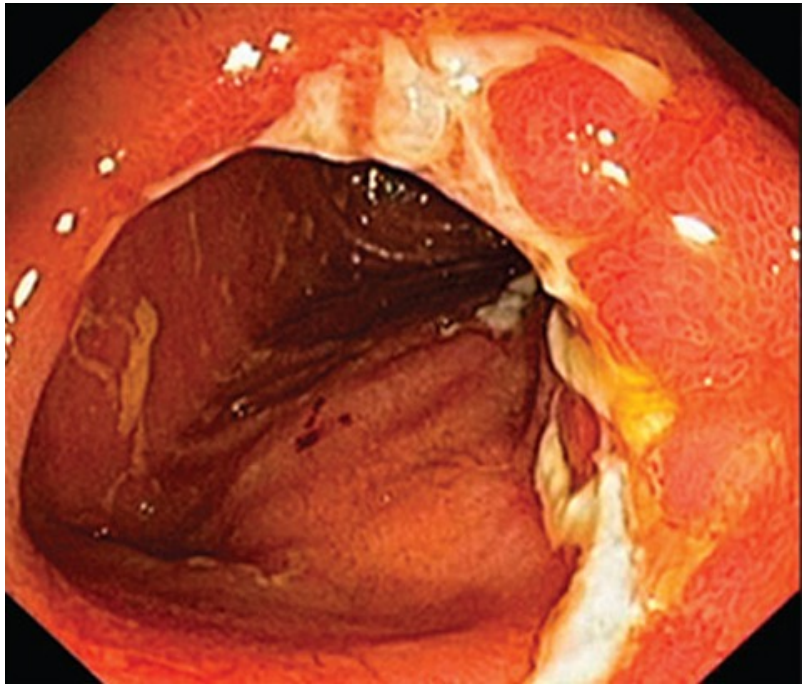
## Investigations in ER

- Hgb 101, MCV 75, WBC 12.3, platelets 494
- CRP 19.3
- ANA/RF negative
- Stool tests negative for infection

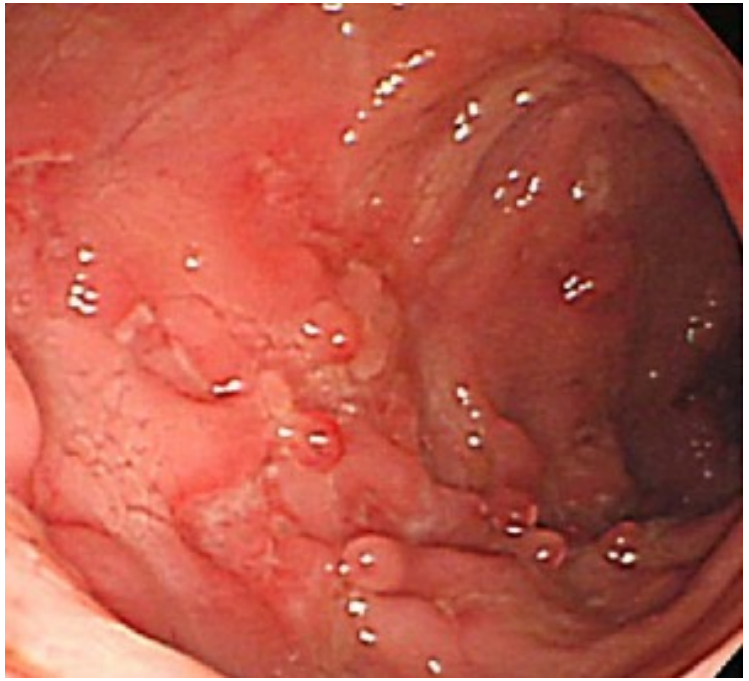
### CT abdomen/pelvis

- Mural enhancement with wall thickening at terminal ileum for 15 cm
- No upstream dilation
- Questionable mural enhancement of right colon
- Reactive lymphadenopathy

# Case



Terminal ileum



Right colon

# Case

## Repeat investigations

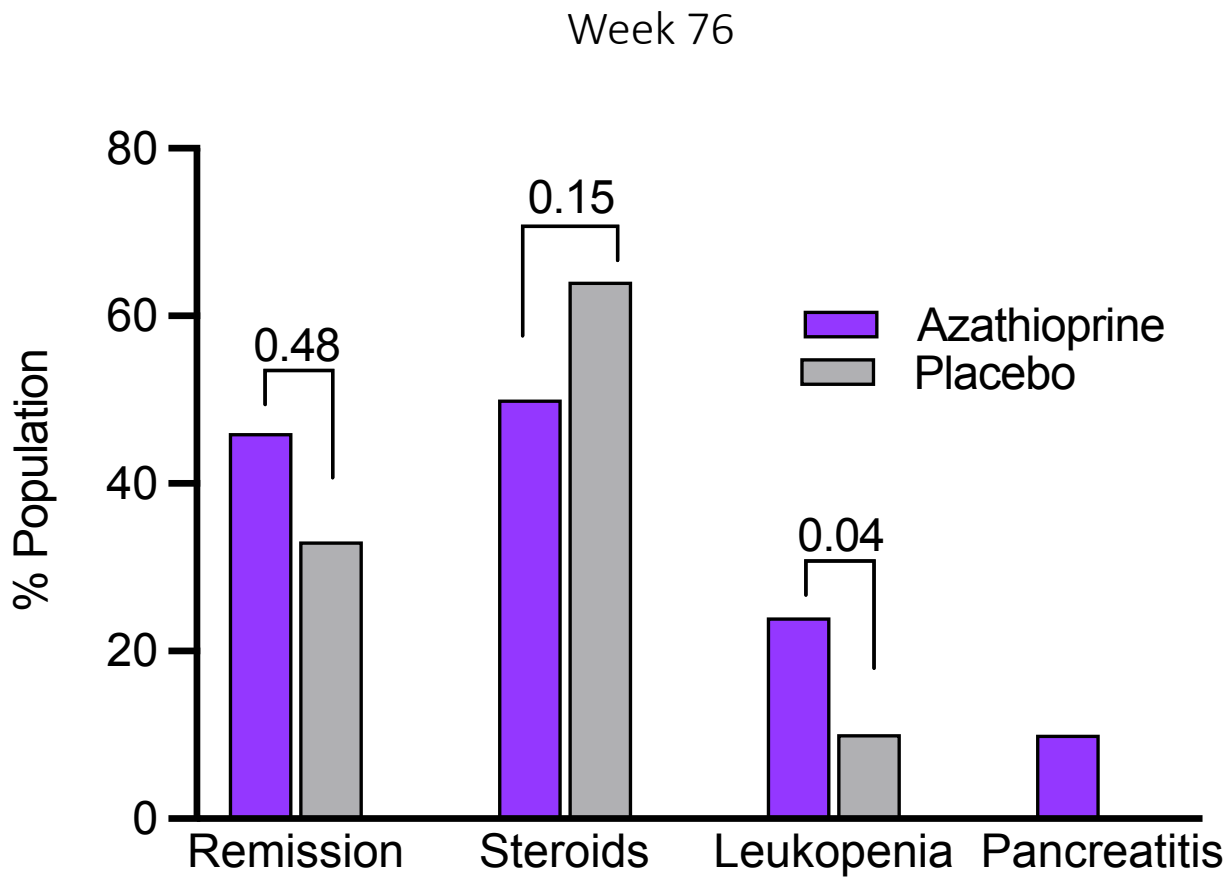
- CRP 21.5
- Fecal calprotectin 941

## Initial management plan

- Prednisone 40 mg od
- Symptoms flared with prednisone tapering - consider azathioprine
- Consultation for Personalized Medicine

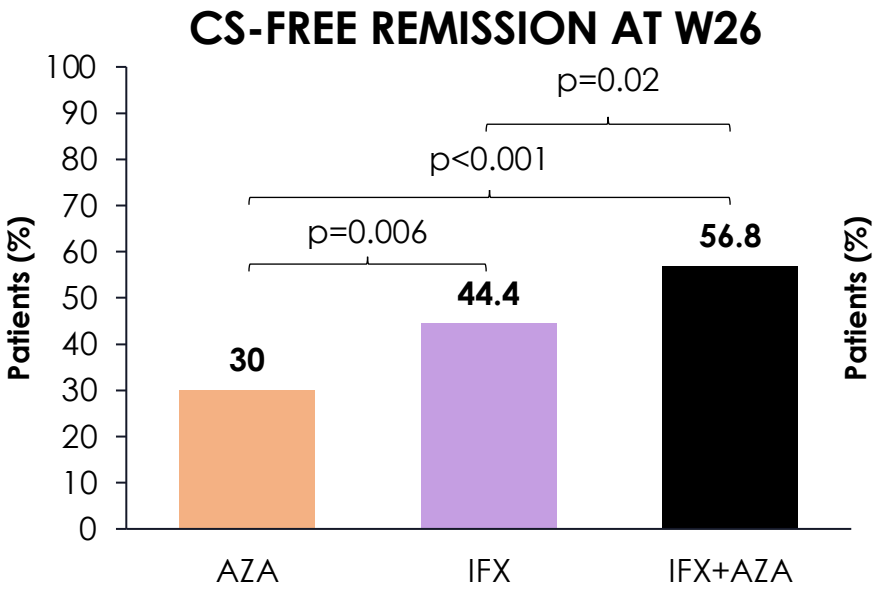
# Azathioprine in newly diagnosed Crohn's Disease

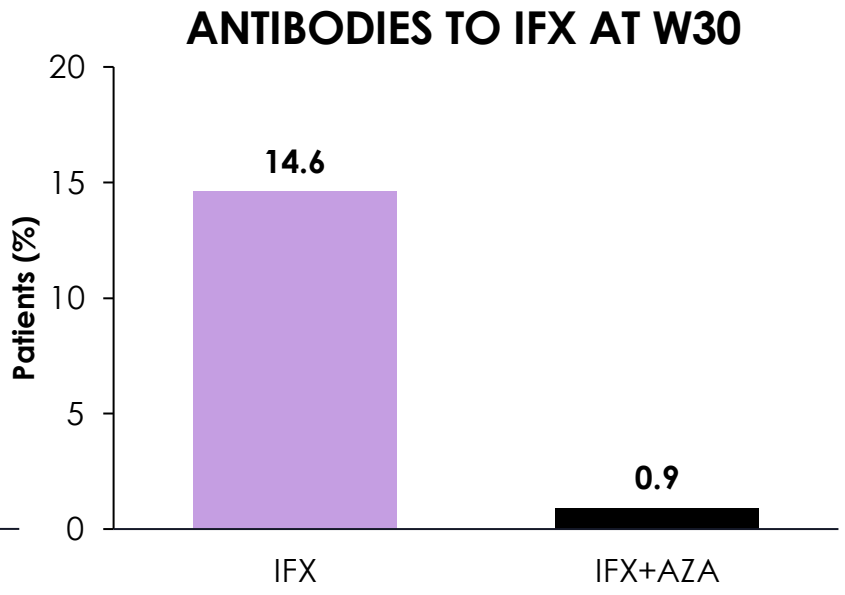
- 131 patients, diagnosed within 8 weeks
  - 68 AZA, 63 placebo
  - Mean age 36, 45% male
  - 70% on corticosteroids
- No previous IM's or biologics
- AZA 2.5 mg/kg vs placebo
- Primary outcome corticosteroid free clinical remission (CDAI< 150) at week 76
- Relapse CDAI> 175 after week 12
- Primary AE's
  - Leukopenia (neutrophils < 3.5)
  - Pancreatitis

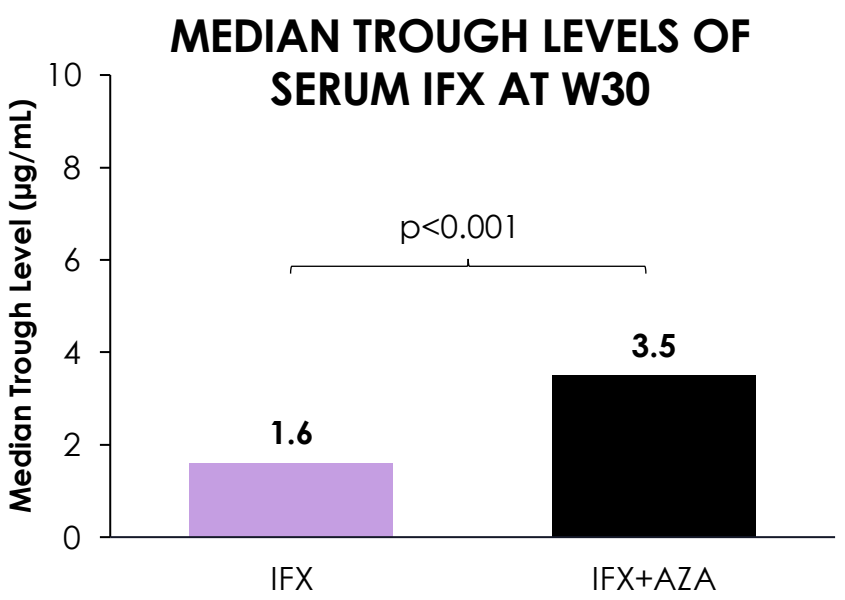



Panes *et.al.* Gastroenterology 2013 (AZTEC)

# Patients treated with IFX + AZA or IFX monotherapy were more likely to have CS-free clinical remission than those receiving AZA alone




Results

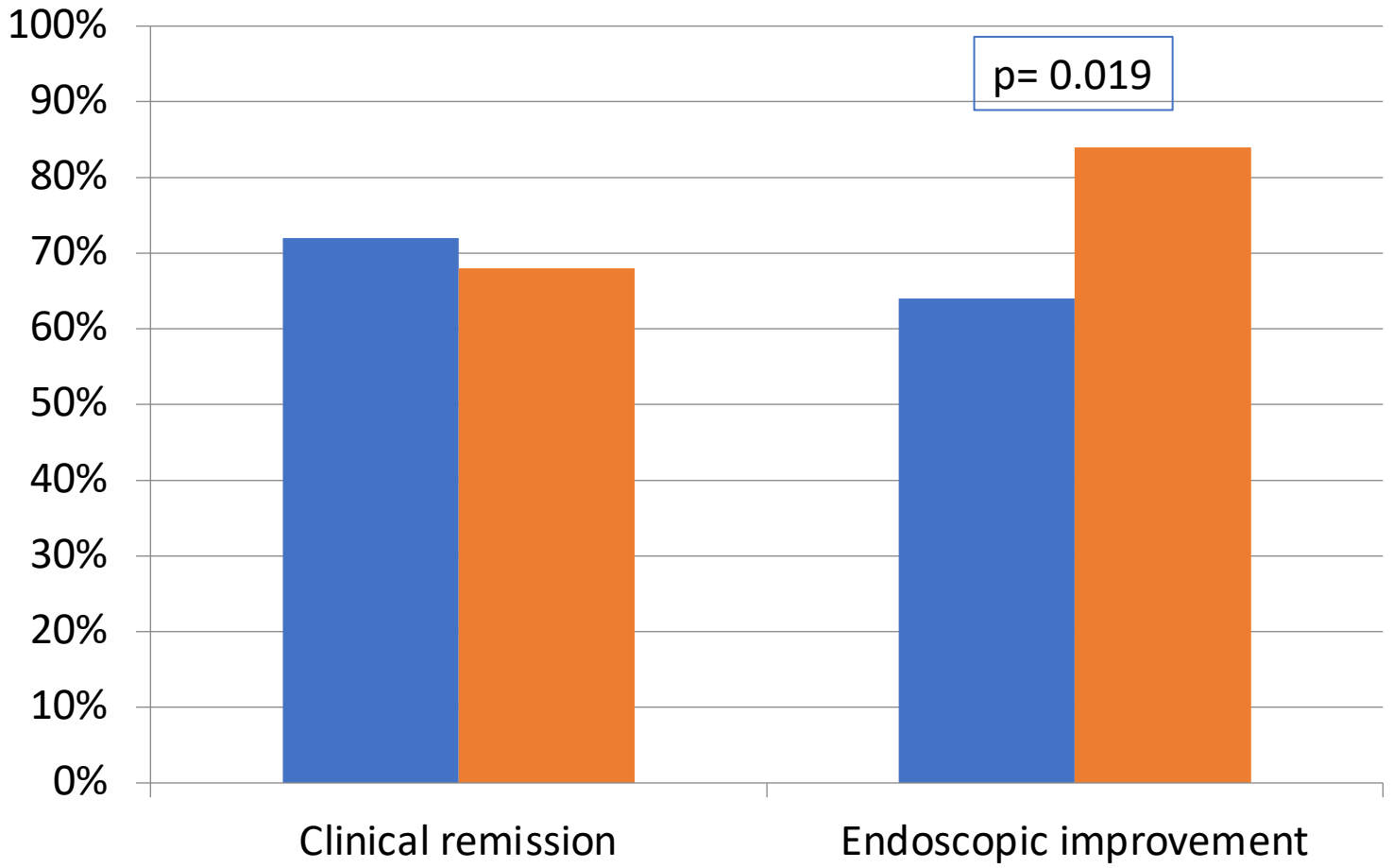
AZA: azathioprine; CS: corticosteroid; IFX: infliximab; W: week.

1. Colombel et al. N Engl J Med. 2010; 362:1383-95.

# OP012: DIAMOND

- Japanese open-label RCT
- 176 patients with Crohn's, naïve to biologics and thiopurines
- Adalimumab alone vs adalimumab + AZA
  - 25-100 mg daily
- 52 week follow up
- Primary outcome clinical remission at 26 weeks
- Secondary outcome endoscopy

# Clinical and endoscopic outcome




**Trough levels**

7.56 µg/mL combo vs 6.50 µg/mL mono

**Antibodies to adalimumab**

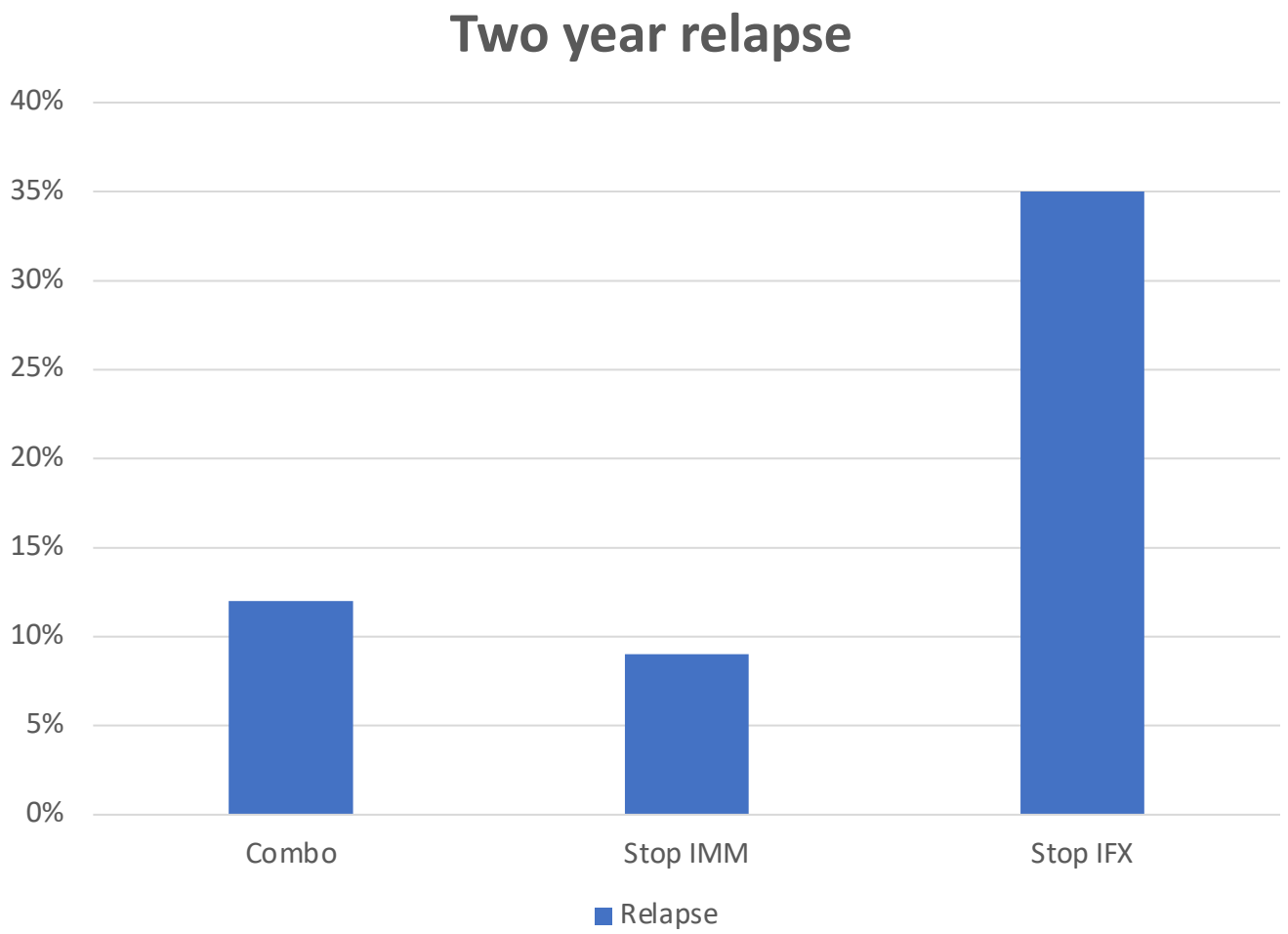
4.0% combo vs 13.2% mono

# SPARE trial

- Multi-centre open-label randomized trial of withdrawal of:
  - AZA/MTX (n= 69)
  - IFX (n= 71)

  OR
  - Continuing combination therapy (n= 67)
- Two year follow up
- Relapse
  - CDAI >250 (or ↑70)

    + CRP >5 or FCP >250




*Louis E. Lancet Gastroenterol Hepatol 2023*

# International IBD guidelines recommend the use of *TPMT* screening prior to the use of thiopurines

Gastroenterology 2017;153:827–834

**AGA SECTION**

## American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease

Joseph D. Feuerstein,[1] Geoffrey C. Nguyen,[2] Sonia S. Kupfer,[3] Yngve Falck-Ytter,[4] and Siddharth Singh[5]; on behalf of American Gastroenterological Association Institute Clinical Guidelines Committee

”In adult patients with IBD being started on thiopurines, the AGA suggests routine TPMT testing to guide thiopurine dosing.”

2019 Guidelines

OPEN ACCESS

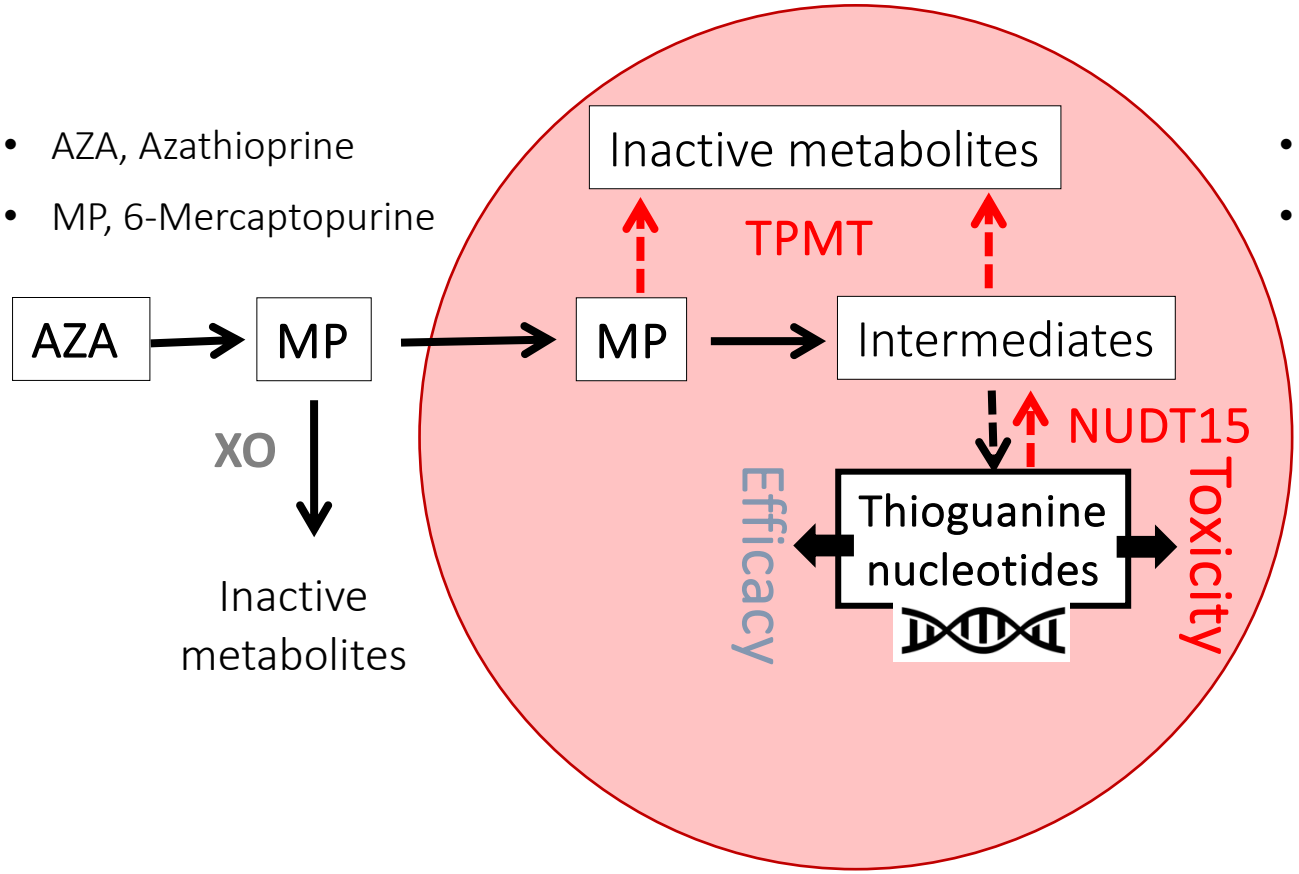
## British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults

“Check TPMT and start [thiopurine] at target dose once result available..”

Feuerstein *et.al.* Gastro 2017; Lamb *et.al.* Gut 2019

# Azathioprine metabolism: More than just *TPMT*

- AZA, Azathioprine
- MP, 6-Mercaptopurine




- TPMT, thiopurine-s-methyltransferase
- NUDT15, nudix hydrolase

***NUDT15* variants** were recently linked with azathioprine toxicity in East and South Asians (frequency Asians >> Caucasians)

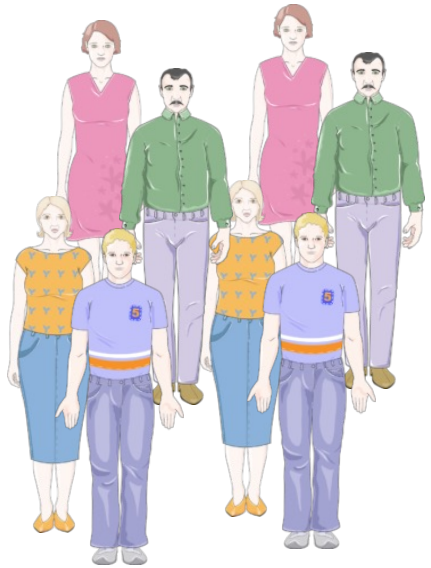
Tanaka & Saito J Pers Med 2021

WILEY AP&T Alimentary Pharmacology & Therapeutics

# HLA-DQA1-HLA-DRB1 polymorphism is a major predictor of azathioprine-induced pancreatitis in patients with inflammatory bowel disease

A. Wilson[1,2,3] | L. E. Jansen[4] | R. V. Rose[5] | J. C. Gregor[2] | T. Ponich[2] | N. Chande[2] | R. Khanna[2] | B. Yan[2] | V. Jairath[2,5] | N. Khanna[2] | M. Sey[2] | M. Beaton[2] | K. McIntosh[2] | W. A. Teft[1] | R. B. Kim[1]

Azathioprine-exposed IBD patients



Retrospective cohort study (n=373)

A/A = 0.5% risk of pancreatitis

A/C = 4% risk of pancreatitis

C/C = 15% risk of pancreatitis

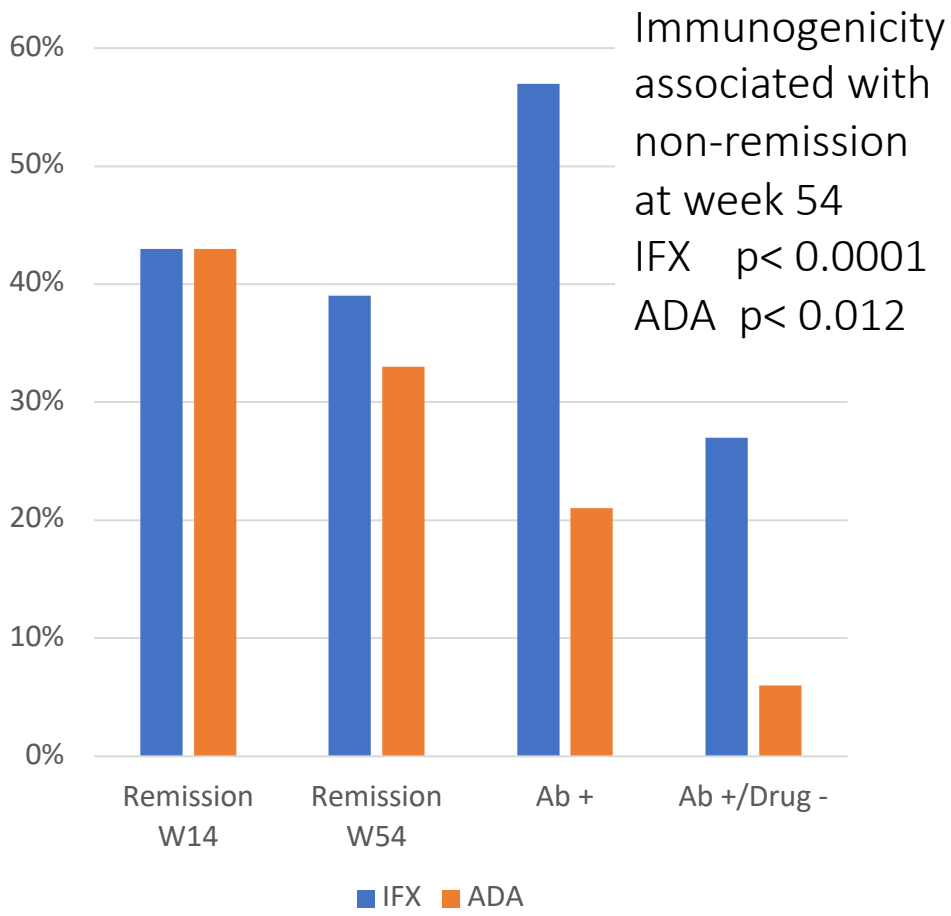
Wilson...Kim *et.al.* APT 2018; Medical art adapted with permission from http://smart.servier.com

# Immunogenicity of anti-TNF drugs

- British cohort, 1610 patients initiating anti-TNF naïve patients with clinical and biomarker evidence of active Crohn's disease

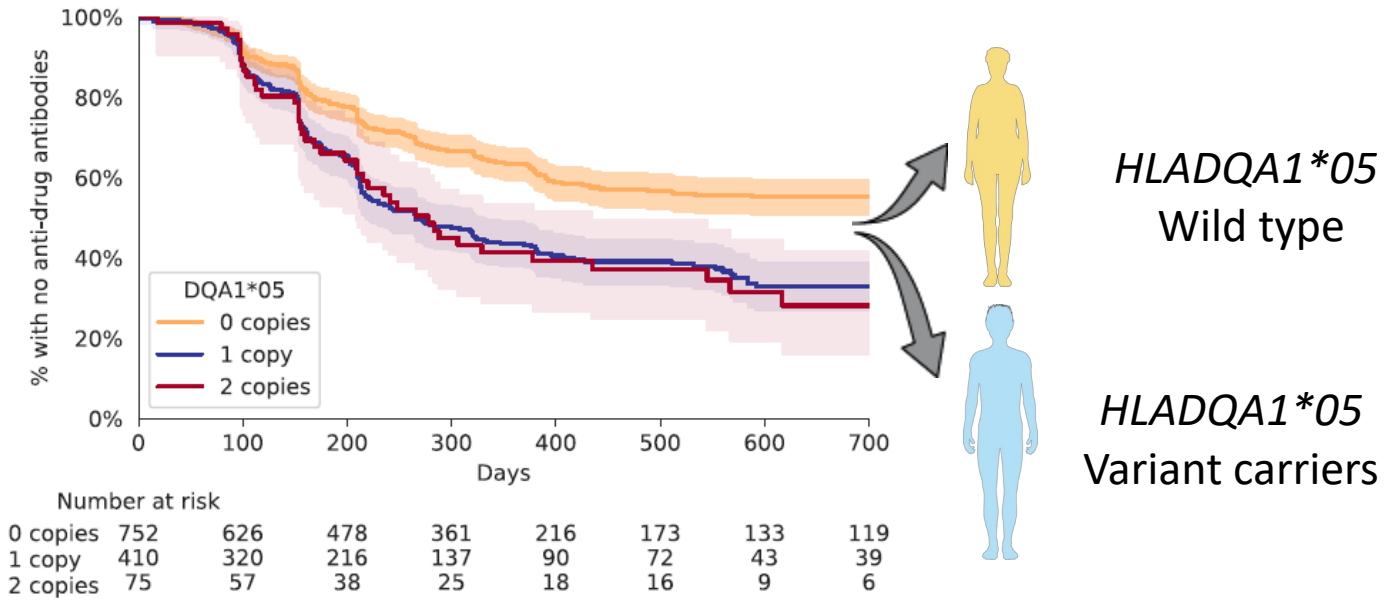
- 60% received concurrent IM therapy
  - 52% AZA/6-MP
  - 6% MTX

- Both protective against antibody formation with statistically significant hazard ratios
  - IFX 0.39
  - ADA 0.44




Kennedy *et.al.* Lancet Gastroenterol Hepatol 2019 (PANTS)

# PANTS Consortium




*HLADQA1*05*
Wild type

*HLADQA1*05*
Variant carriers

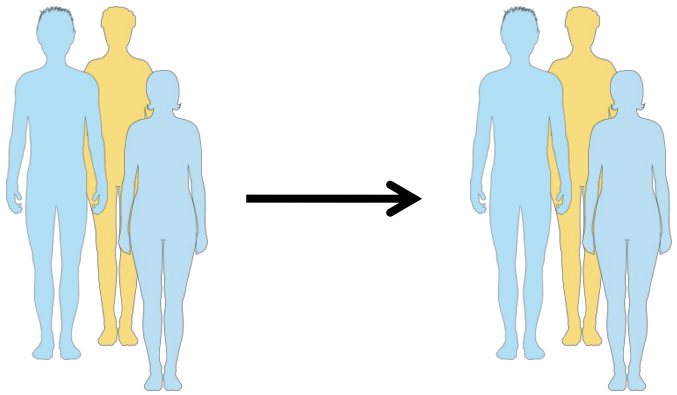
The risk of infliximab anti-drug antibody formation

Sazonovs *et.al.* Gastro 2020; Medical art adapted with permission from http://smart.servier.com

AP&T Alimentary Pharmacology & Therapeutics WILEY

# *HLADQA1*05* genotype predicts anti-drug antibody formation and loss of response during infliximab therapy for inflammatory bowel disease

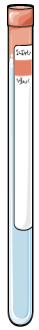
Aze Wilson[1,2,3] | Celeste Peel[4] | Qian Wang[5] | Athanasios Demetri Pananos[6] | Richard B. Kim[1,2]



Retrospective
IBD TPMT cohort
(n=889)



Infliximab-exposed
IBD cohort
(n=262)



HLADQA1*05
rs74291249
genotyping

**Collect clinical variables:**

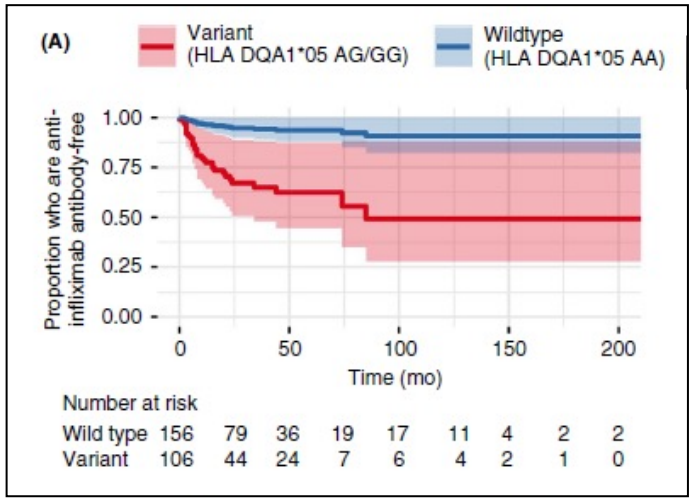
Demographic data
Infliximab ADA
Infliximab response
- Loss of response
- Adverse drug event

Infliximab discontinuation

Wilson..Kim *et.al.* APT 2020; Medical art adapted with permission from http://smart.servier.com

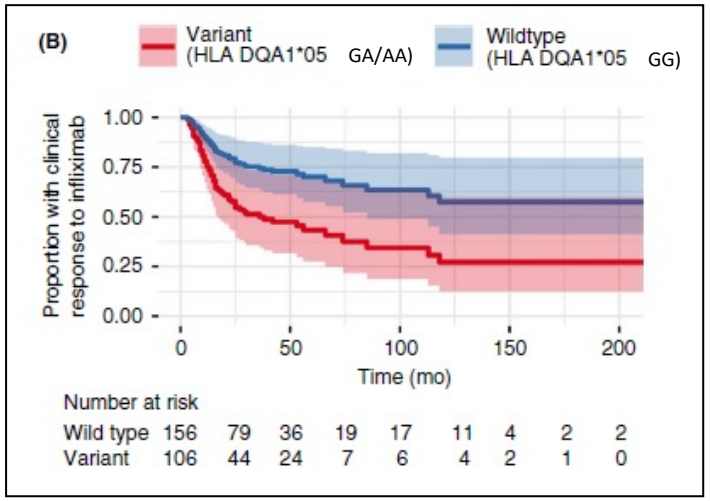
# Outcomes with infliximab

Anti-drug antibody formation



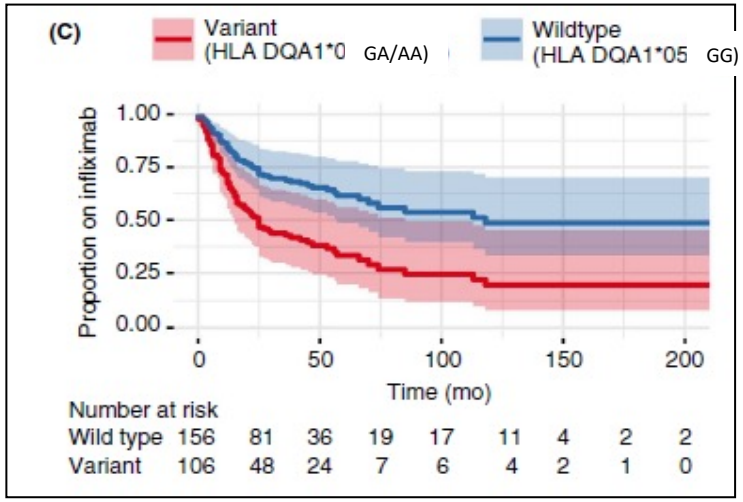

Adjusted HR = 7.29, 95% CI 2.97-17.91, $p=1.46X10^{-5}$

Loss of response




Adjusted HR = 2.34, 95% CI 1.41-3.88, p<0.001

Treatment discontinuation



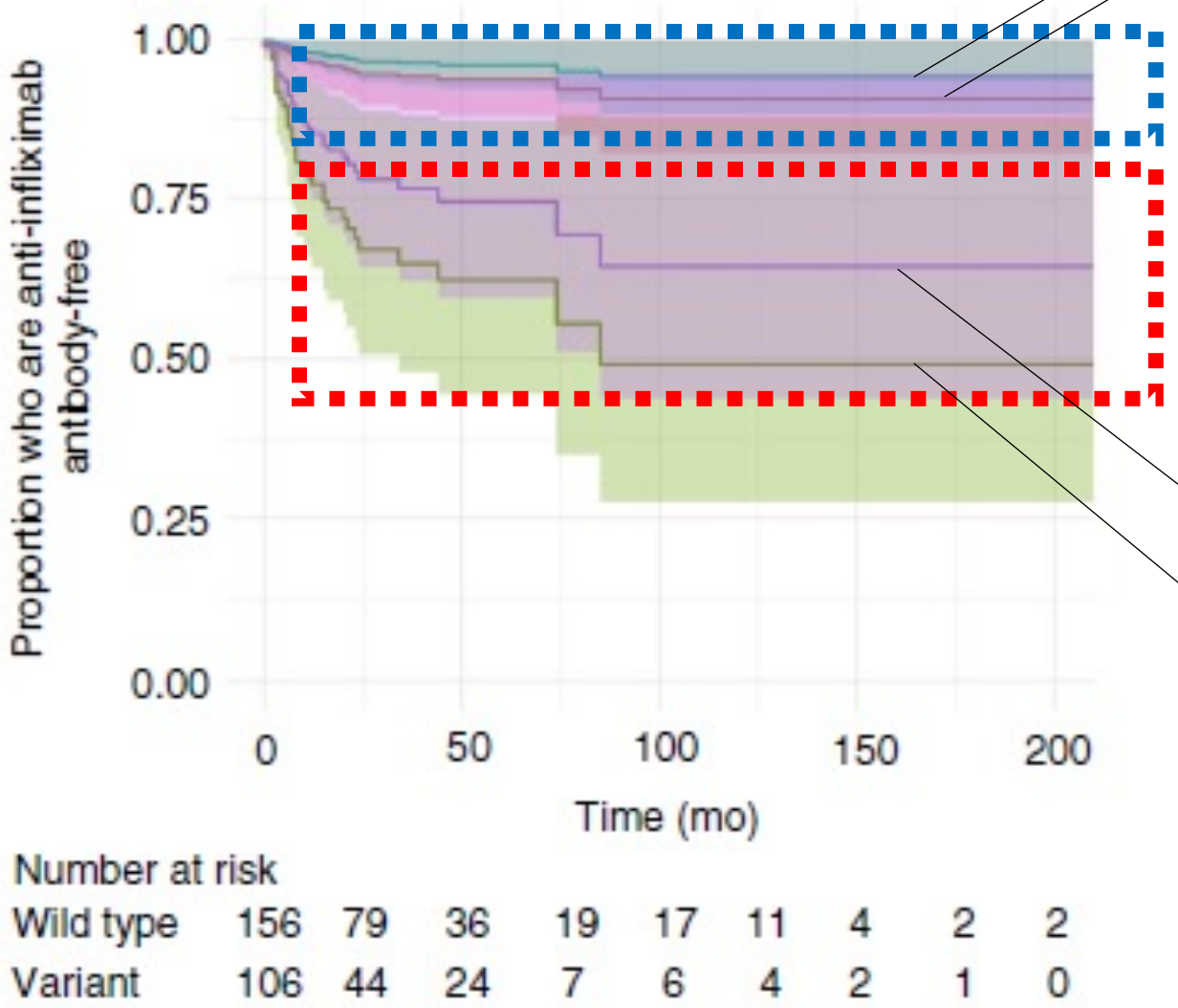

Adjusted HR = 2.27, 95% CI 1.46-3.53, $p=2.53x10^{-4}$

**<u>Take home message:</u>**

Variant carriers (G/A or A/A) are higher risk for infliximab anti-drug antibody formation; loss of response; treatment discontinuation

Wilson…Kim *et.al.* APT 2020

# Can the risk be modified?




Combination therapy

No combination therapy

Wildtype
(HLA DQA1*05 GG)

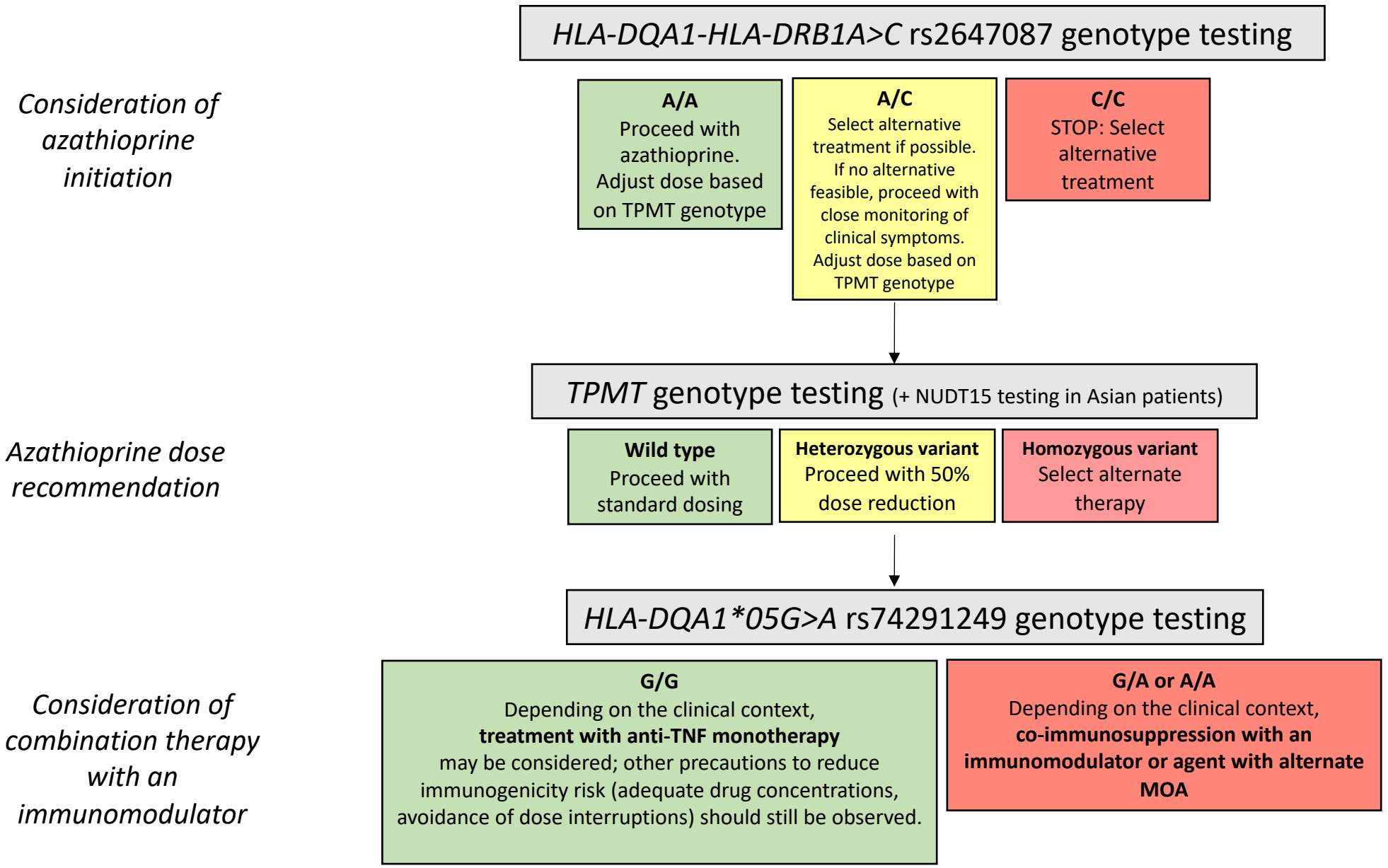
Variant
(HLA DQA1*05 GA or AA)

Combination therapy

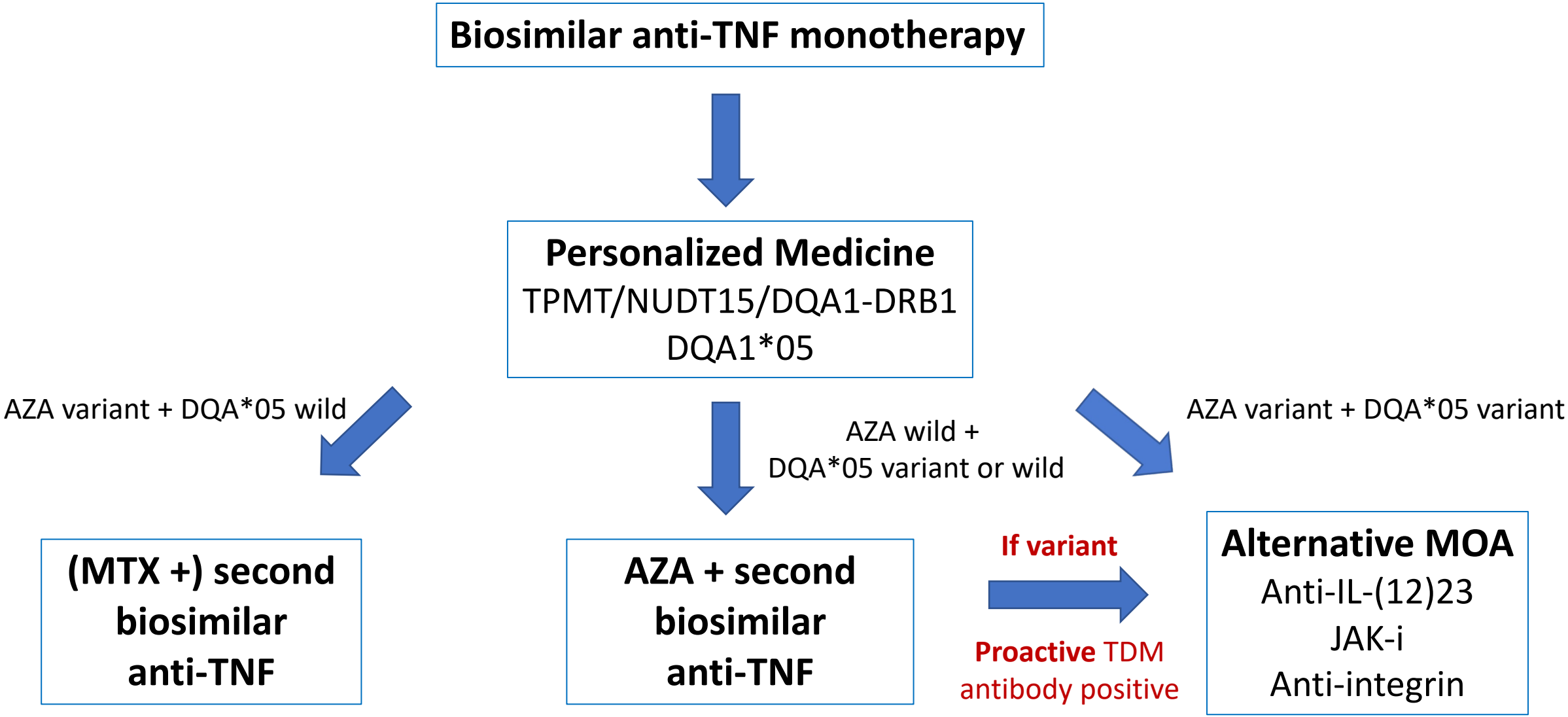
No combination therapy

Wilson…Kim *et.al.* APT 2020

# ODB eligible CD (2018)



# ODB eligible steroid refractory CD (2024)



# QUESTIONS?