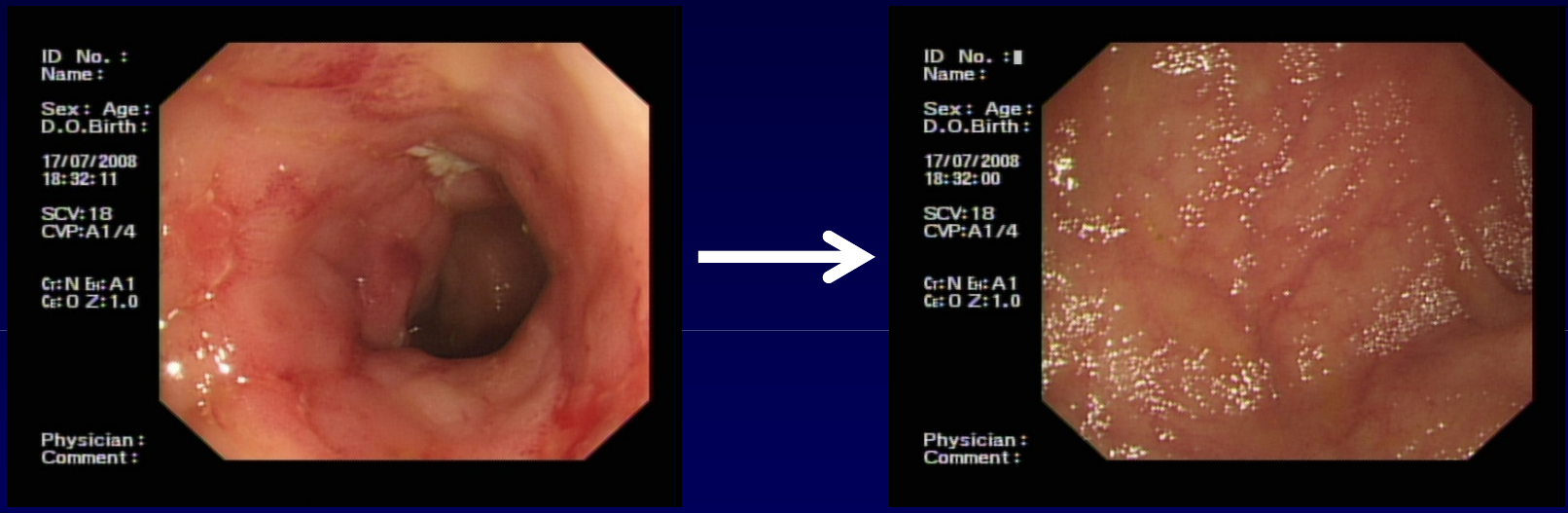
06.12.2013

INNOVATIONacademy

Personalising thiopurine therapy in IBD

Dr. Jeremy Sanderson

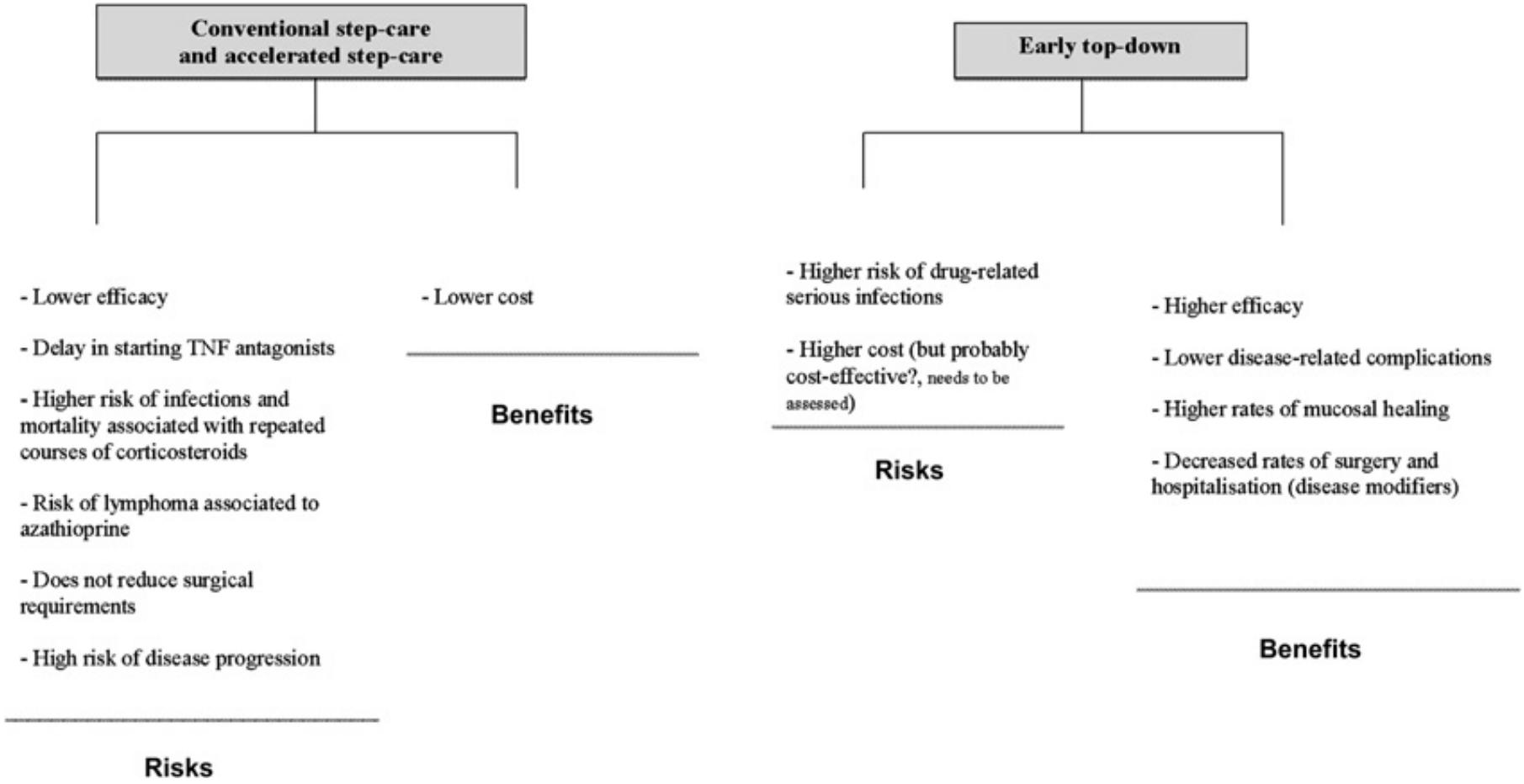
Mucosal healing in Crohn's disease……..



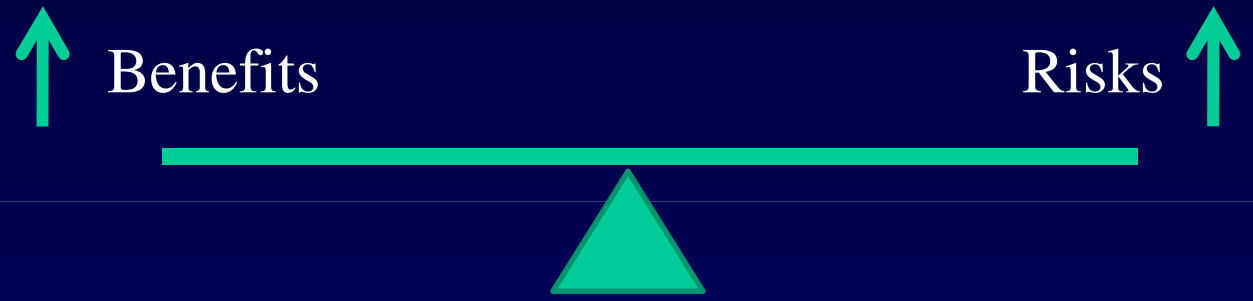
…… the holy grail

Early use of immunosuppressives or TNF antagonists for the treatment of Crohn's disease: time for a change

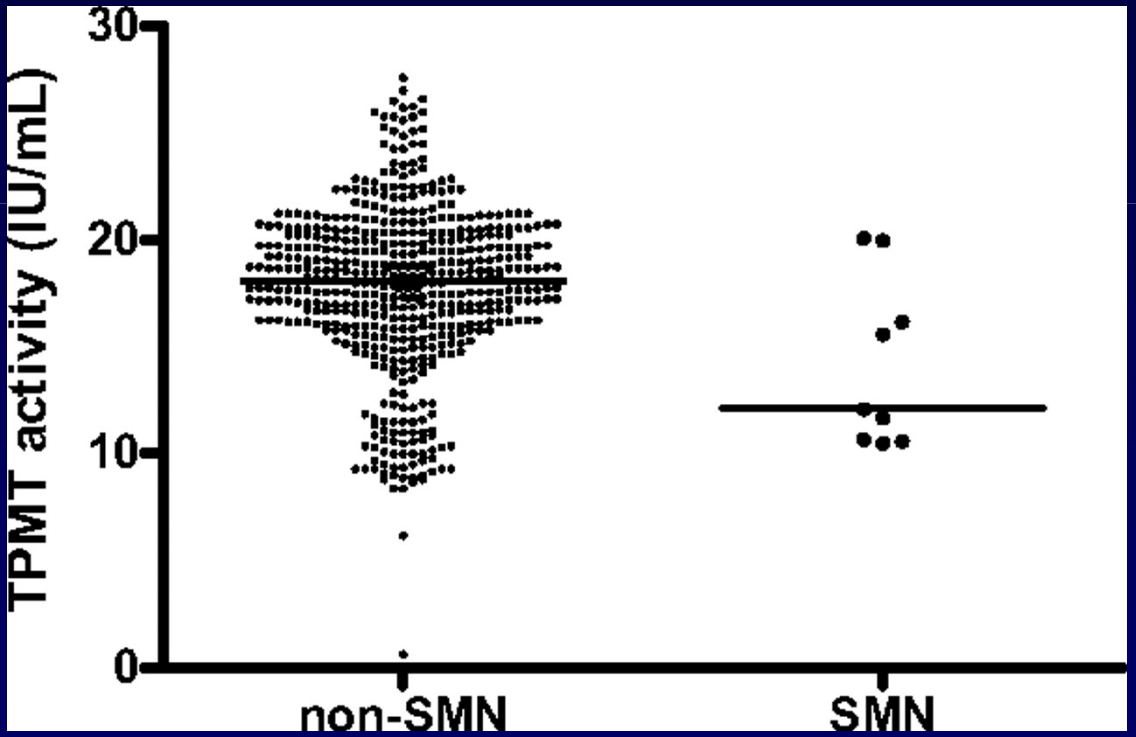
Ingrid Ordás,[1,2] Brian G Feagan,[3] William J Sandborn[1]

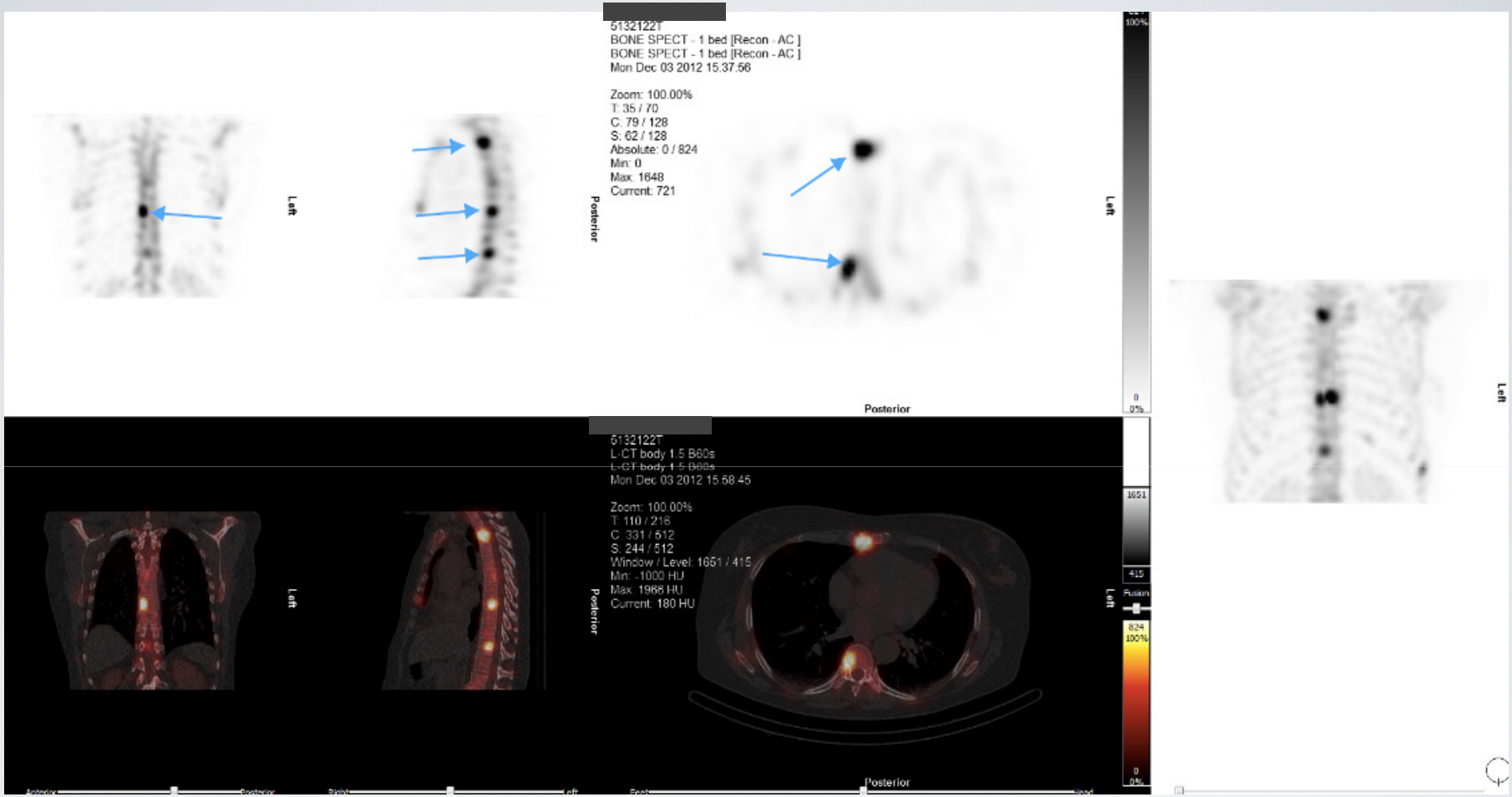

Conventional step-care
and accelerated step-care
- Lower efficacy
- Delay in starting TNF antagonists
- Higher risk of infections and mortality associated with repeated courses of corticosteroids
- Risk of lymphoma associated to azathioprine
- Does not reduce surgical requirements
- High risk of disease progression
Risks
- Lower cost
Benefits
Early top-down
- Higher risk of drug-related serious infections
- Higher cost (but probably cost-effective?, needs to be assessed)
Risks
- Higher efficacy
- Lower disease-related complications
- Higher rates of mucosal healing
- Decreased rates of surgery and hospitalisation (disease modifiers)
Benefits

Optimising outcomes in Crohn's disease……



Methotrexate/6-mercaptopurine maintenance therapy influences the risk of a second malignant neoplasm after childhood acute lymphoblastic leukemia: results from the NOPHO ALL-92 study

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BONE SPECT - 1 bed [Recon - AC]
BONE SPECT - 1 bed [Recon - AC]
Mon Dec 03 2012 15:37:56
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L-CT body 1.5 B60s
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Max: 1966 HU
Current: 180 HU
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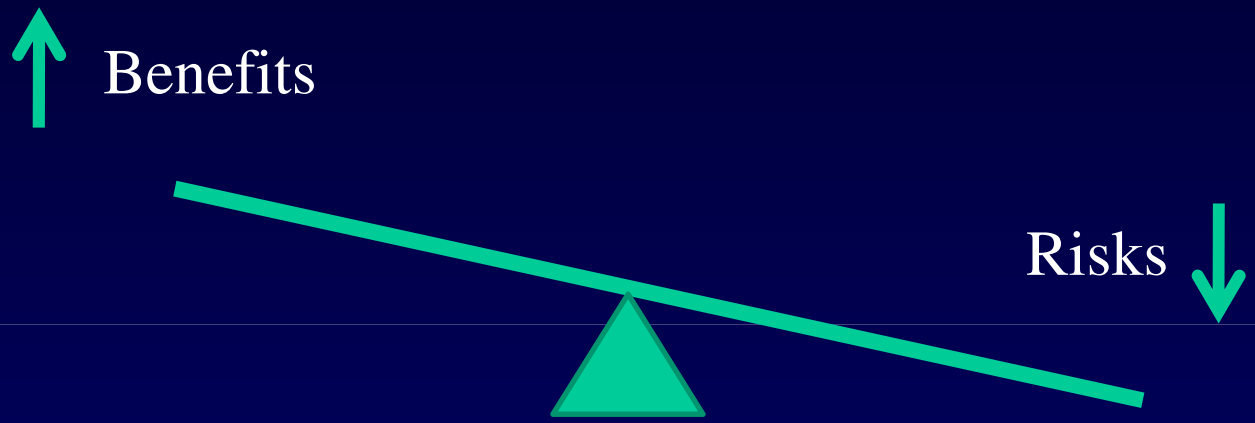
Foot
Head

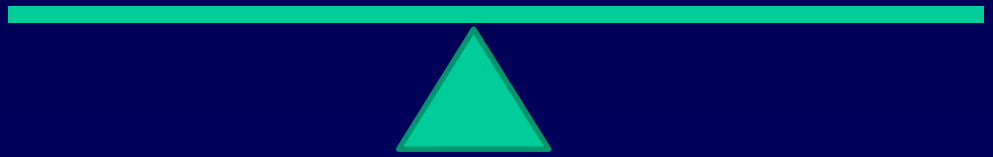
Optimising outcomes in Crohn's disease……

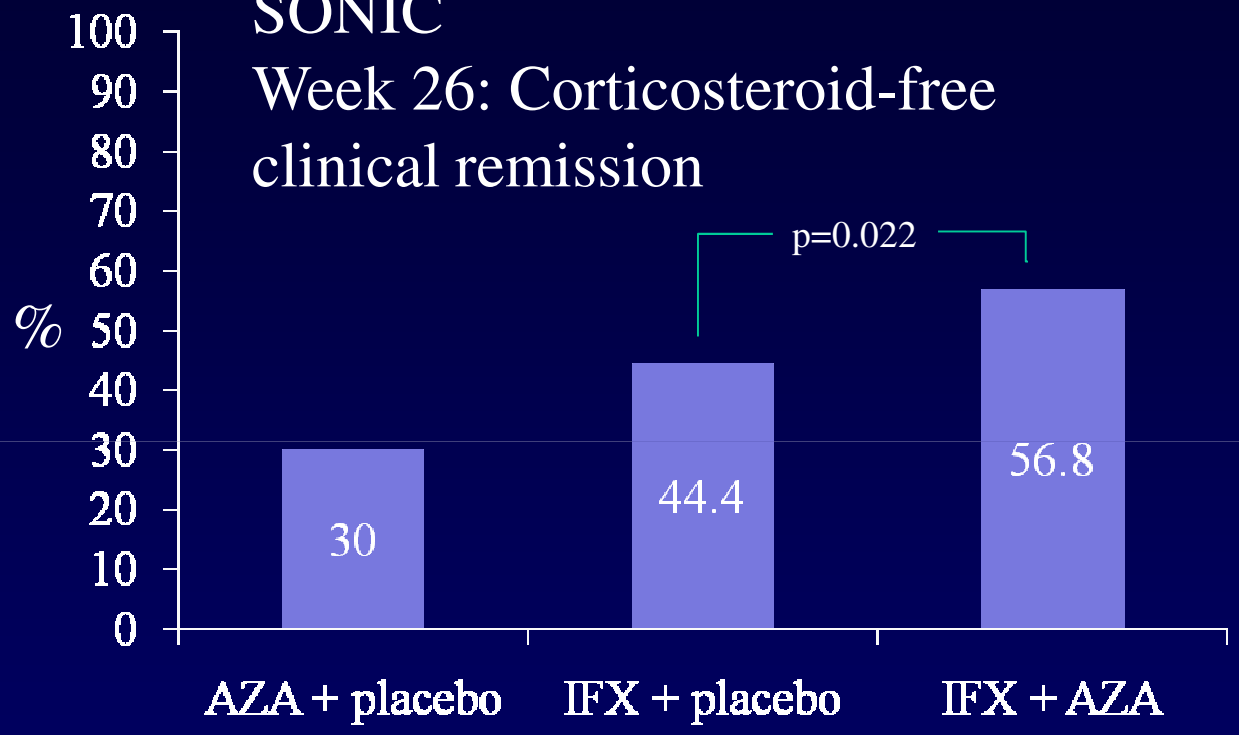


…..hence we need to optimise the use of drug Rx

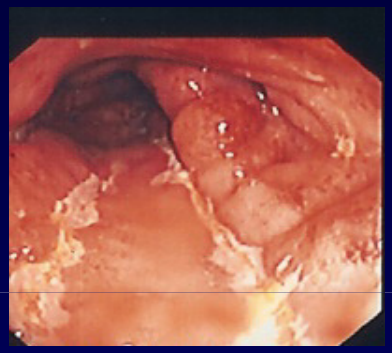
Are biologics actually safer than conventional immunosuppression?

IS :	Biologics:
Thiopurines	Infliximab
MTX	Adalimumab





Severe CD

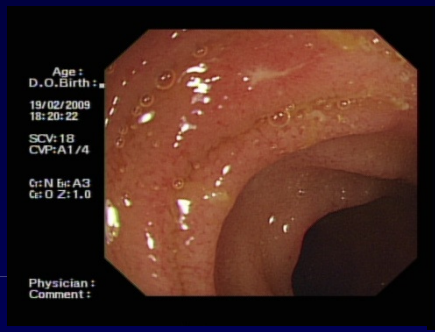


Biologics

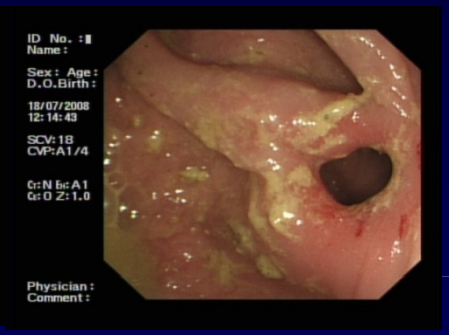
AZA / 6-MP

All roads lead to a thiopurine?

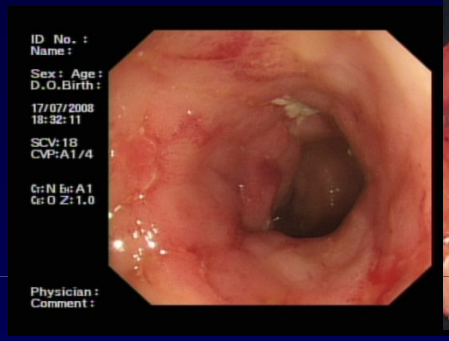
Mild CD



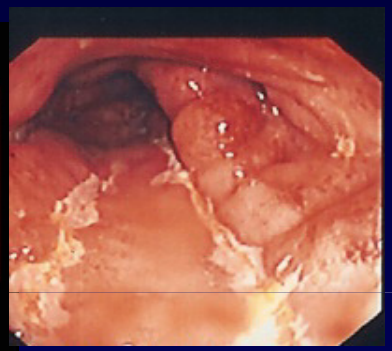
Post-op CD



Moderate CD



Severe CD



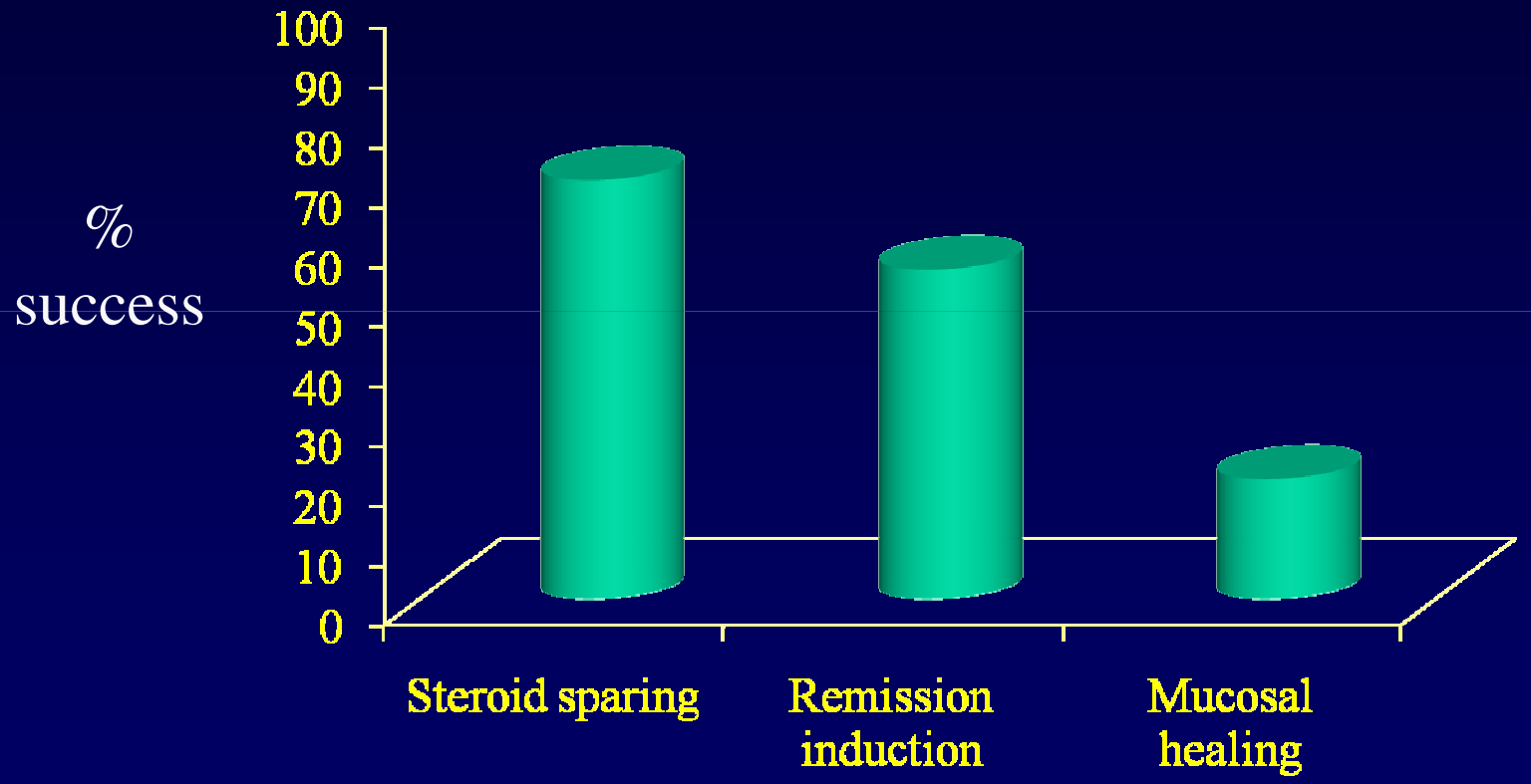
"Mild"
Non-healing Rx
5-ASA
Diet
Antibiotics

Steroids

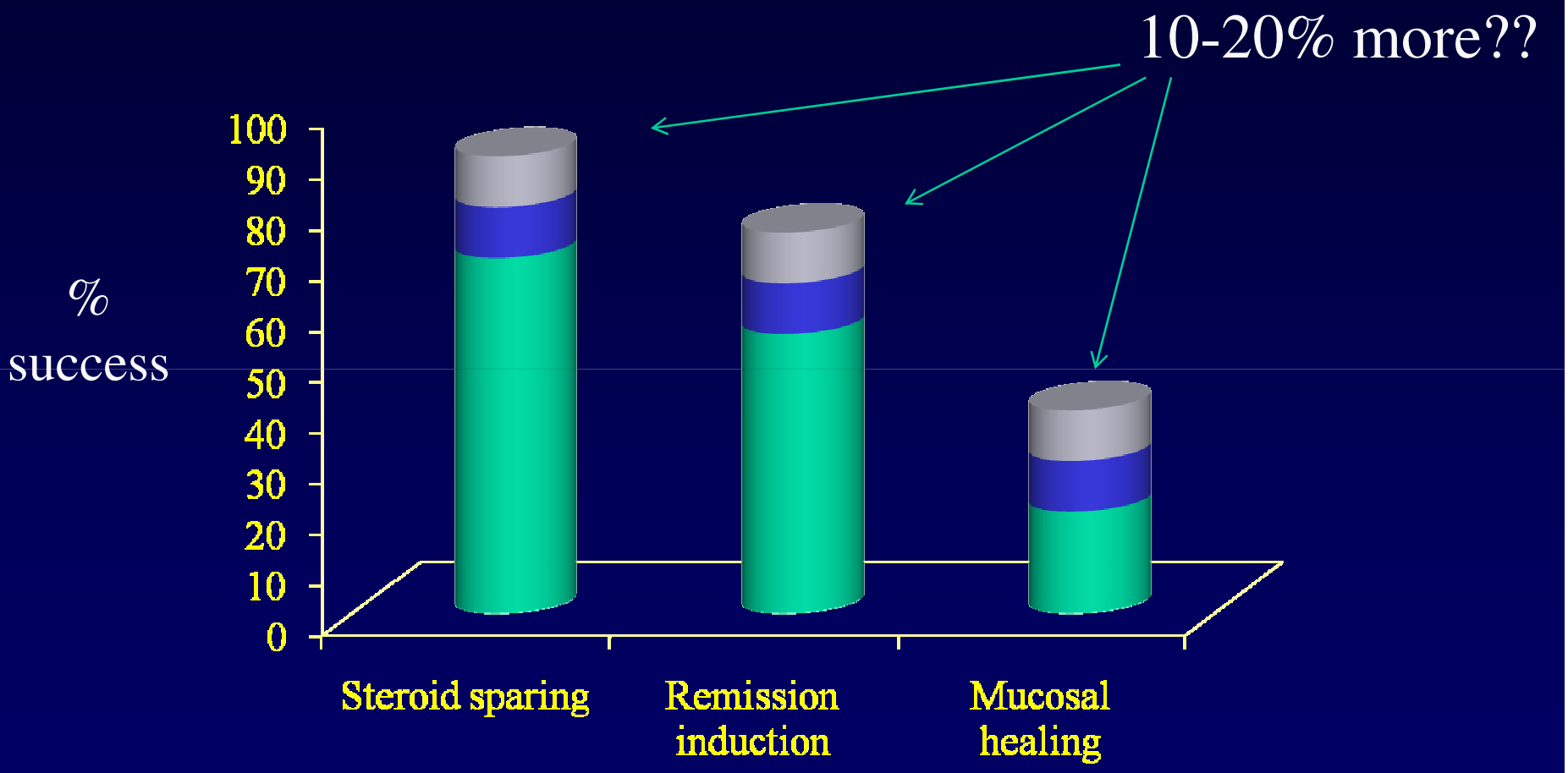
Biologics

AZA / 6-MP

Getting more out of thiopurines in Crohn's disease



Getting more out of thiopurines in Crohn's disease



.... Application of knowledge from pharmacogenetics and therapeutic monitoring

What is Pharmacogenetics ?

… individual variation in the handling of drugs in the body according to genetically determined factors.

Pharmacogenetics: not a new concept…….

1950's

N-acetyl transferase activity (fast and slow acetylators)
Isoniazid, hydralazine, procainamide

Butyrylcholinesterase
Suxamethonium chloride

Pharmacogenetics: why is it important ?

Efficacy of nearly all 1st line drug therapy limited by:

Toxicity

Variable response / drug resistance

Adverse drug reactions (ADR) and hospital admissions

- 6.5% admissions due to ADR in 6 months
- In 80% of cases, median bed stay 8 days – 4% of hospital bed capacity
- Overall fatality 0.15%
- Projected cost to NHS - £466 million pa
- Most ADR avoidable

Pirmohamed et al , BMJ 3 July 2004

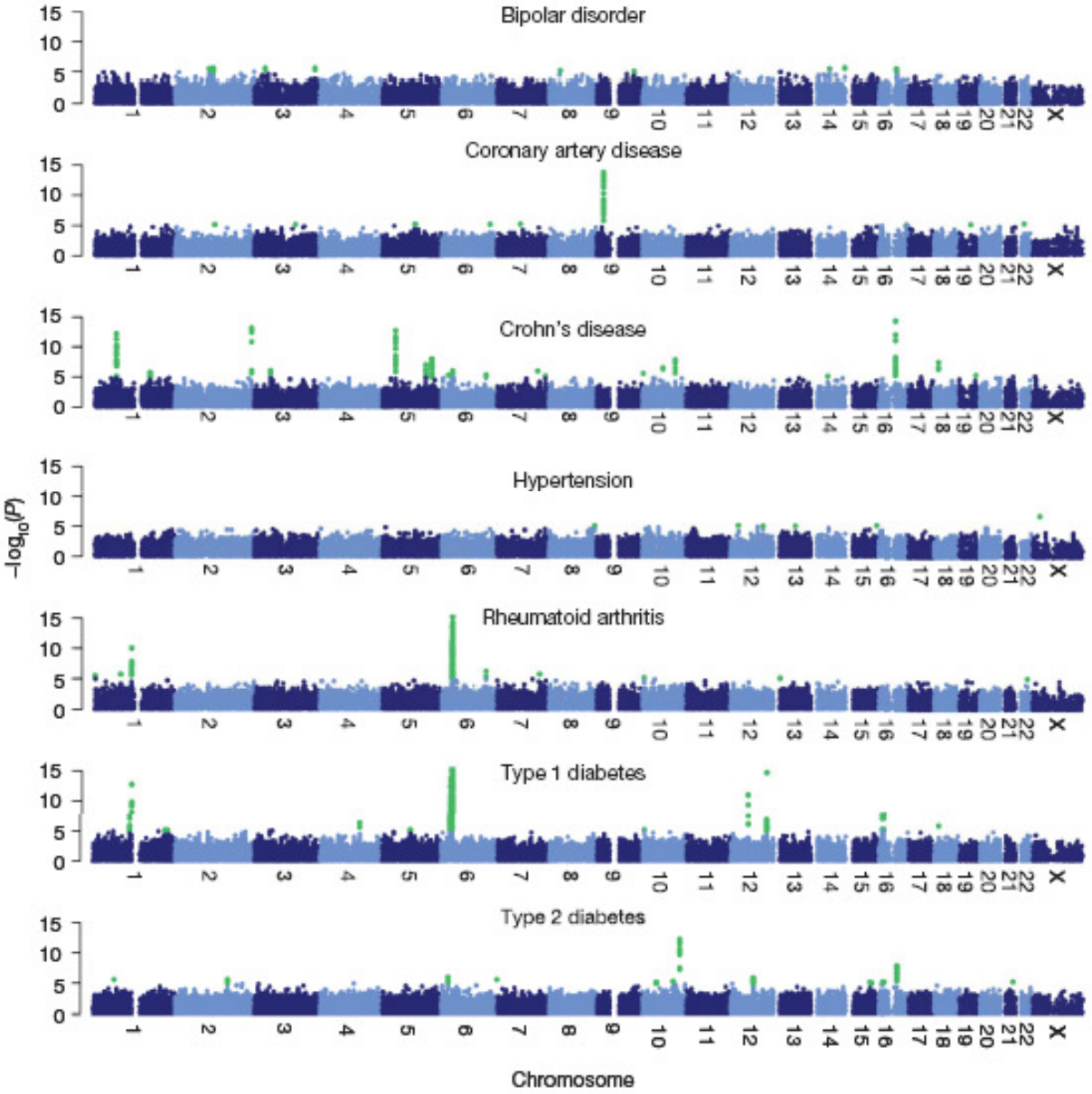
Pharmacogenomics

- Classical genetics approach
- Whole genome SNP screen.
- Identify haplotypes and test for association with clinical response

Pharmacogenetics

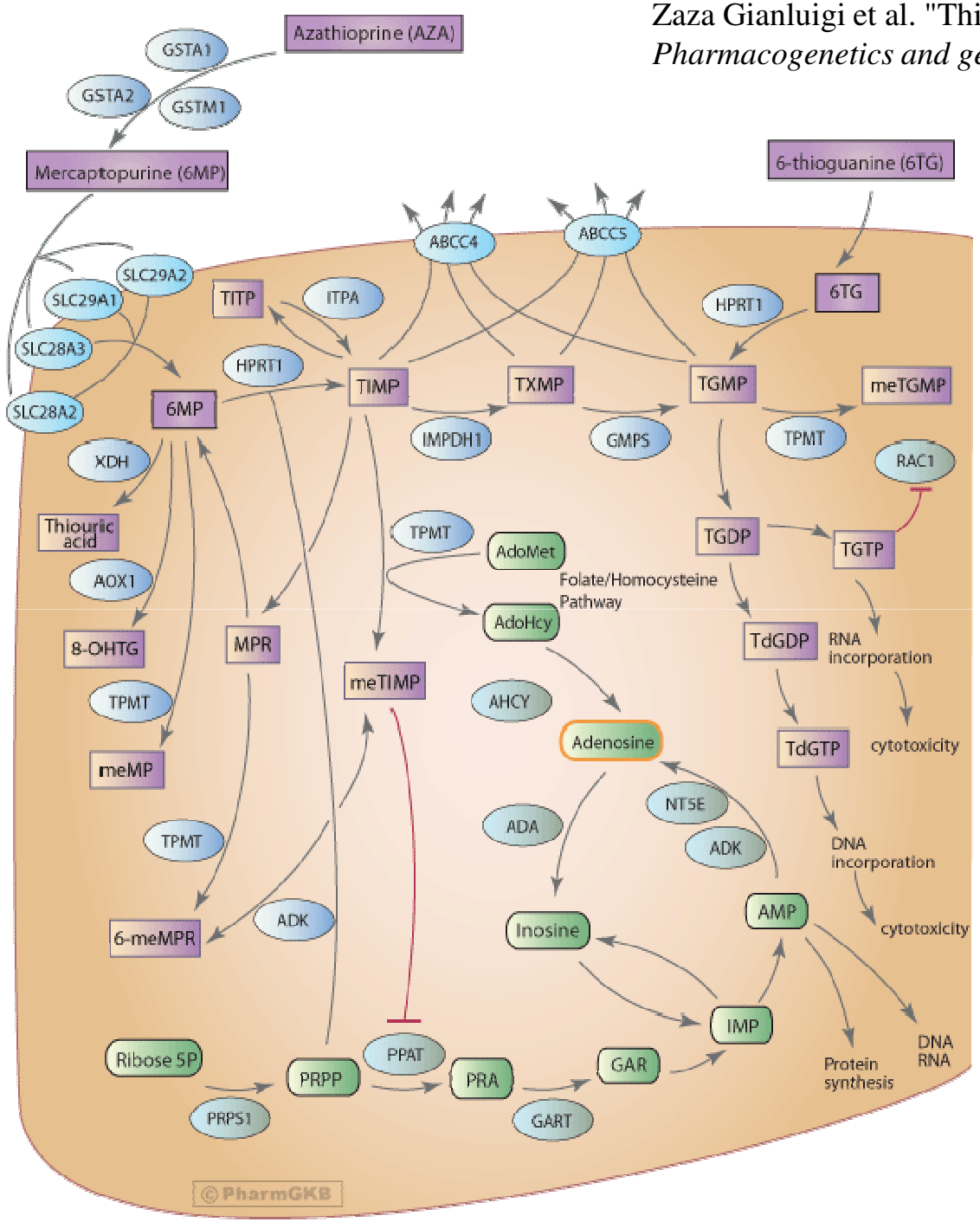
- Knowledge of drug metabolism necessary to identify candidate genes
- Identify SNPs and test for association

Wellcome Trust Case Control Consortium
Genome scan of 7 common diseases



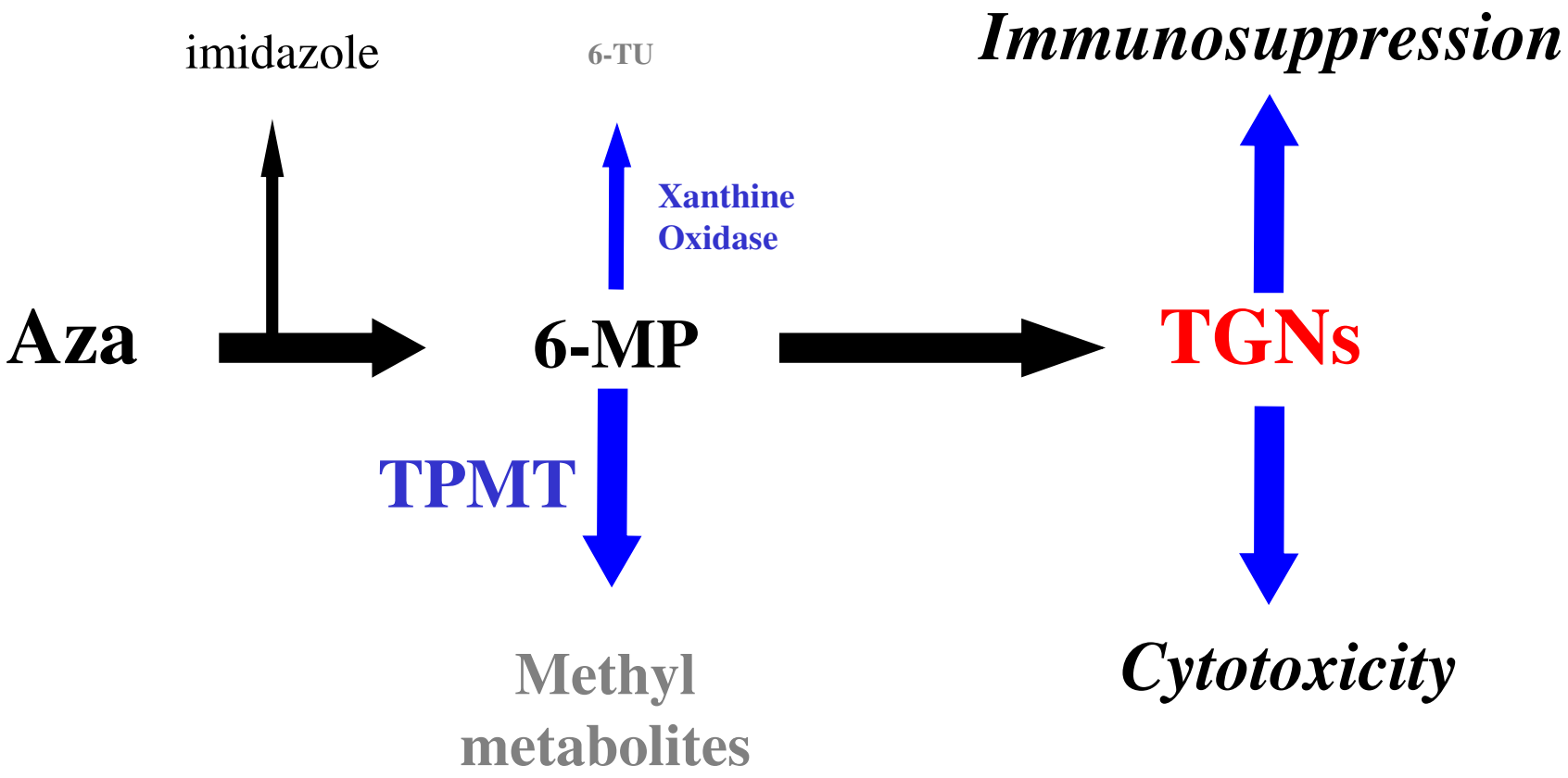
rs17095545	14	58555364	33/151	37/643	3.89E-08	Intergenic between DAAM1 and DACT1 - both involved in Wnt signalling pathway
rs11158240	14	58524528	32/150	37/643	9.25E-08	Intergenic between DAAM1 and DACT1 - both involved in Wnt signalling pathway
rs1480039	12	26313915	28/156	32/648	3.87E-07	Between ITPR2 and SSPN
rs276229	10	106071926	13/171	7/671	1.07E-06	Next to GSTO1 an 2!!!!!
rs276214	10	106080777	13/171	8/672	3.16E-06	Next to GSTO1 an 2!!!!!
rs7749425	6	100538365	95/89	222/456	4.12E-06	In MCHR2 (melanin-concentrating hormone receptor 2)
rs12278342	11	22840459	49/135	89/591	5.96E-06	In EST near GAS2 - modulates cell susceptibility to p53-dependent apoptosis
rs12275725	11	22844222	49/135	89/591	5.96E-06	In EST near GAS2 - modulates cell susceptibility to p53-dependent apoptosis
rs4255538	11	22850700	49/135	89/591	5.96E-06	In EST near GAS2 - modulates cell susceptibility to p53-dependent apoptosis
rs7014476	8	42195203	21/163	22/656	6.14E-06	Near IKBKB - inhibitor of NFKB (PMID: 12697733)
rs2429763	11	22866627	49/133	90/586	6.44E-06	In EST near GAS2 - modulates cell susceptibility to p53-dependent apoptosis
rs2470306	11	22862861	49/135	90/590	7.76E-06	In EST near GAS2 - modulates cell susceptibility to p53-dependent apoptosis
rs2429752	11	22875997	49/135	90/590	7.76E-06	In EST near GAS2 - modulates cell susceptibility to p53-dependent apoptosis
rs7773011	6	100538275	94/90	223/457	8.16E-06	In MCHR2 (melanin-concentrating hormone receptor 2)
rs11015025	10	26606462	30/154	43/635	8.75E-06	In Glutamic Acid Decarboxylase 2
rs10869038	9	73376056	44/138	78/600	9.84E-06	Between TRPM3 and TMEM2
rs4279668	9	73374683	45/139	80/600	1.16E-05	Between TRPM3 and TMEM3
rs11253562	10	148946	86/96	205/469	1.47E-05	
rs1536864	9	73387245	45/139	81/599	1.52E-05	Between TRPM3 and TMEM2

Zaza Gianluigi et al. "Thiopurine pathway"
Pharmacogenetics and genomics (2009)

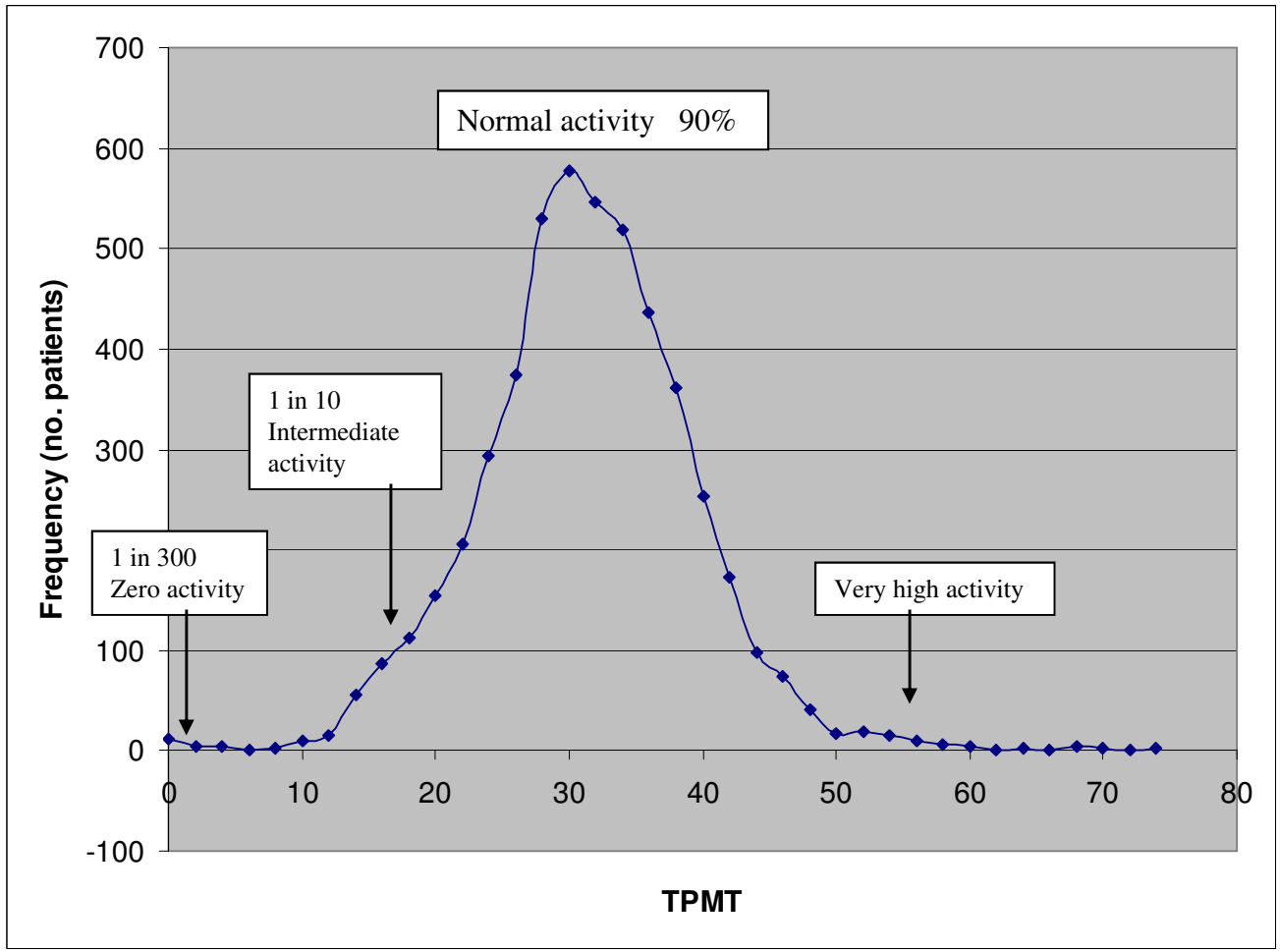


Old dogs……..new tricks……..

Biotransformation of 6-MP to thioguanine nucleotides



Polymorphic Trimodal distribution of TPMT activity



TPMT activity distribution in 5000 PRL samples, 1990 - 2001

Sanderson et al ACB 2004

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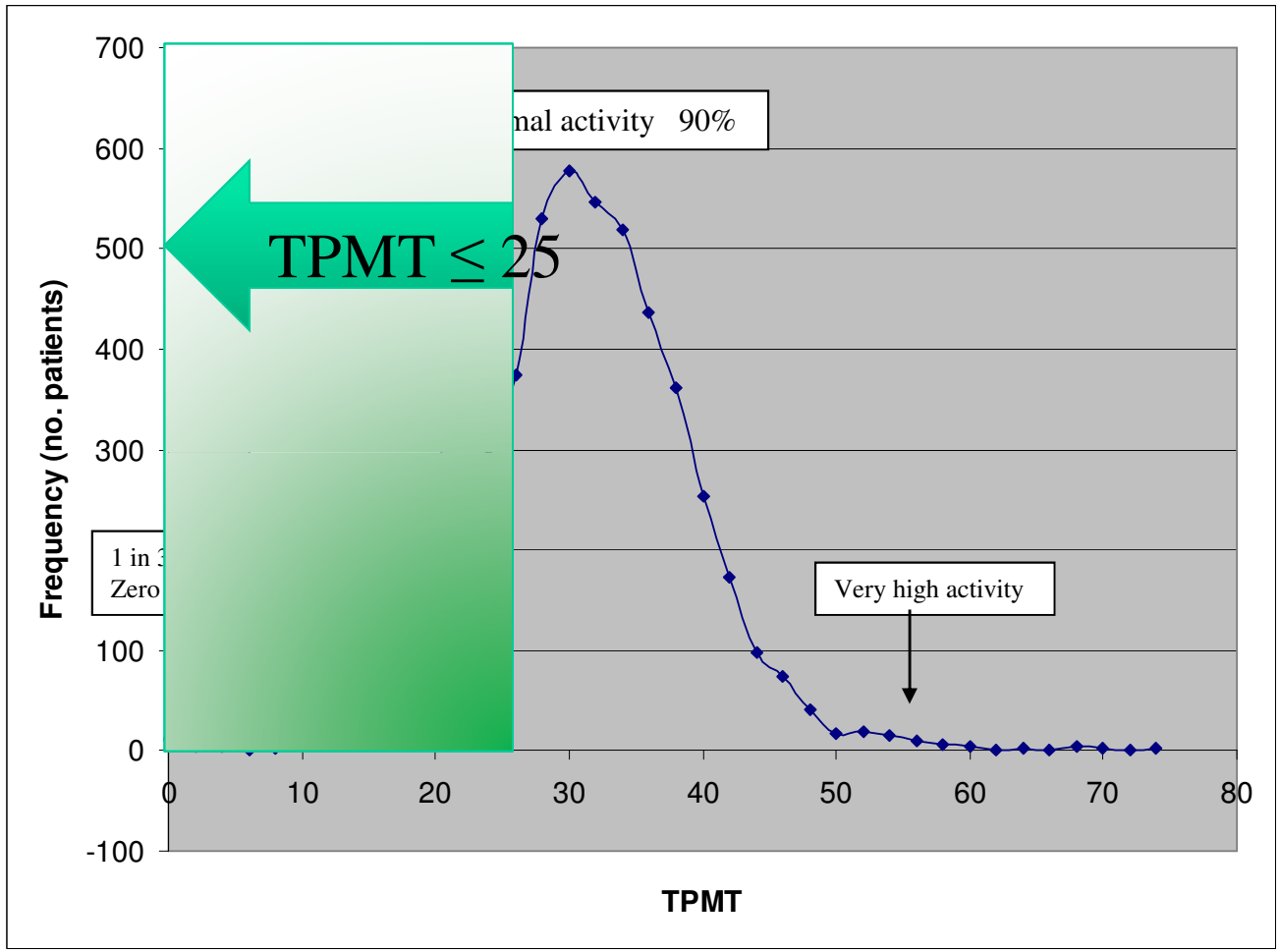

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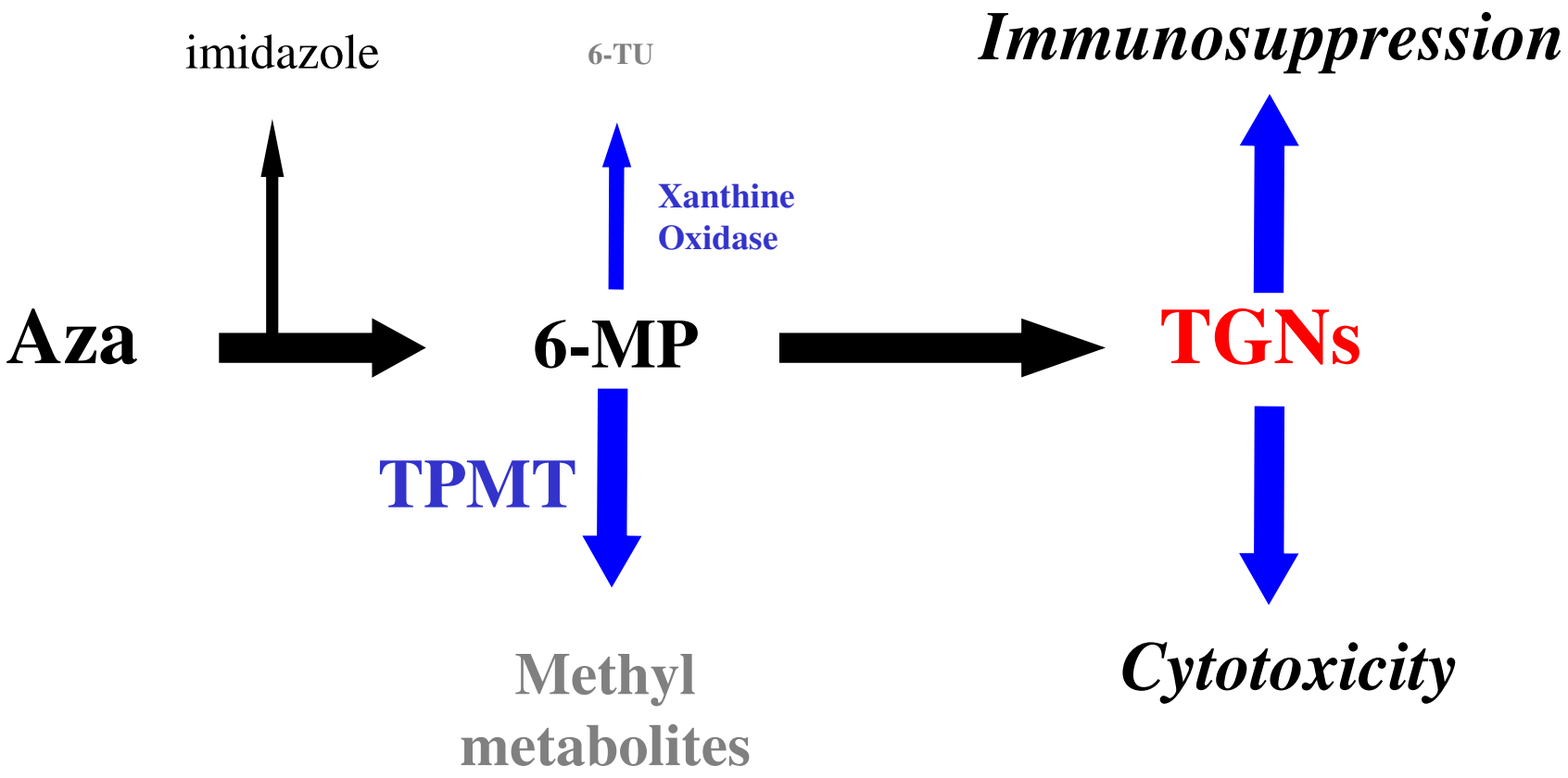
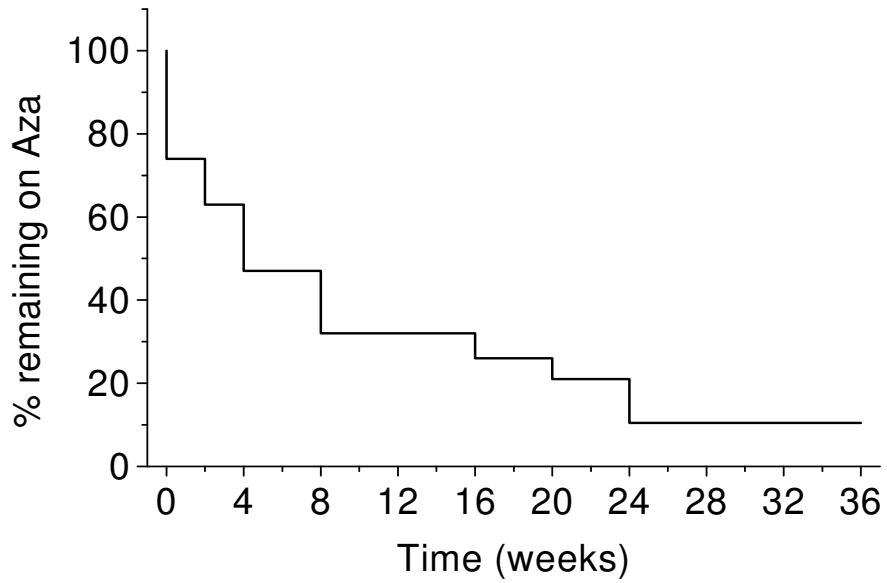
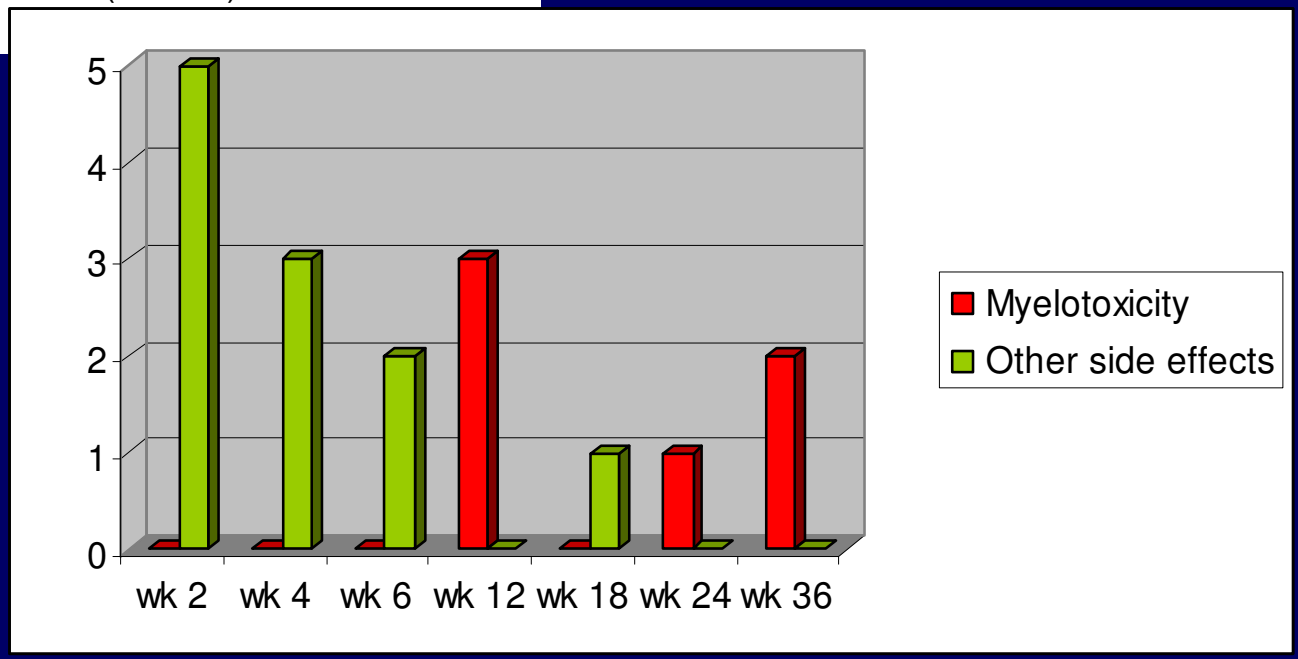


Heterozygous TPMT deficiency
Time to withdrawal on Aza 2mg/kg





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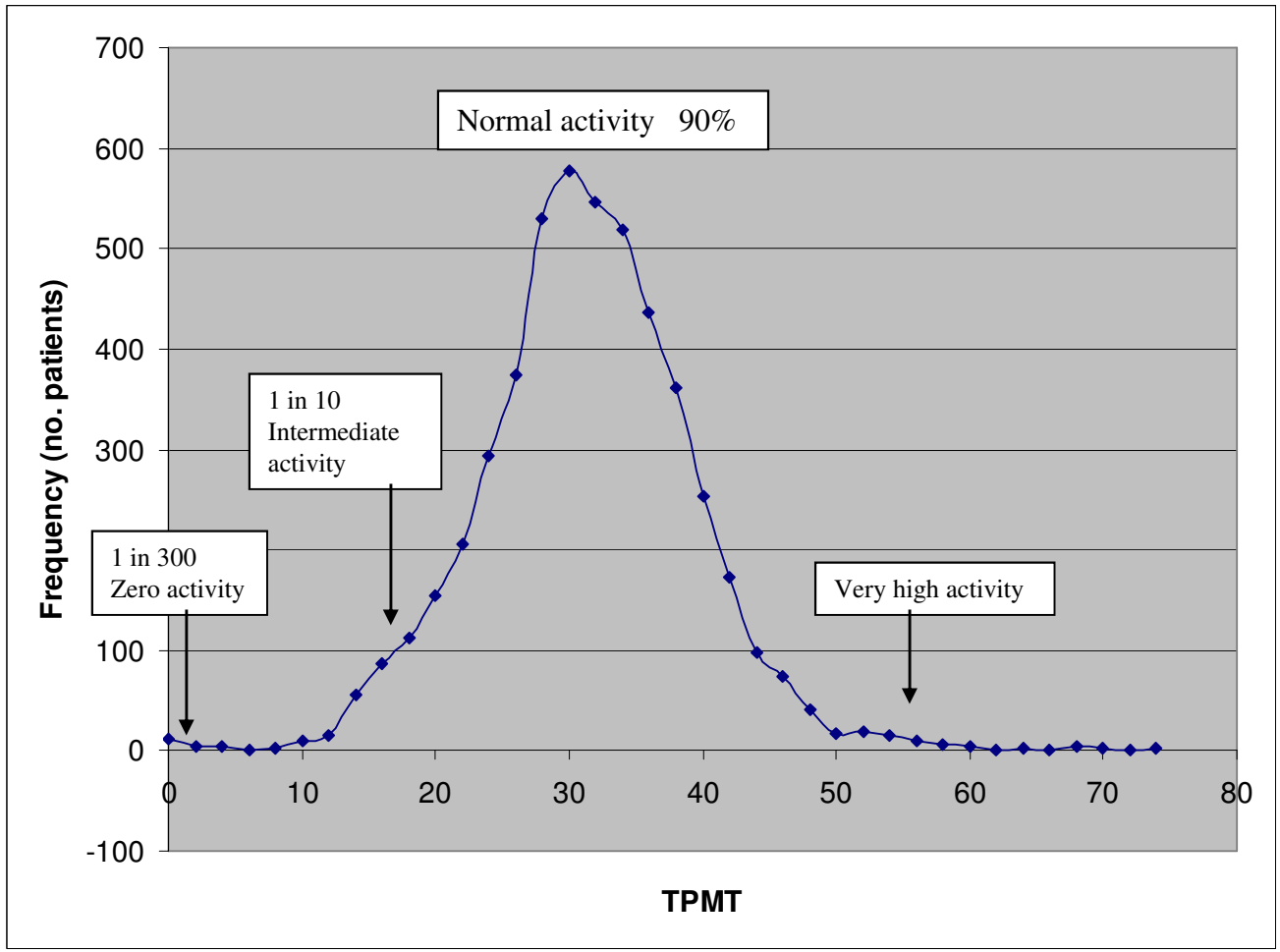

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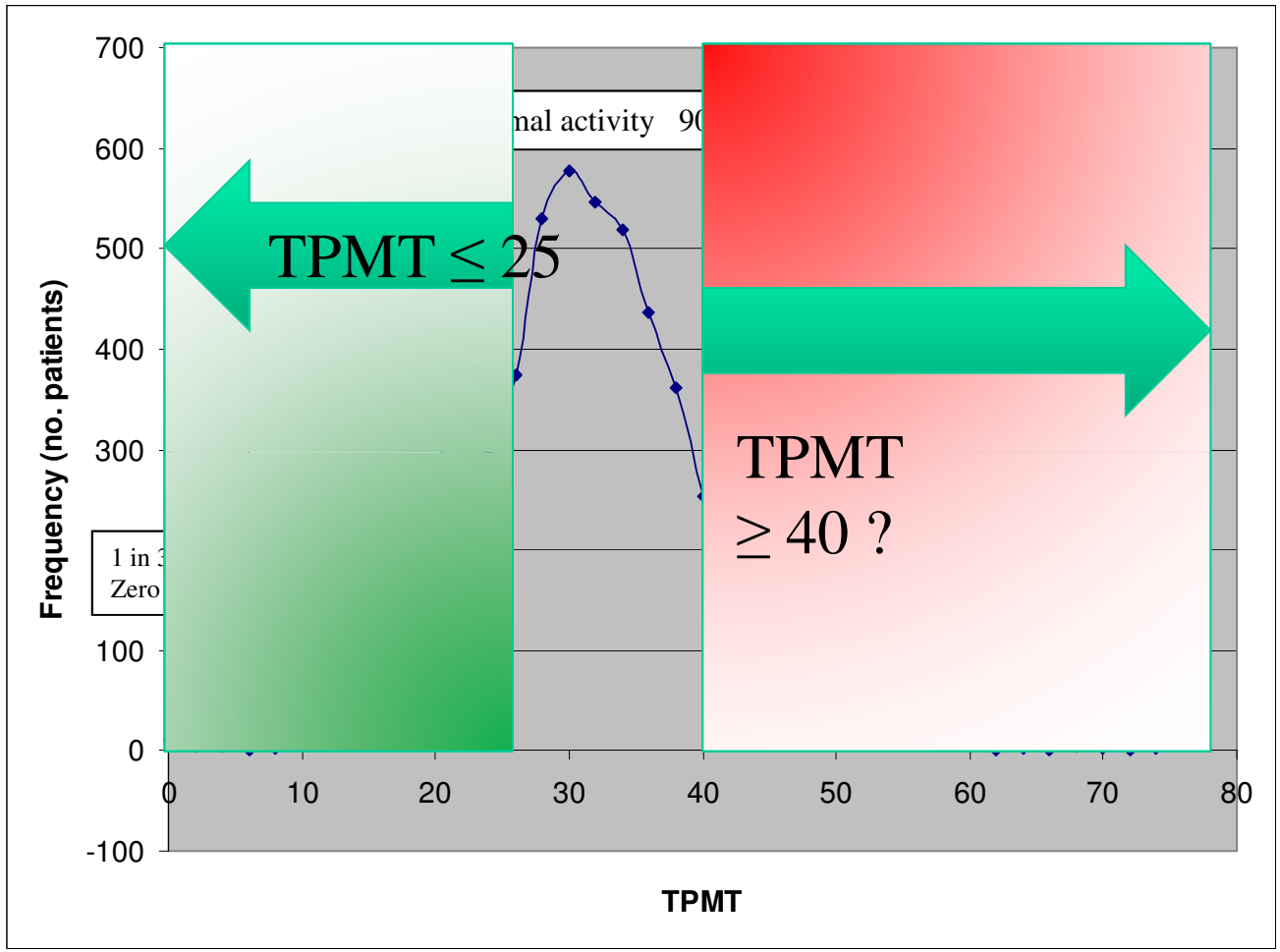
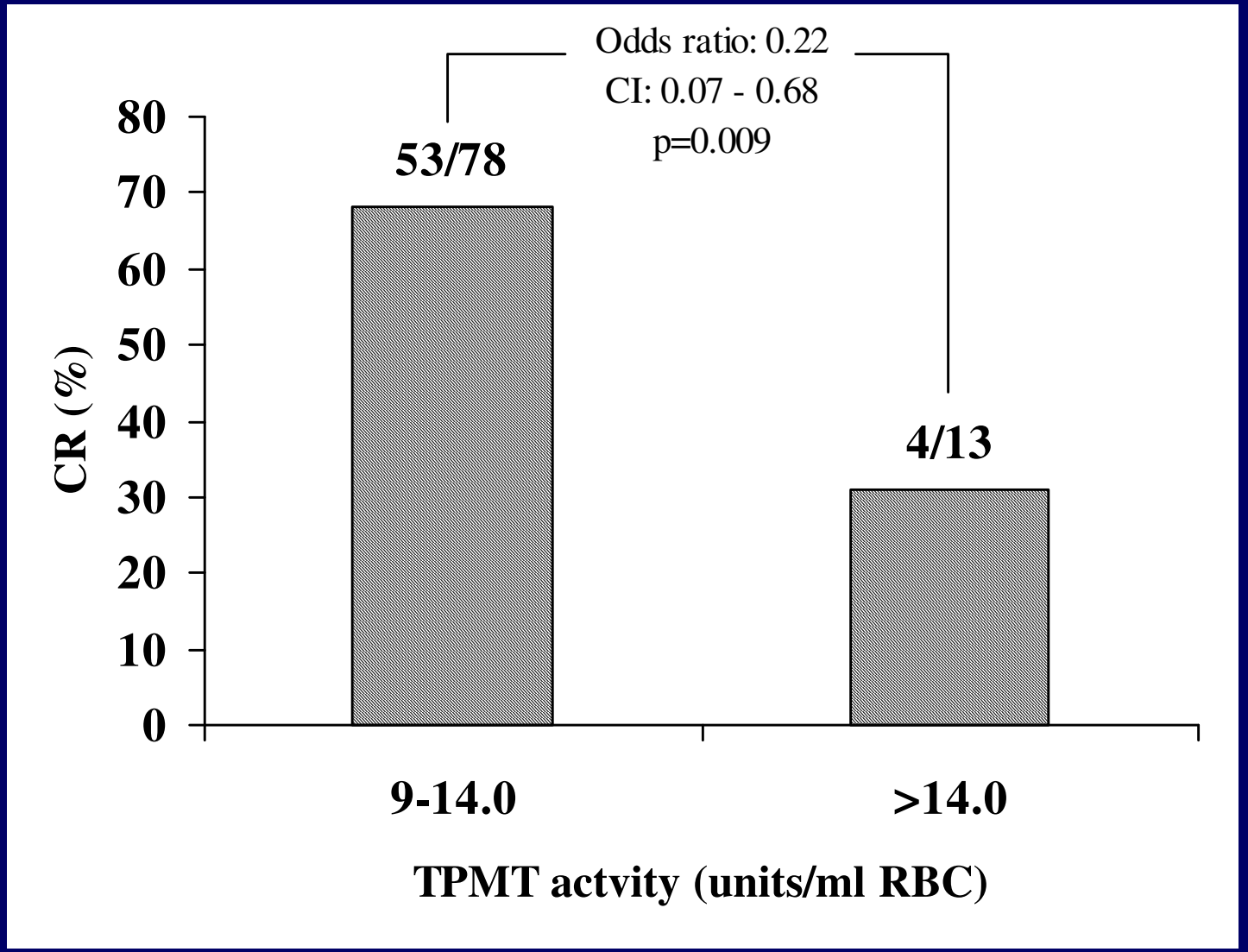


TPMT activity distribution in 5000 PRL samples, 1990 - 2001

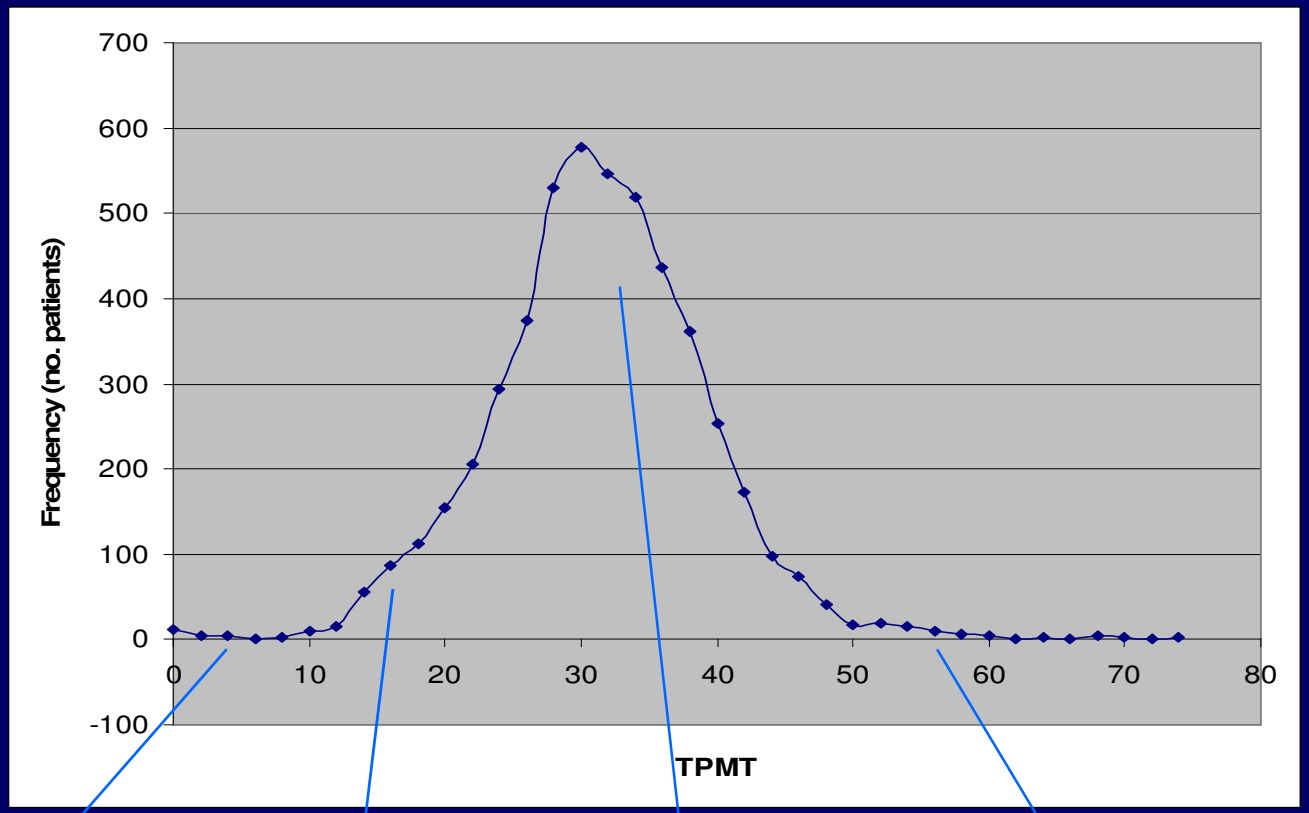
Sanderson et al ACB 2004

TPMT activity versus clinical response to AZA in IBD



Adjusted for dose and time on AZA

Translation of Aza pharmacogenetics into clinical practice



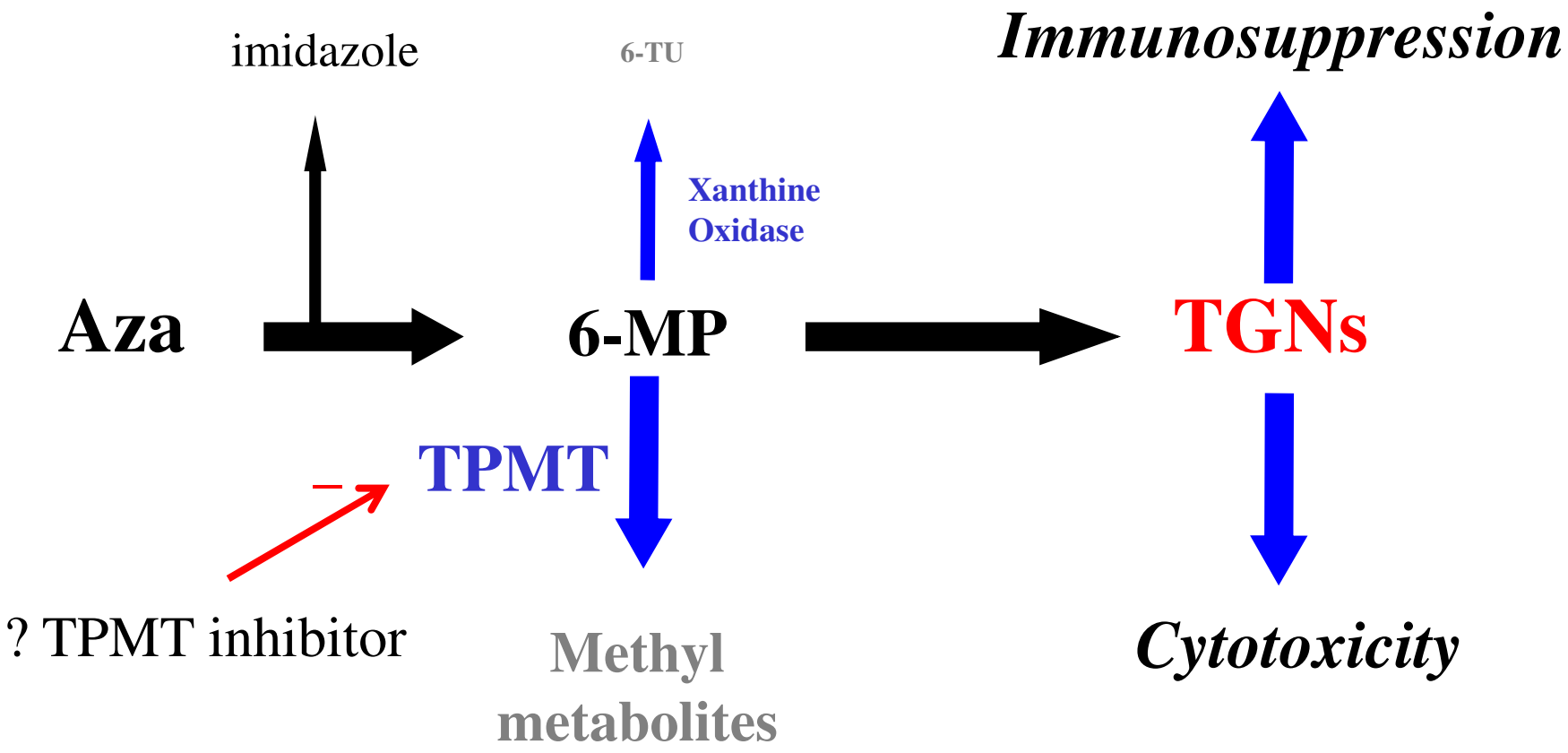
Avoid : High risk of fatal toxicity

50% dosing strategy

Usual dosing strategy

Hypermethylation : ?higher dose AZA

Biotransformation of 6-MP to thioguanine nucleotides



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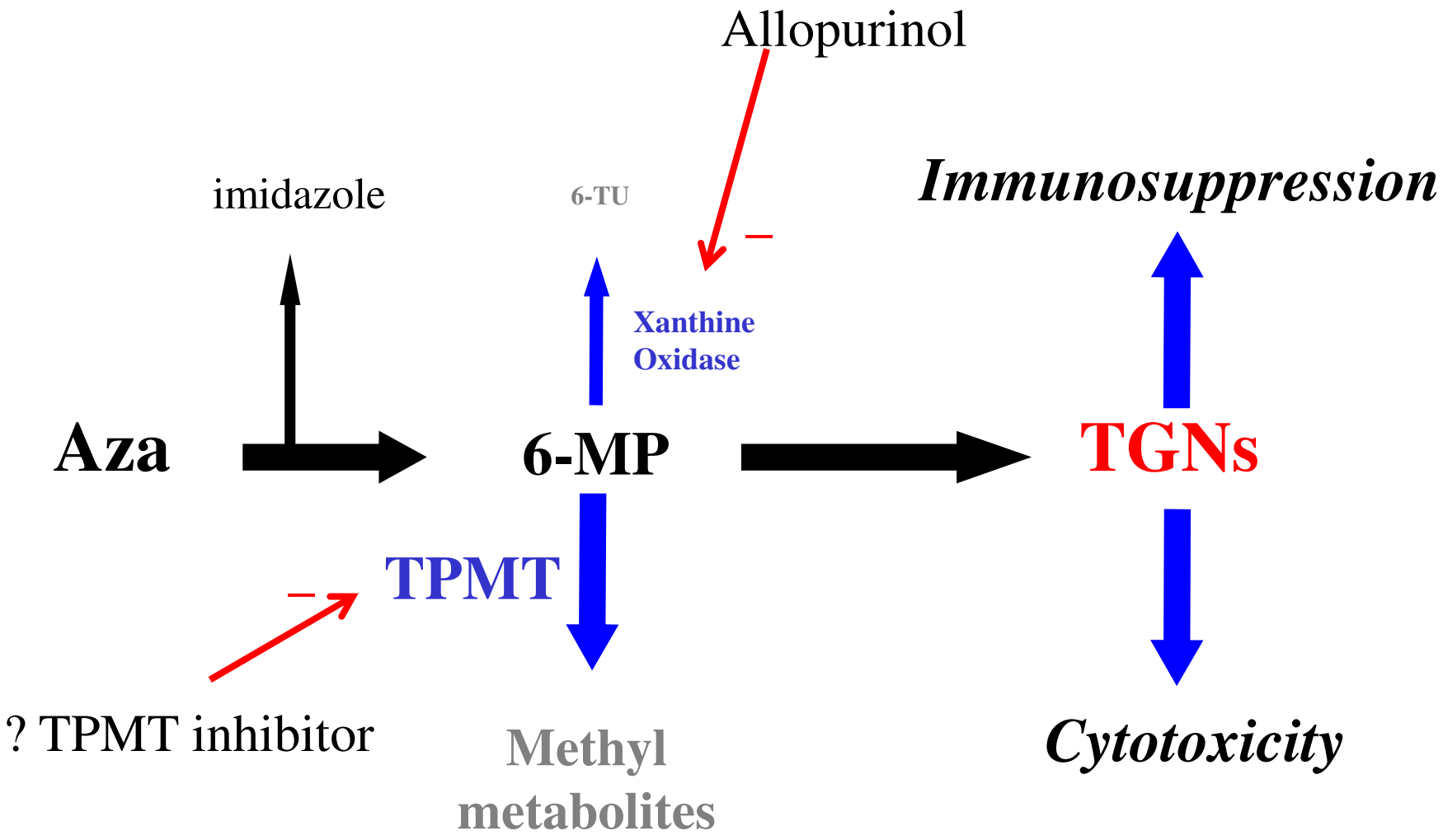


Allopurinol for thiopurine non-response and toxicity

Sparrow et al Clin Gast Hep 2007 JCC 2009

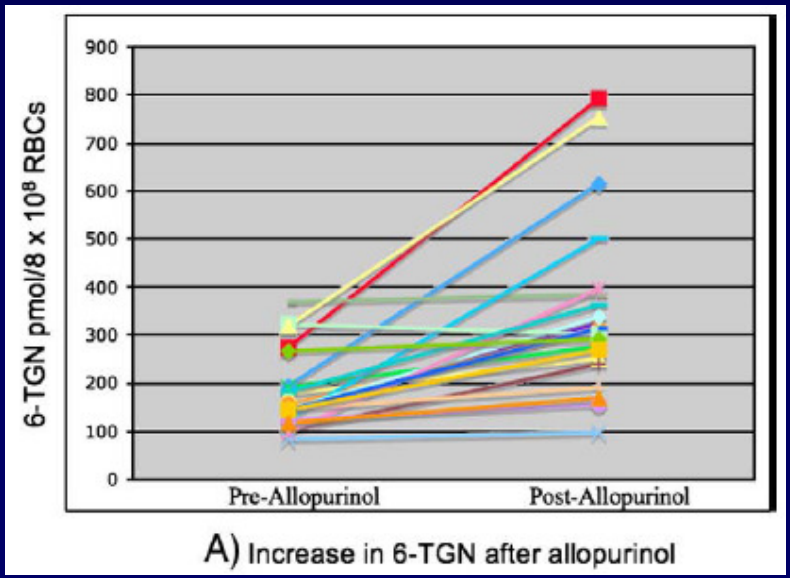
25 non-responders AZA/6-MP, low TGN, high 6-MMP

Allopurinol 100mg + 25-50% dose reduction

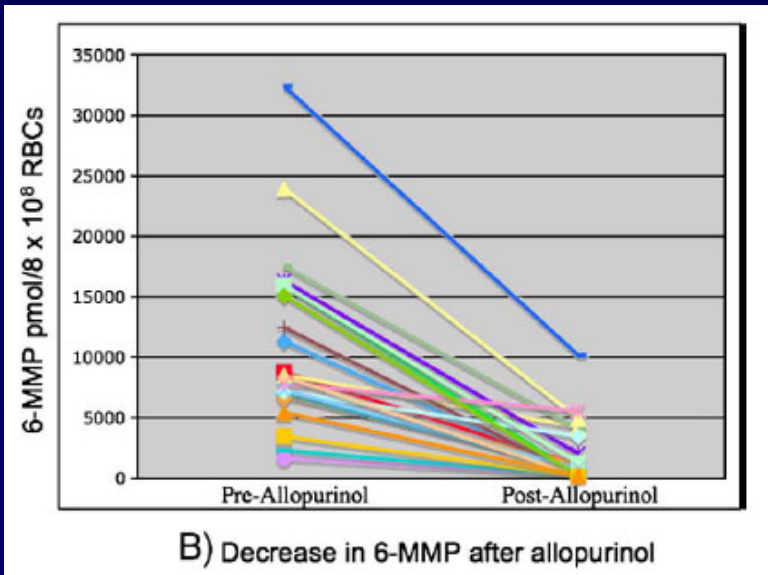
Overall success 17/25 [9/13 at 1 yr] (indices/steroid withdrawal)

Reduction in ALT / AST

Leucopenia in 6 of 25 requiring dose reduction



A) Increase in 6-TGN after allopurinol



B) Decrease in 6-MMP after allopurinol

Allopurinol for thiopurine non-response and toxicity

Sparrow et al Clin Gast Hep 2007 JCC 2009
25 non-responders AZA/6-MP, low TGN, high 6-MMP
Allopurinol 100mg + 25-50% dose reduction
Overall success 17/25 [9/13 at 1 yr] (indices/steroid withdrawal)
Reduction in ALT / AST
Leucopenia in 6 of 25 requiring dose reduction

GSTT experience
109 patients (25 hepatotoxicity, 28 other AE's,35 high 6-MMP/TGN ratio, 23 high TPMT)
60/79 [76%] one year steroid free remission rate
Abnormal LFT's normalised in 20/25
AE's circumvented in 24/28
6/109 [5.5%] allo/thio side –effects.

AZA treatment ?

..before starting...

Check TPMT
Enzyme / genotype

AZA treatment ?

..before starting...

Check TPMT
Enzyme / genotype

- Homozygous deficient → Consider 5 - 10mg AZA or avoid AZA Alternative Rx
- Heterozygous deficient → Initiate at 25mg Build to 1mg/kg
- Very high → NB dominant methylation ? Allo / AZA
- Normal → Initiate at 100mg Build to 2mg/kg

AZA treatment ?

..before starting...

Check TPMT
Enzyme / genotype

- Homozygous deficient → Consider 5 - 10mg AZA or avoid AZA Alternative Rx
- Heterozygous deficient → Initiate at 25mg Build to 1mg/kg
- Very high → Allopur 100mg + AZA 0.5mg/kg
- Normal → Initiate at 100mg Build to 2mg/kg

AZA treatment ?

..before starting...

Check TPMT
Enzyme / genotype

Homozygous deficient → Consider 5 - 10mg AZA or avoid AZA Alternative Rx

Heterozygous deficient

Very high → Allopur 100mg + AZA 0.5mg/kg

Normal → Initiate at 100mg Build to 2mg/kg

Initiate at 25mg Build to 1mg/kg

Tolerant → Intolerant

4mo

Responder ?

Duration of Rx ??

AZA treatment ?

..before starting...

Check TPMT
Enzyme / genotype

- Homozygous deficient → Consider 5 - 10mg AZA or avoid AZA Alternative Rx
- Heterozygous deficient
- Very high → Allopur 100mg + AZA 0.5mg/kg
- Normal → Initiate at 100mg Build to 2mg/kg
- Initiate at 25mg Build to 1mg/kg

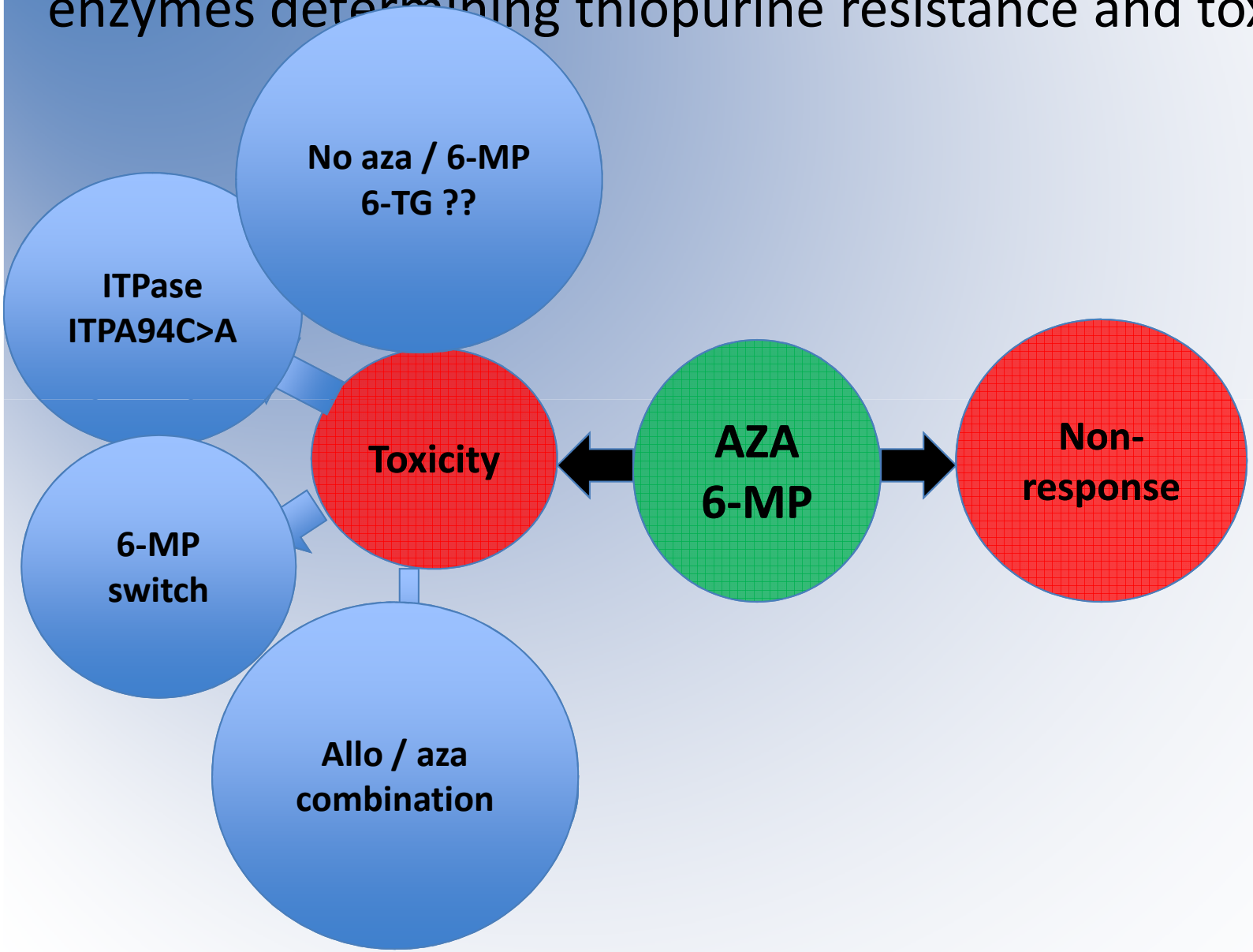
Tolerant → Intolerant

- Nausea
- Flu-like illness
- Pancreatitis
- Hepatitis
- Myelosuppression

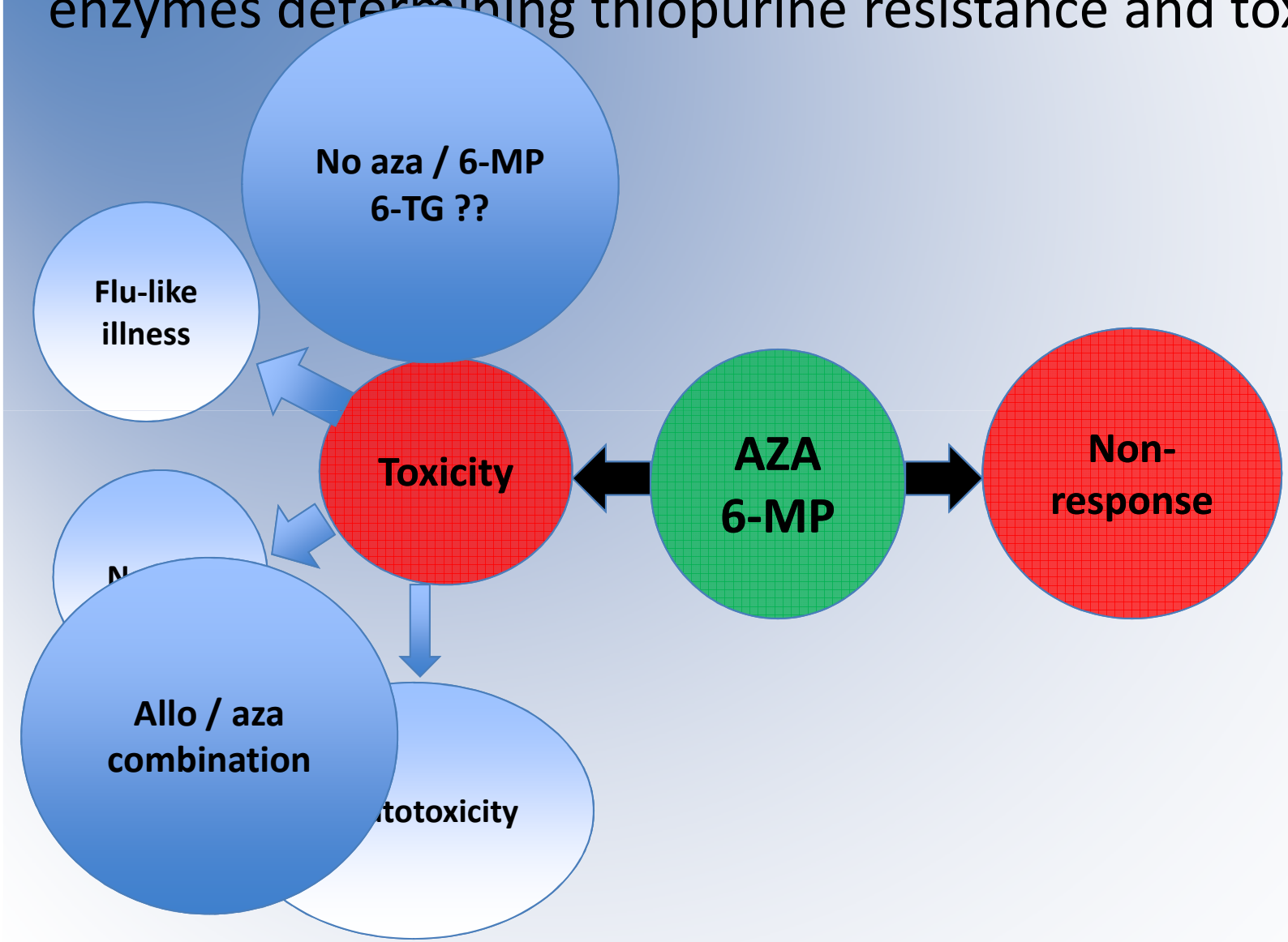
4mo
Responder ?

Duration of Rx ??

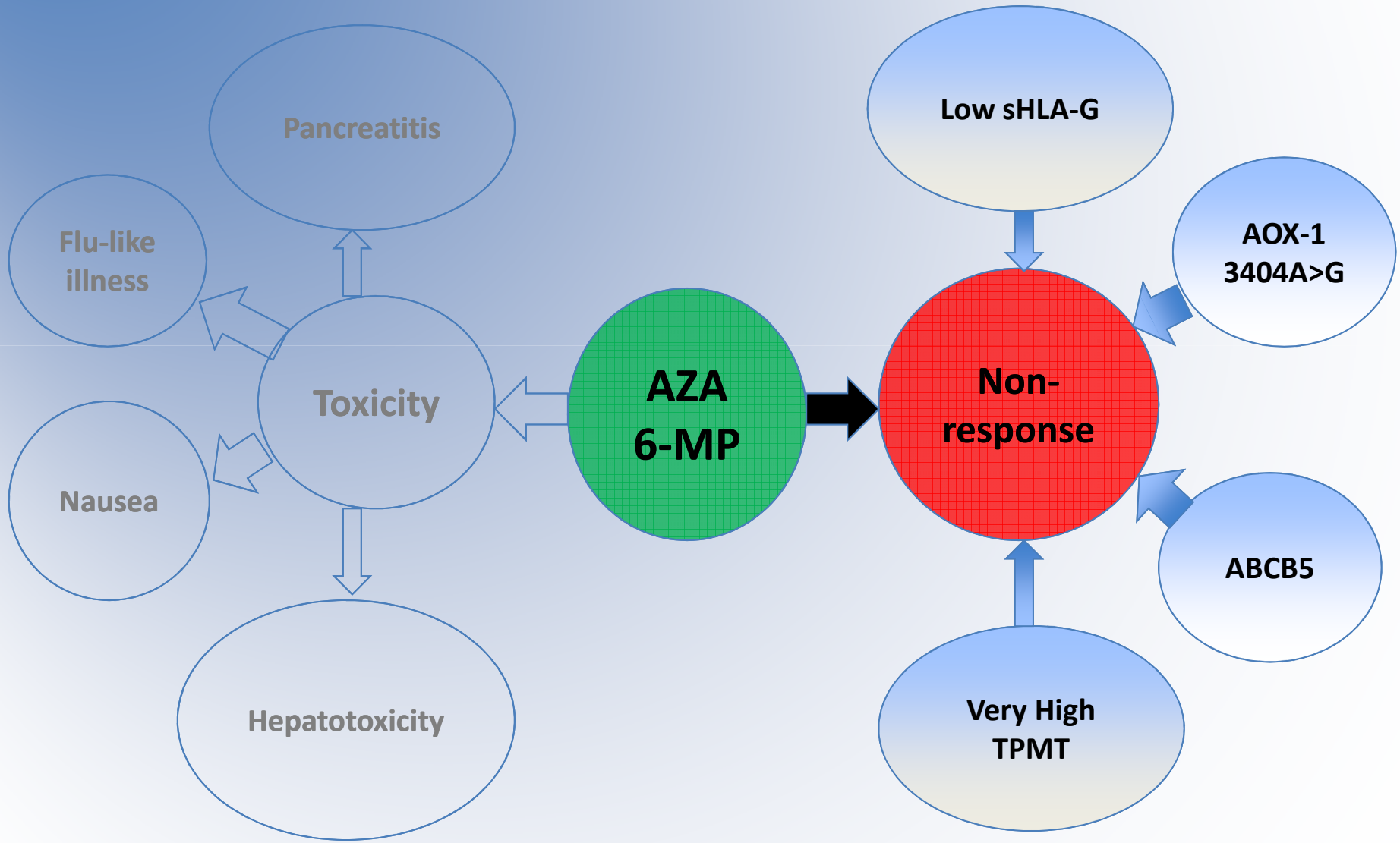
Beyond TPMT – the role of genetic variability within other enzymes determining thiopurine resistance and toxicity



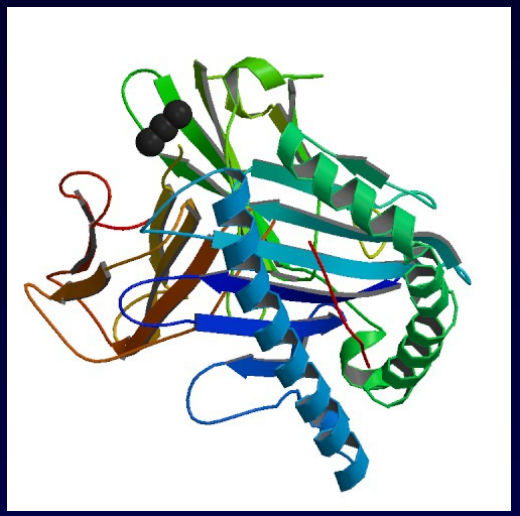
Beyond TPMT – the role of genetic variability within other enzymes determining thiopurine resistance and toxicity

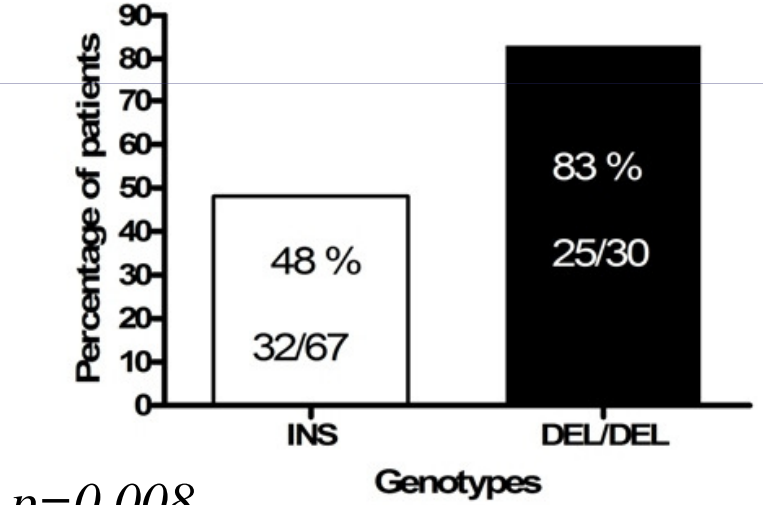


Beyond TPMT – the role of genetic variability within other enzymes determining thiopurine resistance and toxicity

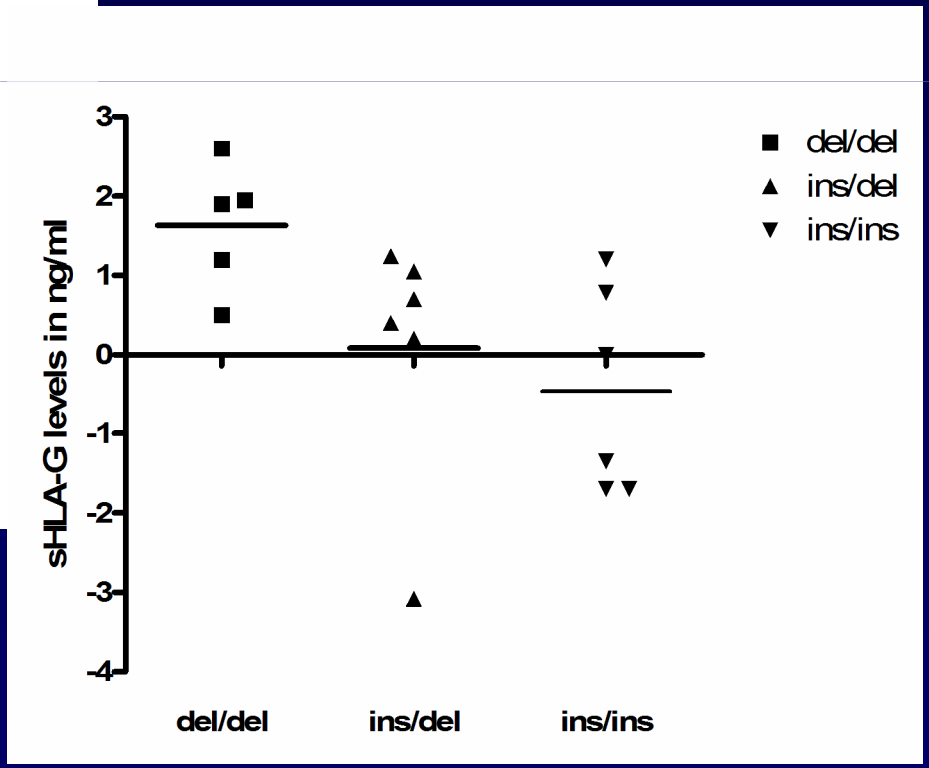


Carriage of 14bp Insertion in HLA-G reduces likelihood of response to azathioprine

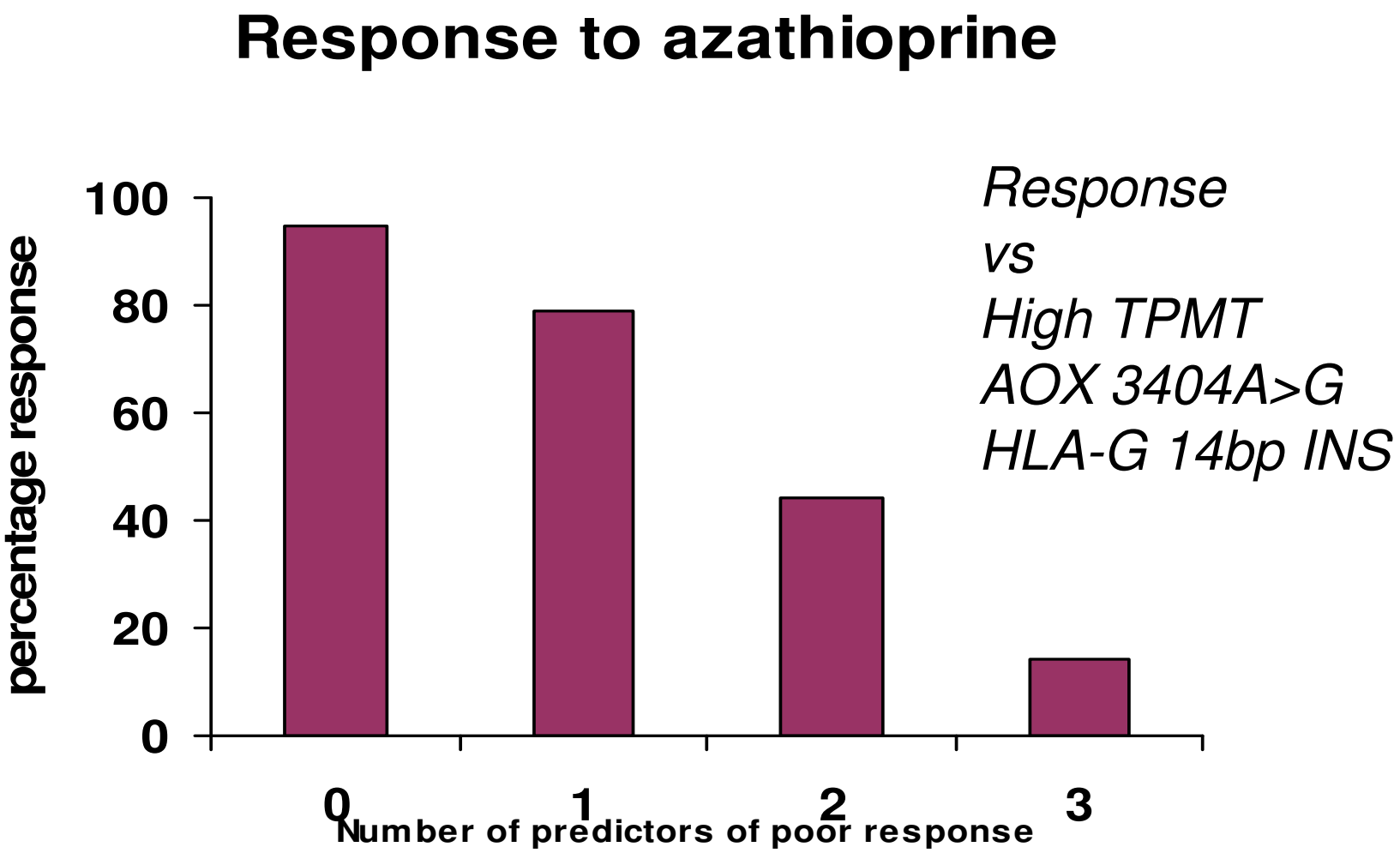




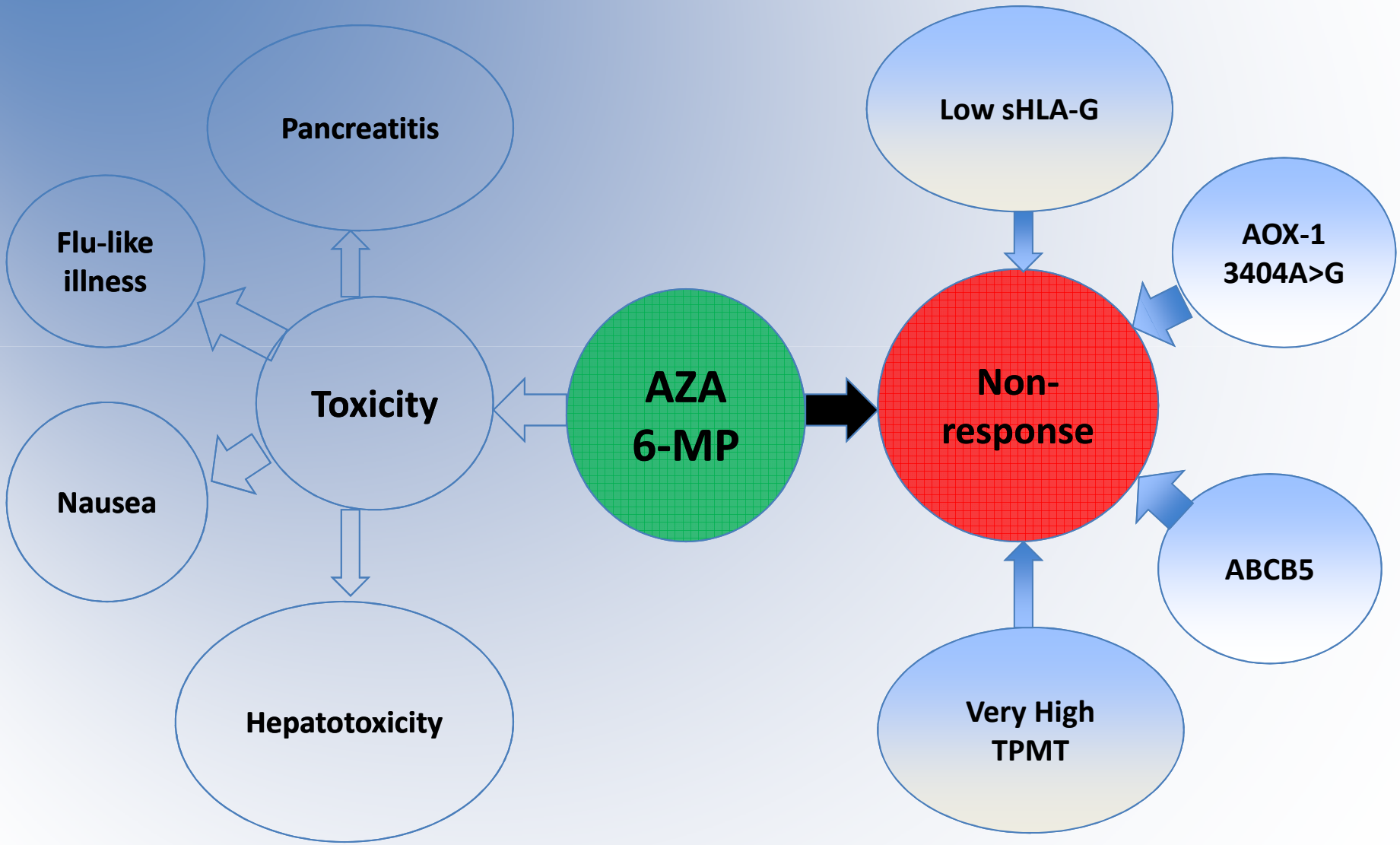
p=0.008



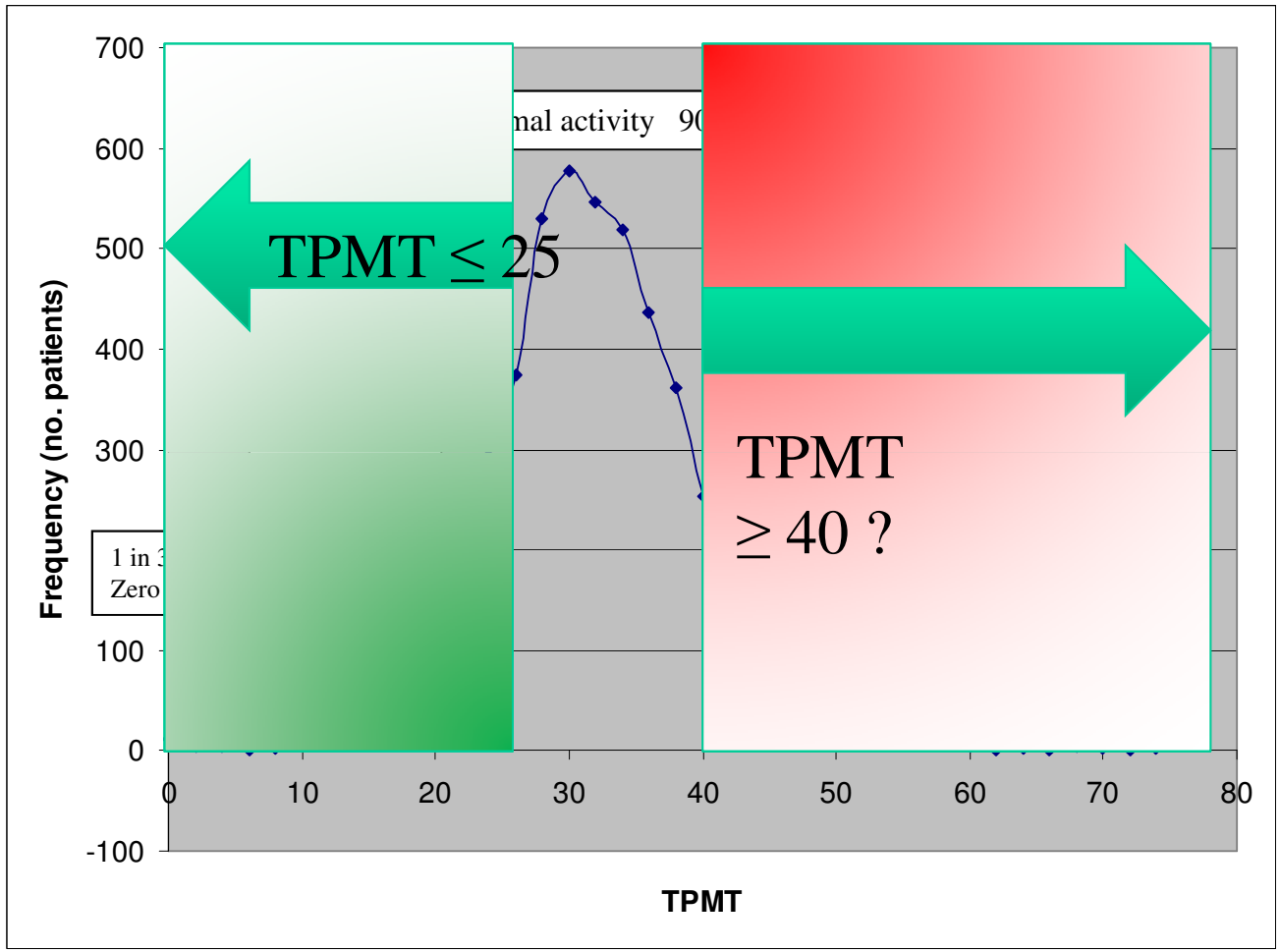
Genetic predictors of AZA response – a pharmacogenetic panel?



Beyond TPMT – the role of genetic variability within other enzymes determining thiopurine resistance and toxicity



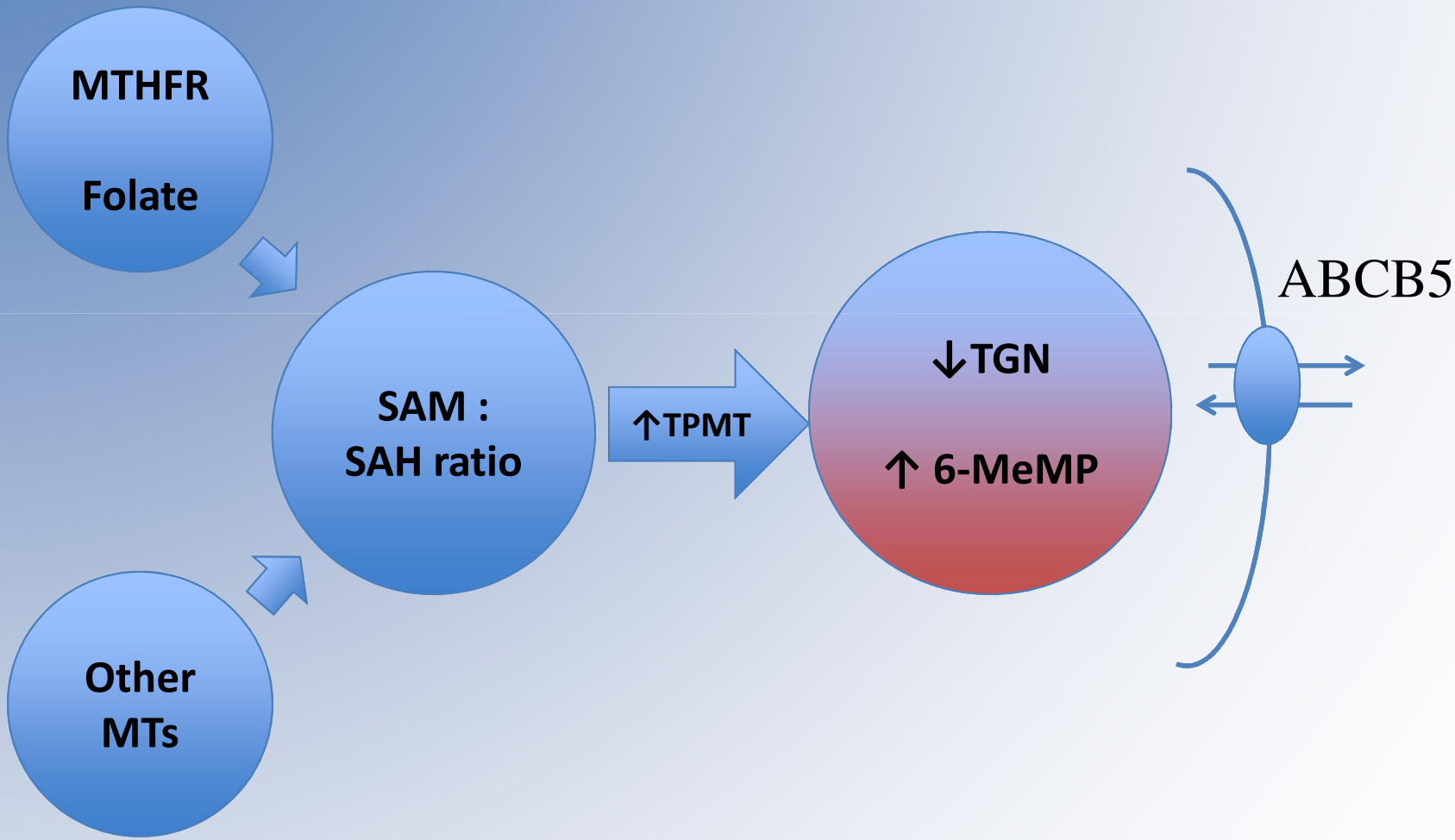
Polymorphic Trimodal distribution of TPMT activity



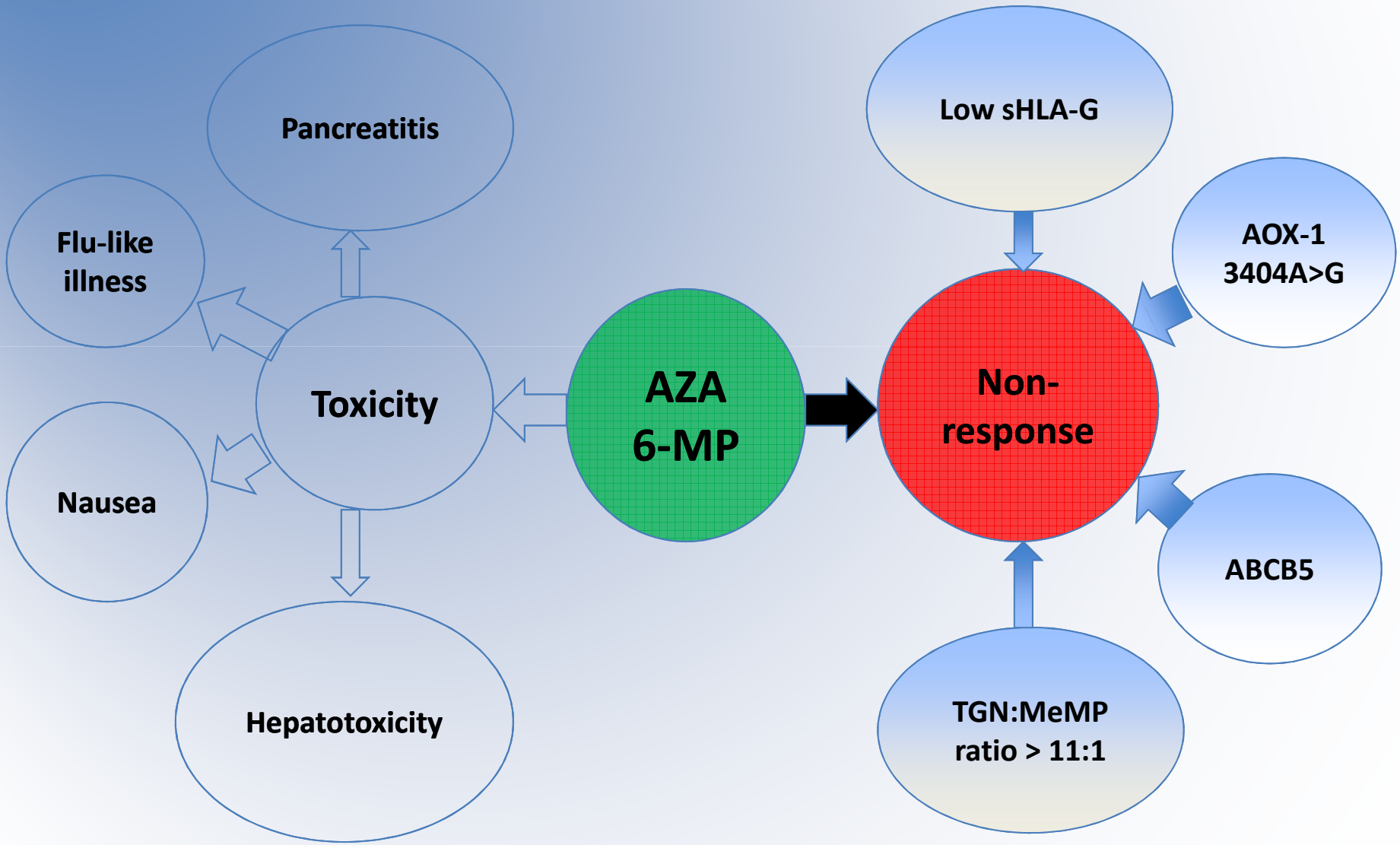
TPMT activity distribution in 5000 PRL samples, 1990 - 2001

Sanderson et al ACB 2004

Factors predicted to affect thiopurine methylation



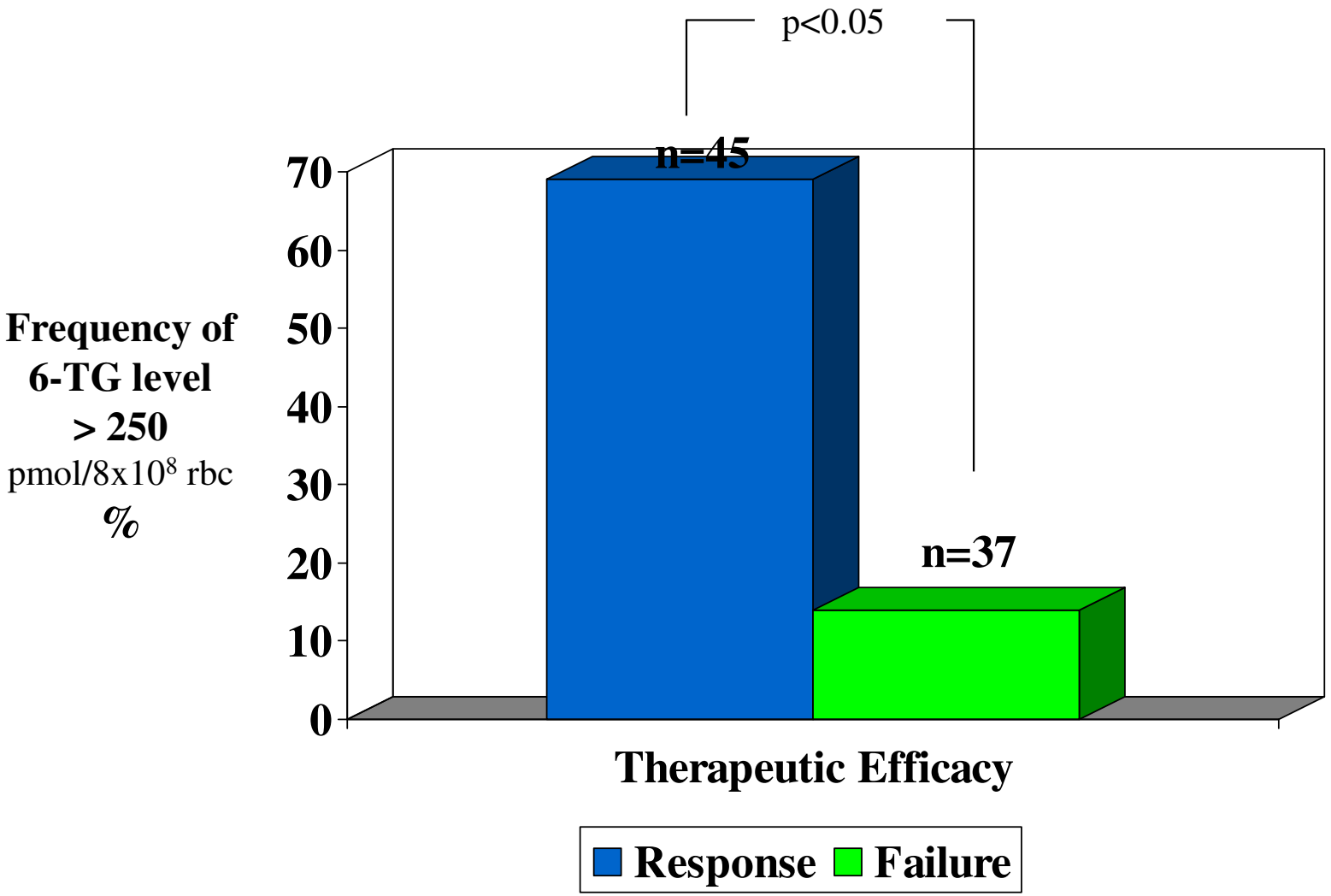
Beyond TPMT – the role of genetic variability within other enzymes determining thiopurine resistance and toxicity



Optimising immunosuppression in IBD

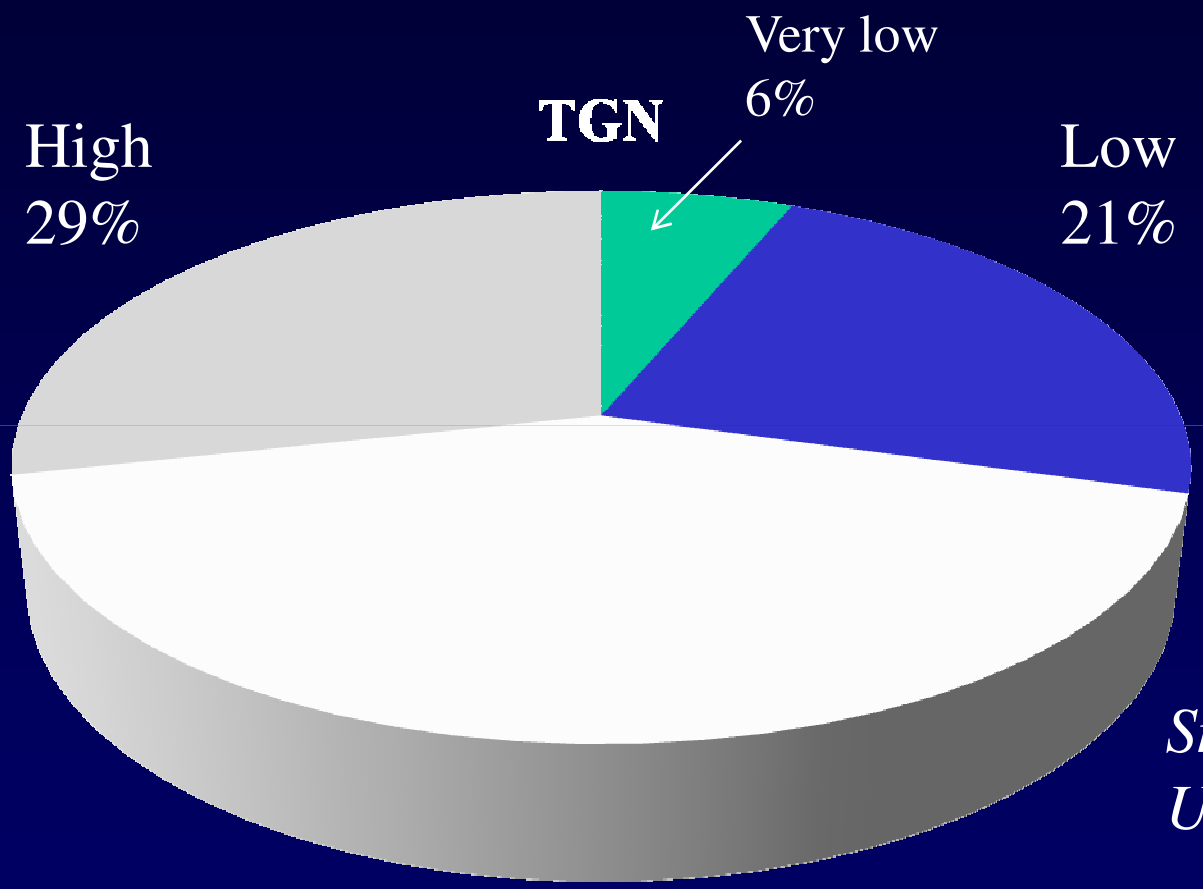
Role of thioguanine nucleotide (TGN) monitoring ?

Relationship between 6-TG levels and clinical response to AZA



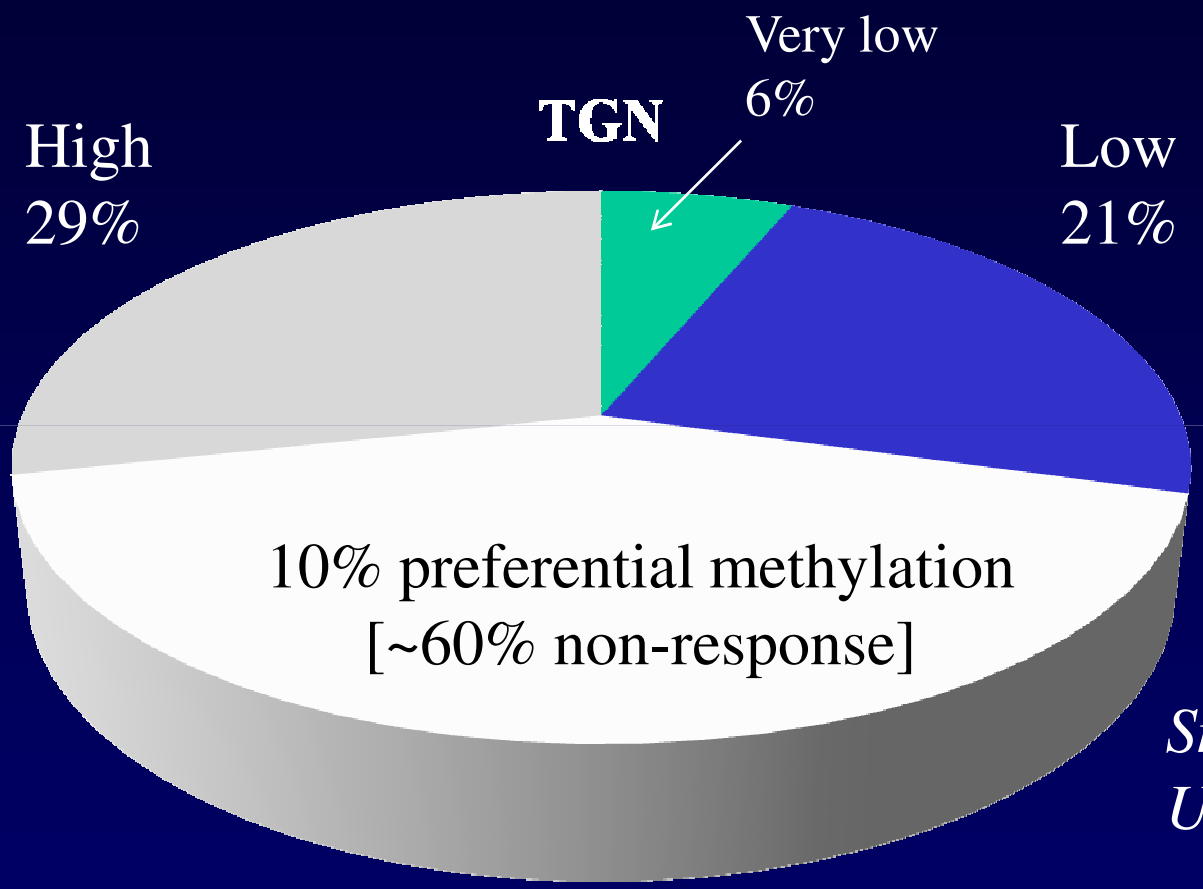
Cuffari et al Gut May 2001

TGN monitoring in routine clinical practice: review of 190 patients on AZA for IBD



Smith M
UEGW 2009

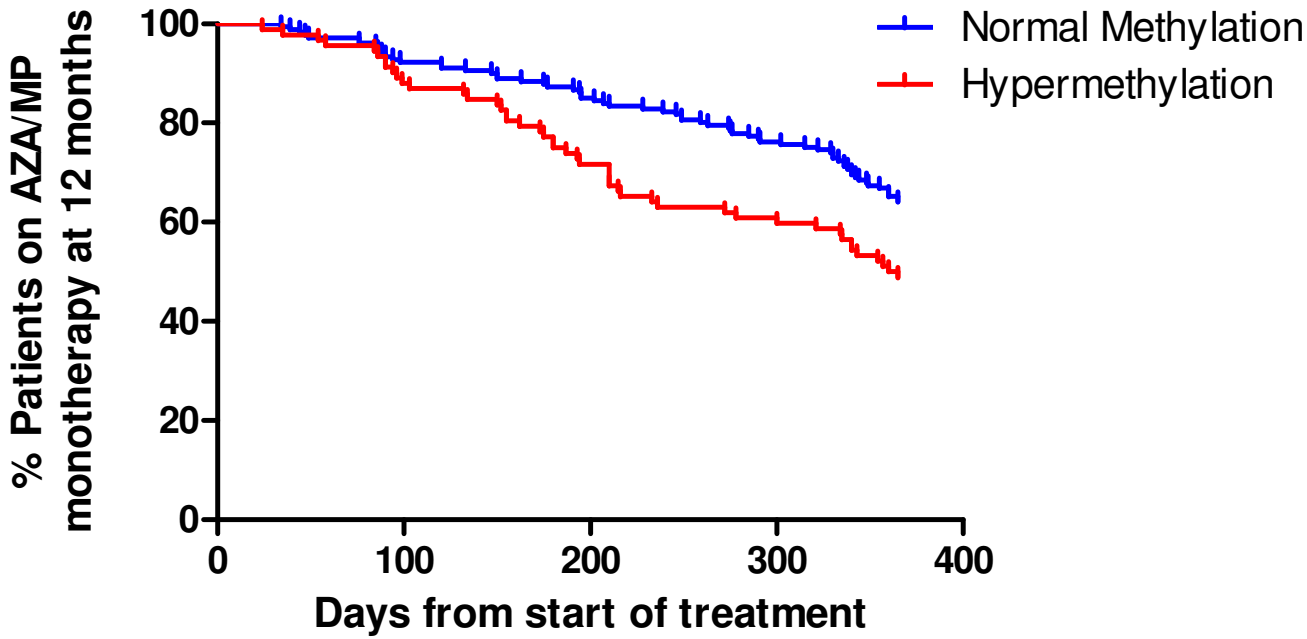
TGN monitoring in routine clinical practice: review of 190 patients on AZA for IBD



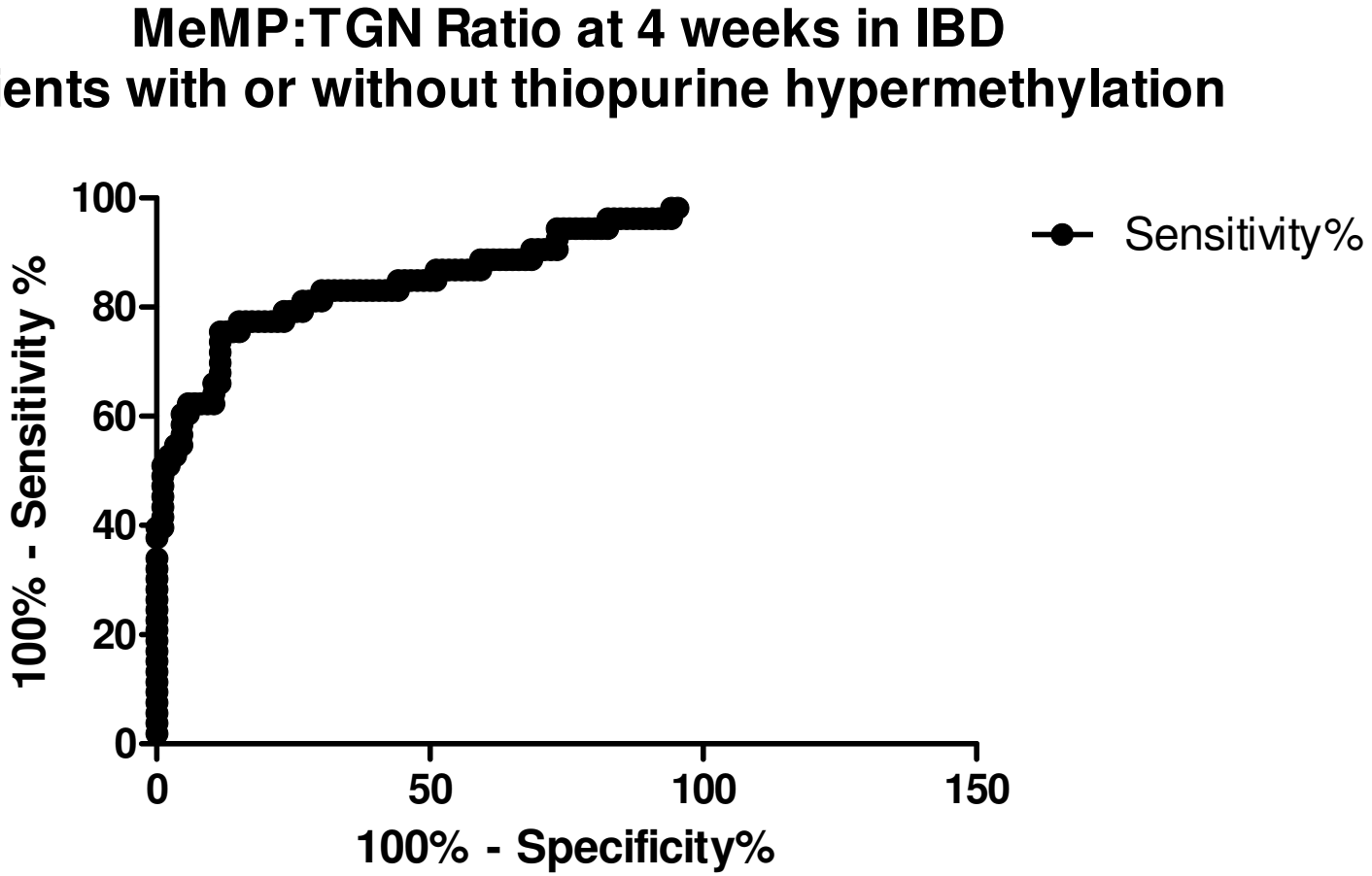
Smith M
UEGW 2009

Treatment failures secondary to hypermethylation over 12/12

Comparison of AZA/MP monotherapy treatment failures between IBD patients with normal thiopurine methylation (n=181) versus thiopurine hypermethylation (n=92)



ROC analysis – Ratio MeMP:TGN >6.35 at 4/52 predicts hypermethylation - Sensitivity 75%, Specificity 88%



AZA treatment ?

..before starting...

Check TPMT
Enzyme / genotype

- Homozygous deficient → Consider 5 - 10mg AZA or avoid AZA Alternative Rx
- Heterozygous deficient
- Very high → Allopur 100mg + AZA 0.5mg/kg
- Normal → Initiate at 100mg Build to 2mg/kg
- Initiate at 25mg Build to 1mg/kg

4 WEEK TGN level

4 MONTH TGN level

Persuade to take!
Increase, continue, decrease dose
Switch to allo/aza
Switch drug

Duration of Rx ??

Nausea	Switch to 6-MP Allo + AZA
Flu-like illness	6-MP, check ITPA Allo + AZA
Pancreatitis	Alternative Rx 6-TG, MTX, MMF
Hepatitis	Allopurinol + AZA
Myelosuppression	Dose by TGNs Check dose Parvovirus, drugs etc

AZA treatment ?

..before starting...

IBD panel : TPMT
+ ITPA, AOX,HLA-G, ABCB5

Homozygous deficient → Consider 5 - 10mg AZA or avoid AZA Alternative Rx

Heterozygous deficient

Very high → Allopur 100mg + AZA 0.5mg/kg

Normal → Initiate at 100mg Build to 2mg/kg

Initiate at 25mg Build to 1mg/kg

4 WEEK TGN level

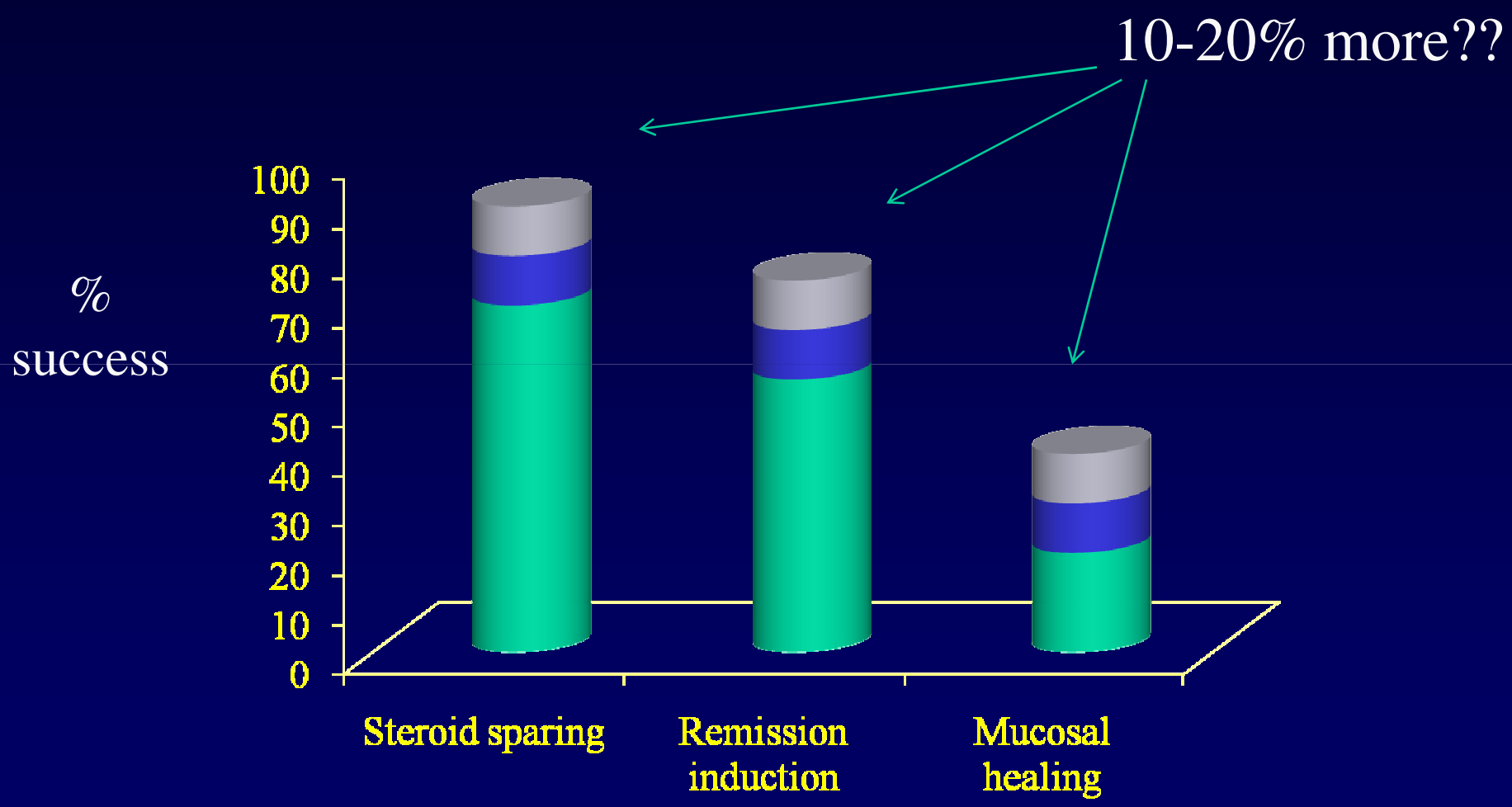
4 MONTH TGN level

Persuade to take!
Increase, continue, decrease dose
Switch to allo/aza
Switch drug

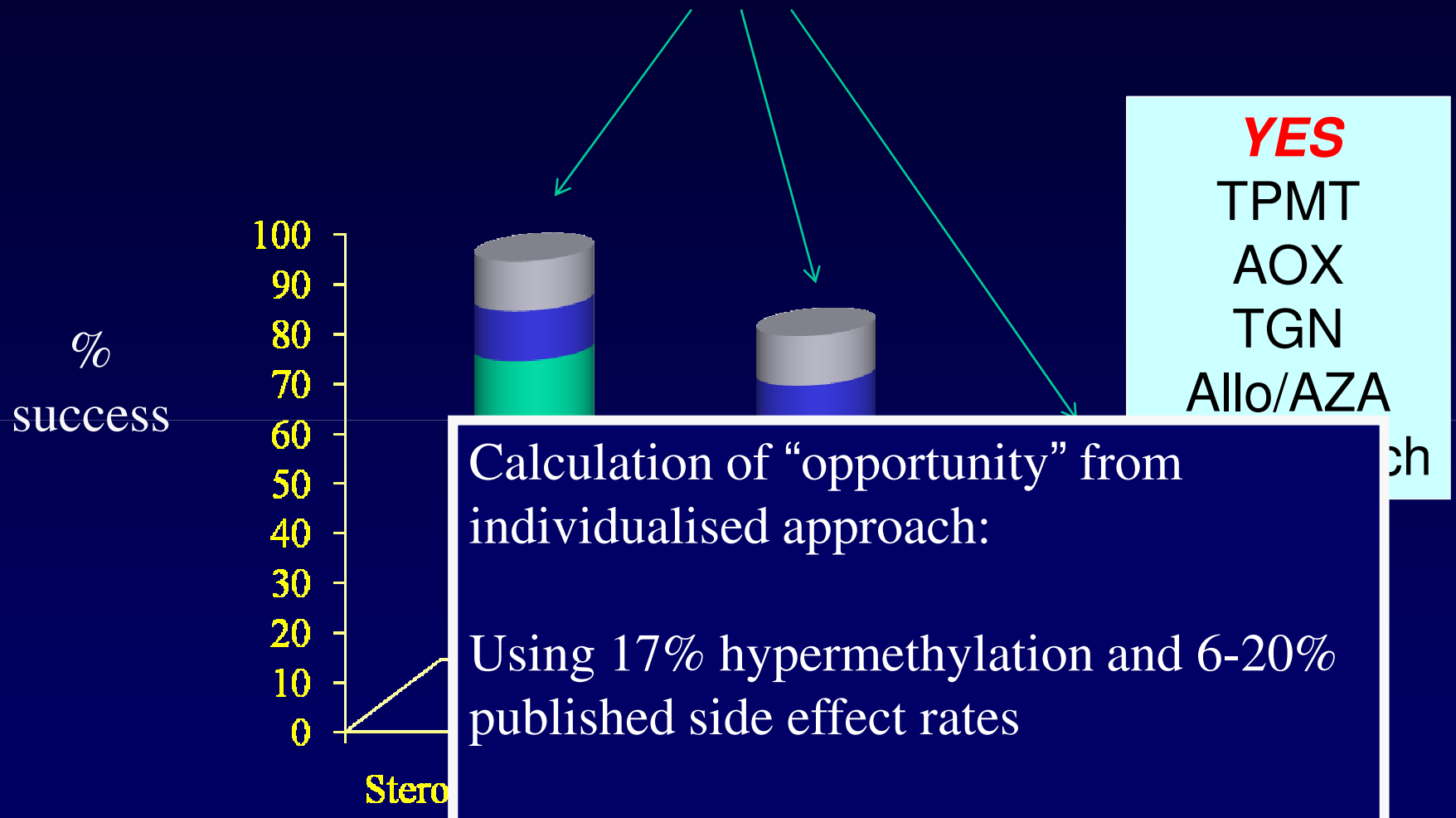
Duration of Rx ??

Nausea	Reduce dose Switch to 6-MP
Flu-like illness	V slow escalation 6-MP, check ITPA
Pancreatitis	Alternative Rx 6-TG, MTX, MMF
Hepatitis	Allopurinol + AZA
Myelosuppression	Dose by TGNs Check dose Parvovirus, drugs etc

Can pharmacogenetics / TGN's achieve this?



Can pharmacogenetics / TGN's achieve this?



YES

TPMT

AOX

TGN

Allo/AZA

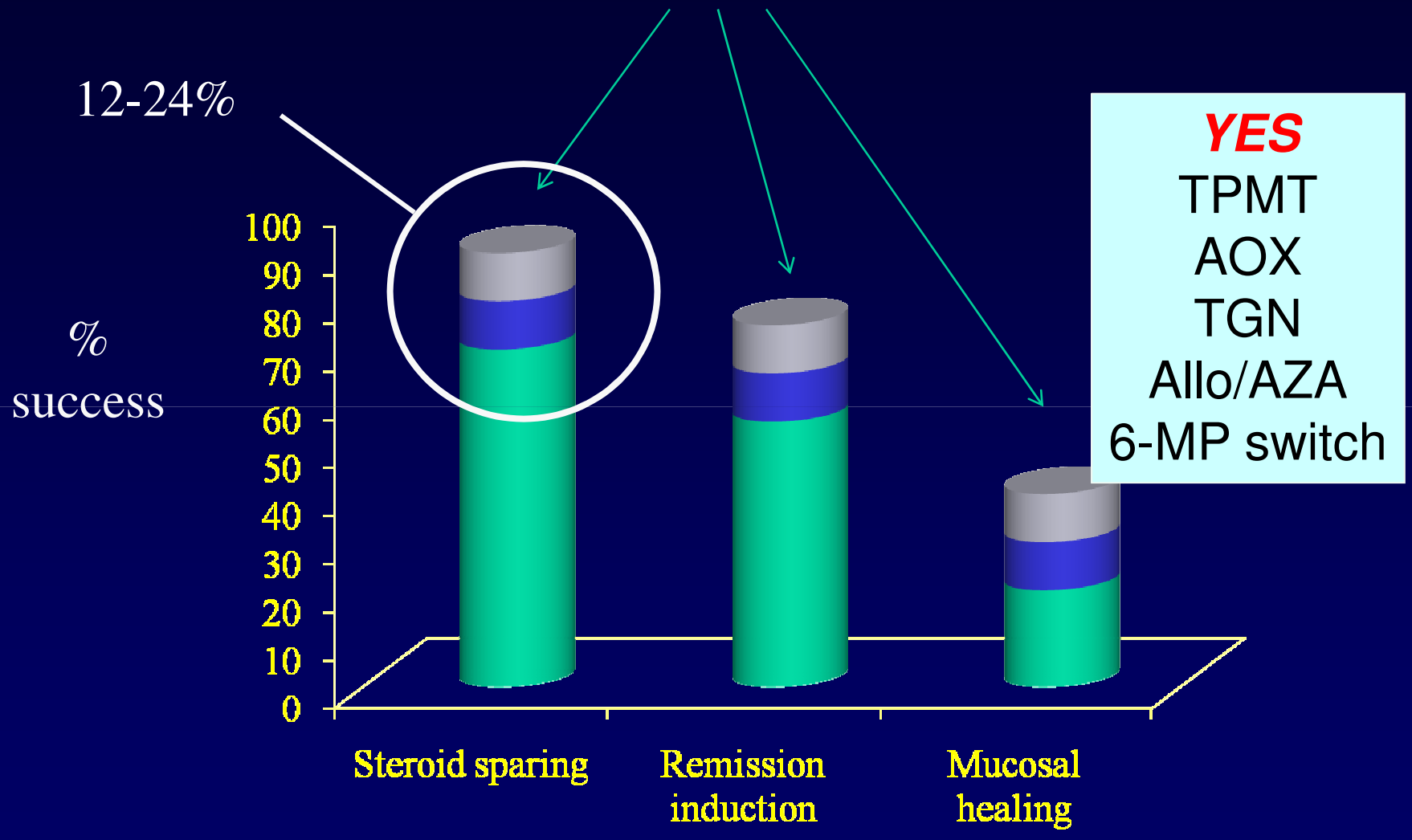
ch

Calculation of "opportunity" from individualised approach:

Using 17% hypermethylation and 6-20% published side effect rates

Opportunity for allopurinol / thiopurine = 12-24%

Can pharmacogenetics / TGN's achieve this?




Personalised medicine – coming your way for everything…….
IBD pharmacogenetic panel
Corticosteroids
Thiopurines
Methotrexate
Ciclosporin
Tacrolimus
Anti-TNFα Ab
New biologics
Levels monitoring
Salivary GC levels
TGN / MMP
MTXPG levels
CyA levels
Tacro levels
Anti-TNF levels/ab
Biologic levels
etc…..

PHARMACOGENETICS GROUP KCL / GSTT

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Jeremy Sanderson

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Jemma Walker
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