

Mechanistic Studies of Aspirin and Prevention of Colorectal Cancer

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Colonoscopy: Effective but with limits

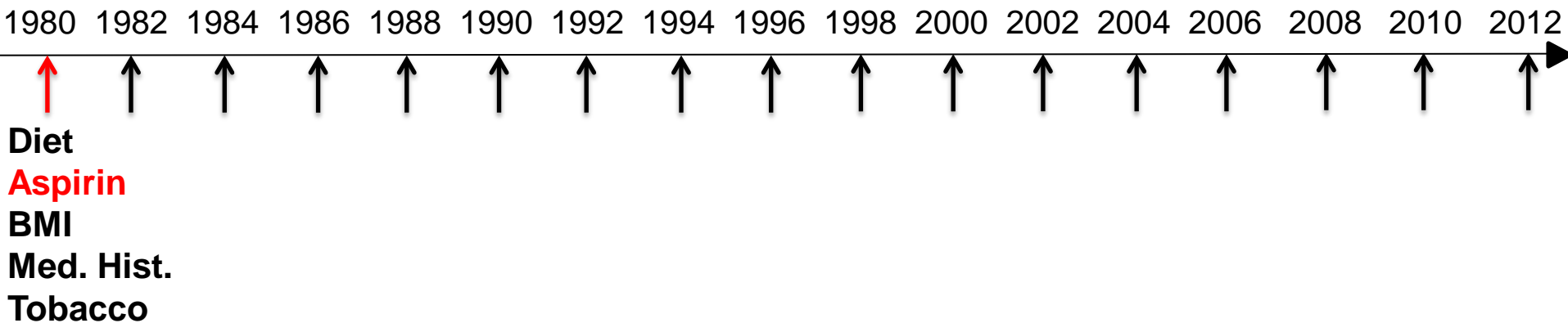
	No screening	Colonoscopy screening
All CRC	1.0	0.44 (0.38-0.52)
Distal colorectal	1.0	0.24 (0.18-0.32)
Proximal colon	1.0	0.73 (0.57-0.92)

Aspirin and adenoma trials

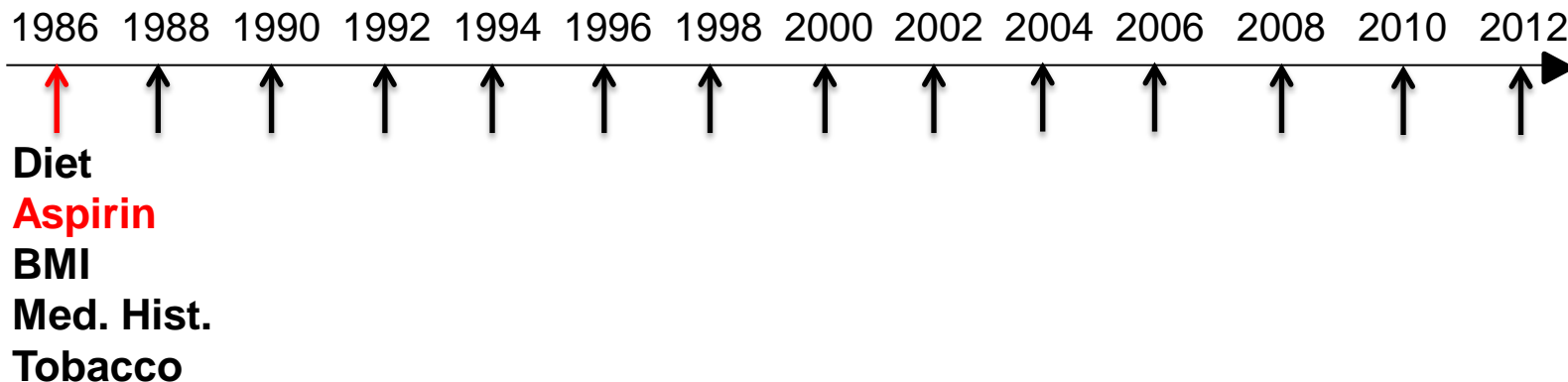
Trial	N	Duration	Dose	Relative Risk
Baron, NEJM 2003	1121 prior adenoma	3 years	81 mg 325 mg	0.83 (0.70-0.98) 0.96 (0.81-1.13)
Sandler, NEJM 2003	635 prior CRC	3 years	325 mg	0.65 (0.46-0.91)
Benamouzig, Gastro 2003	272 prior adenoma	1 year	160 mg 300 mg	0.85 (0.57-1.26) 0.61 (0.37-0.99)
Logan, Gastro 2008	945 prior adenoma	3 years	300mg	0.79 (0.63-0.99)
Ishikawa, Gut 2014	311 prior adenoma	2 years	100 mg	0.60 (0.36-0.98)

Study population

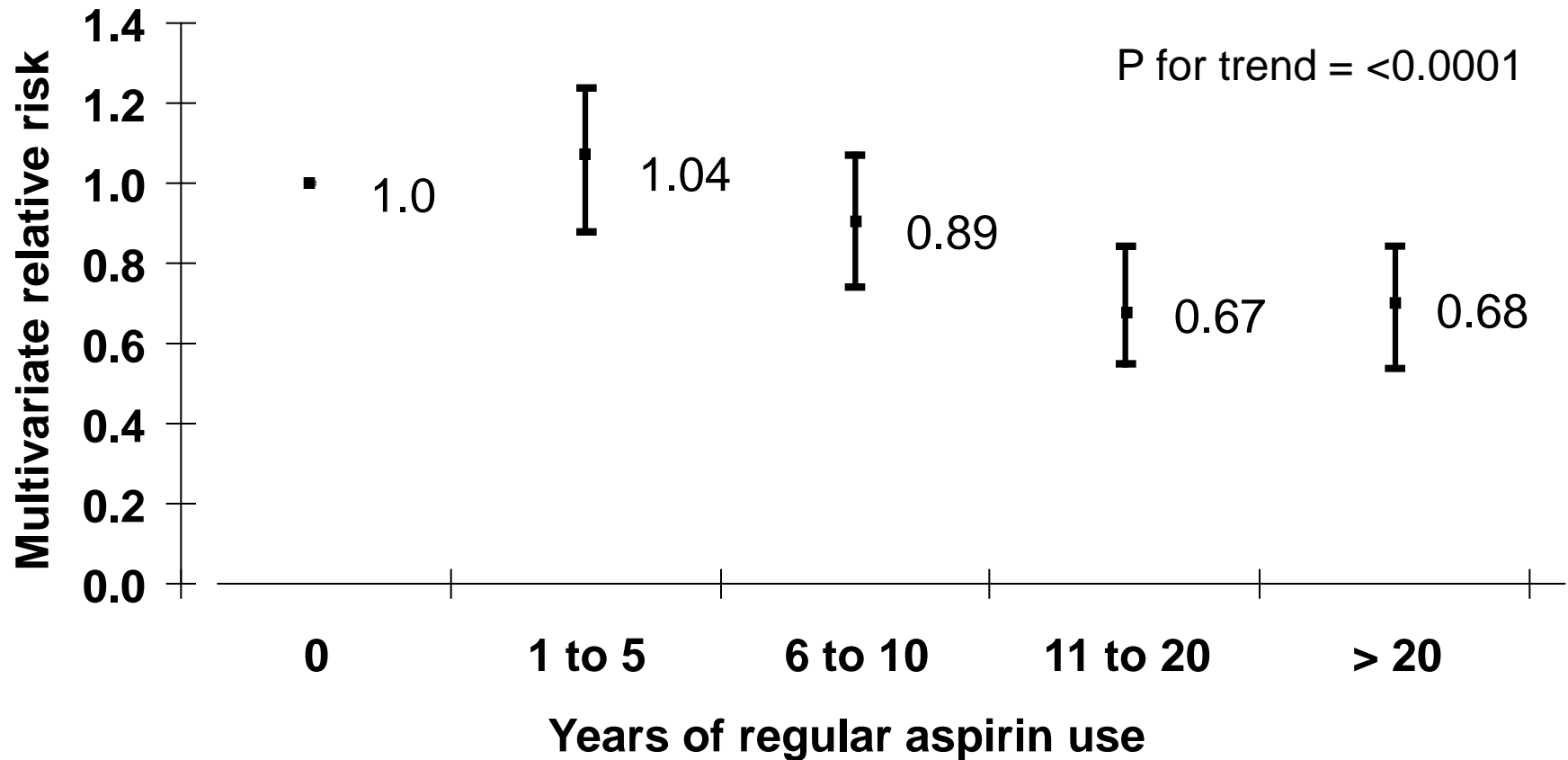
Nurses' Health Study (n=121,700)



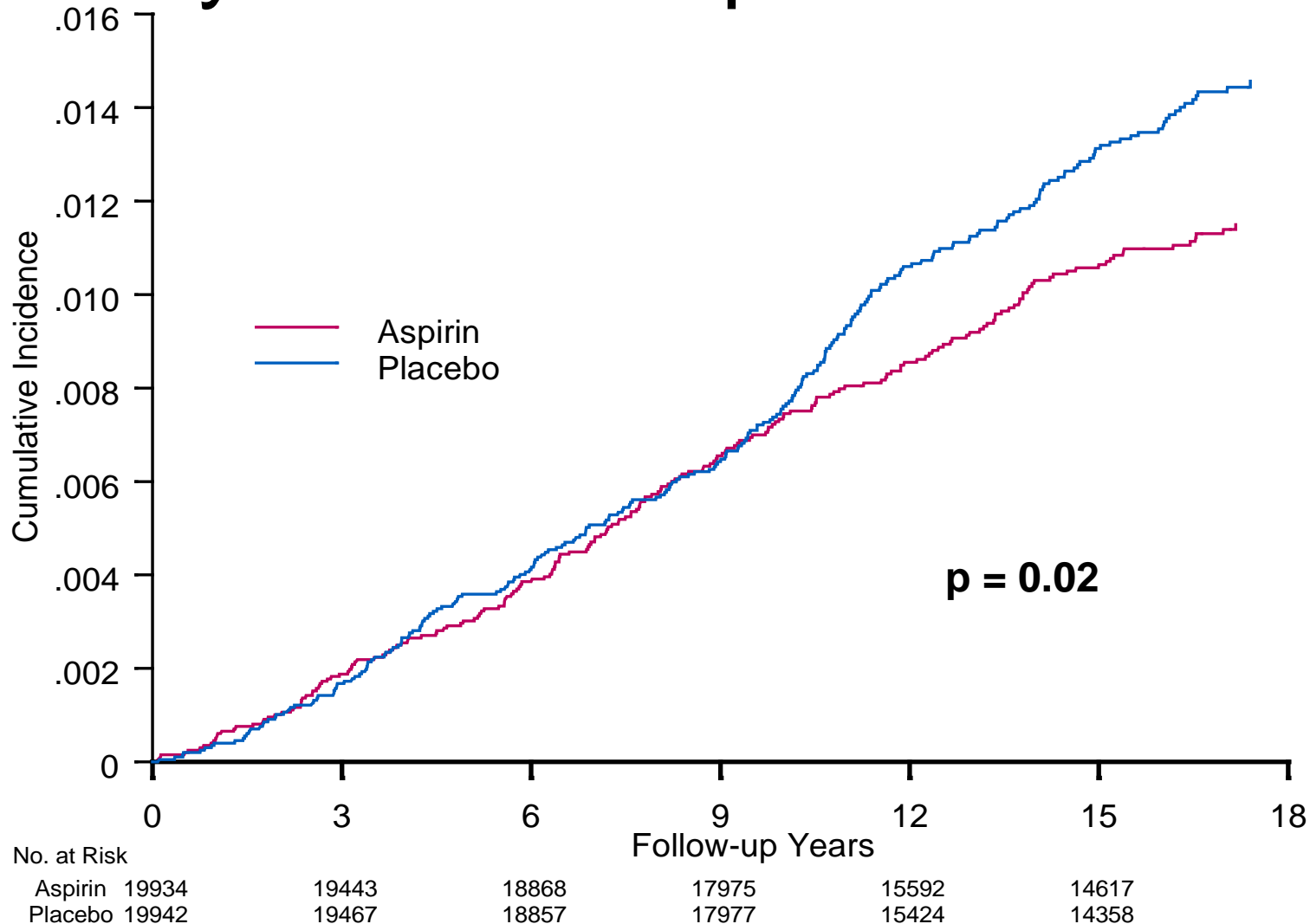
Health Professionals Follow-up Study (n=51,539)



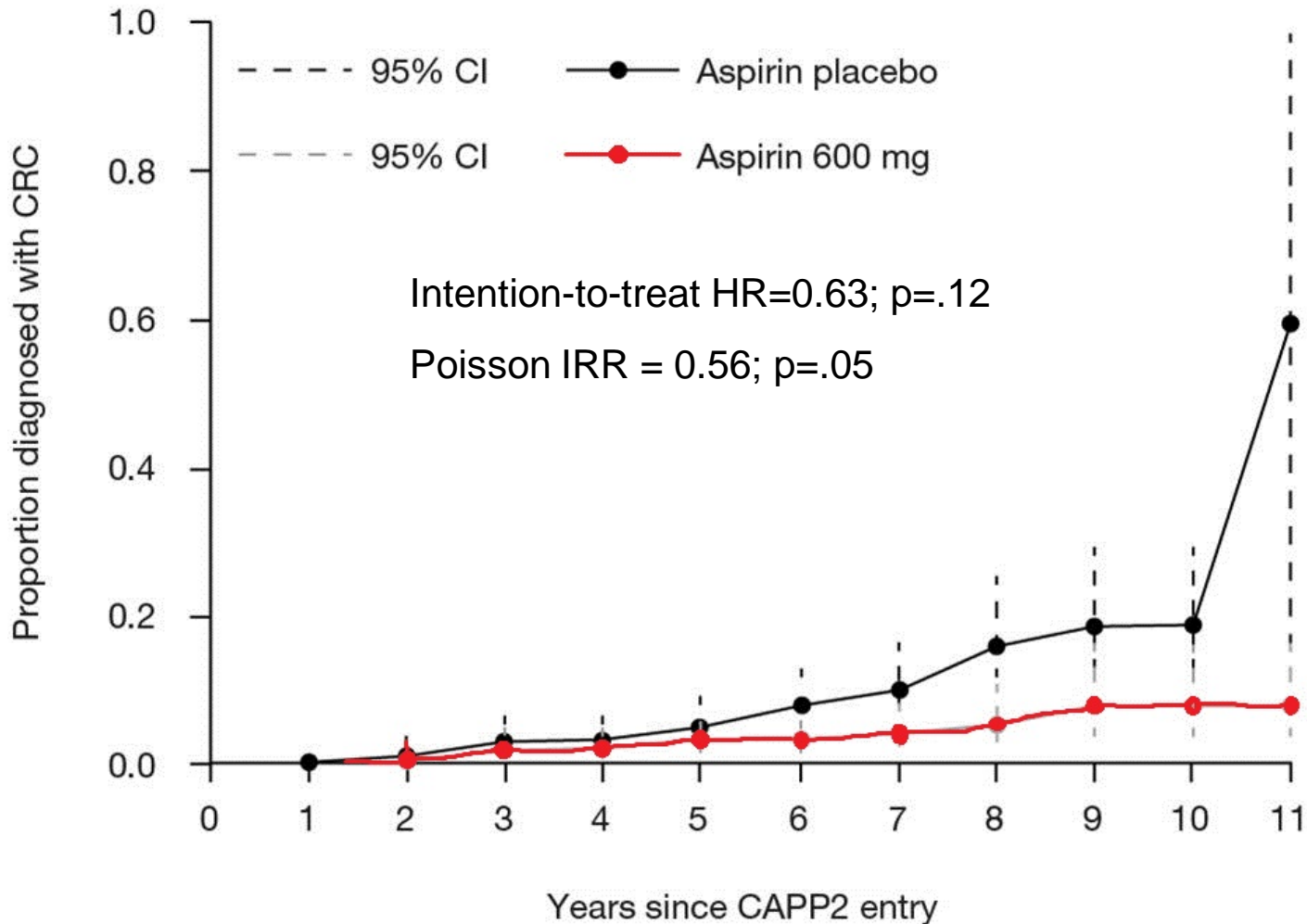
Duration of aspirin use and risk of CRC



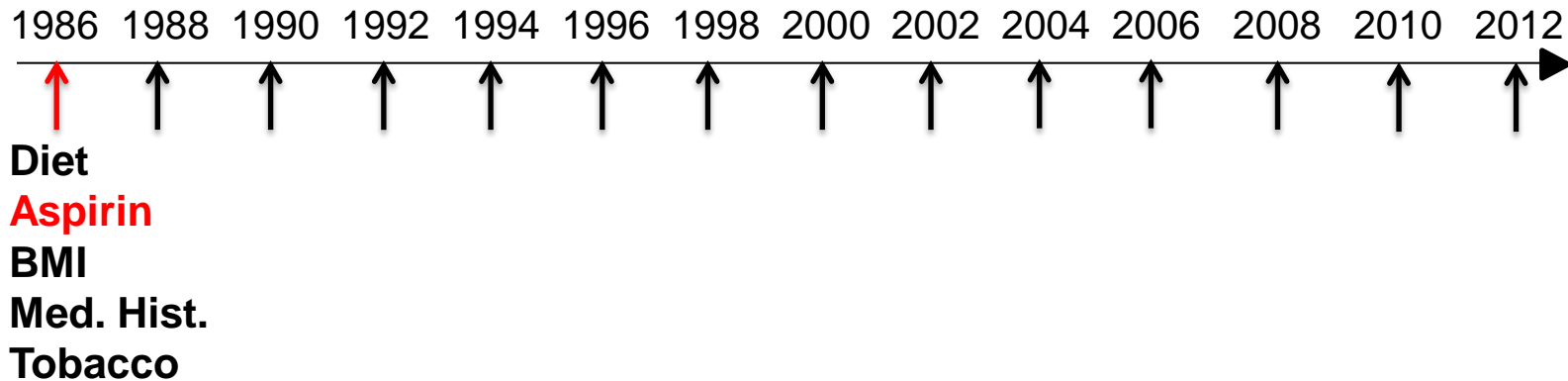
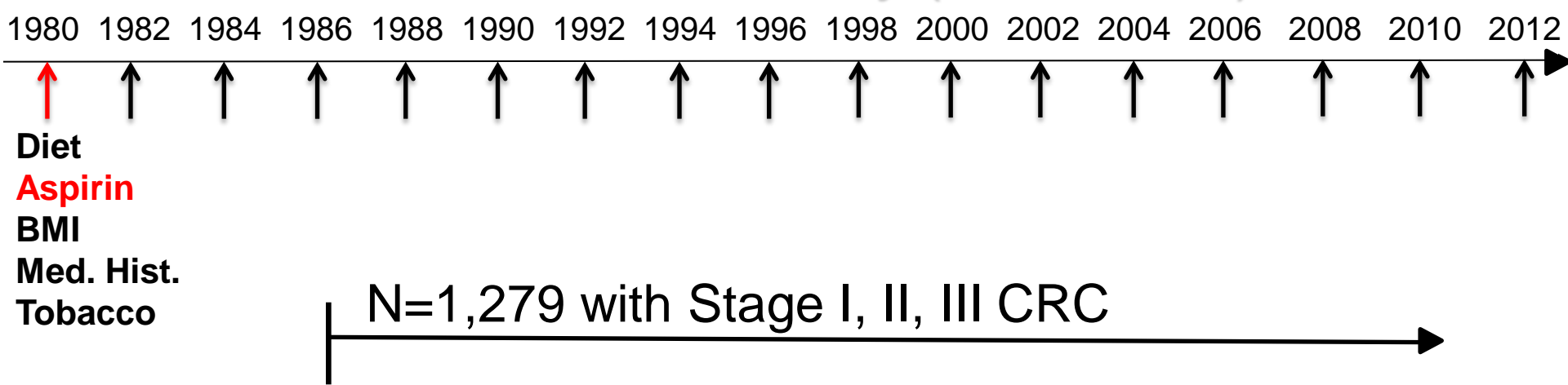
Aspirin use reduces risk of CRC: 18 year follow-up of WHS Trial



Aspirin reduces CRC in Lynch after long-term follow-up

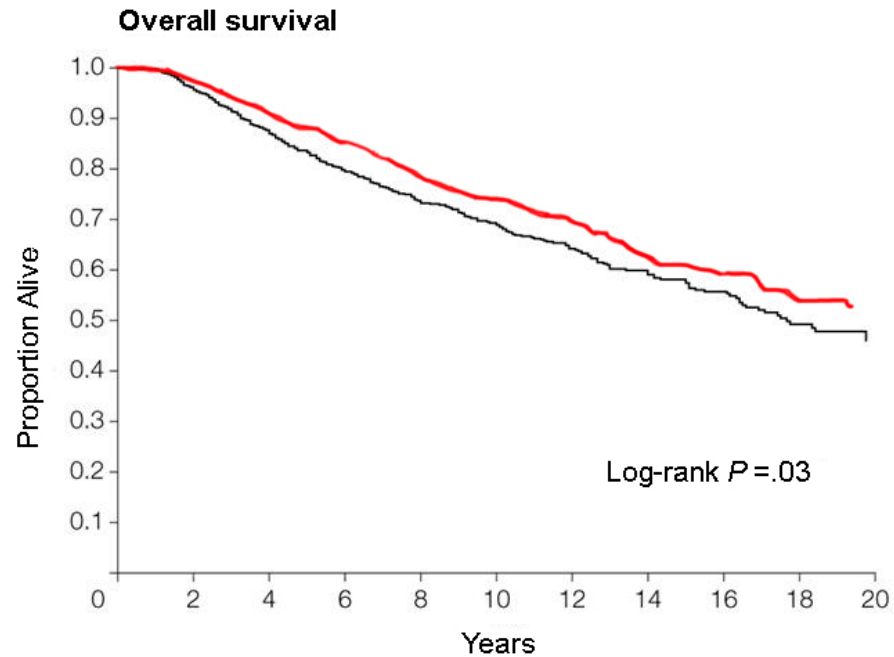
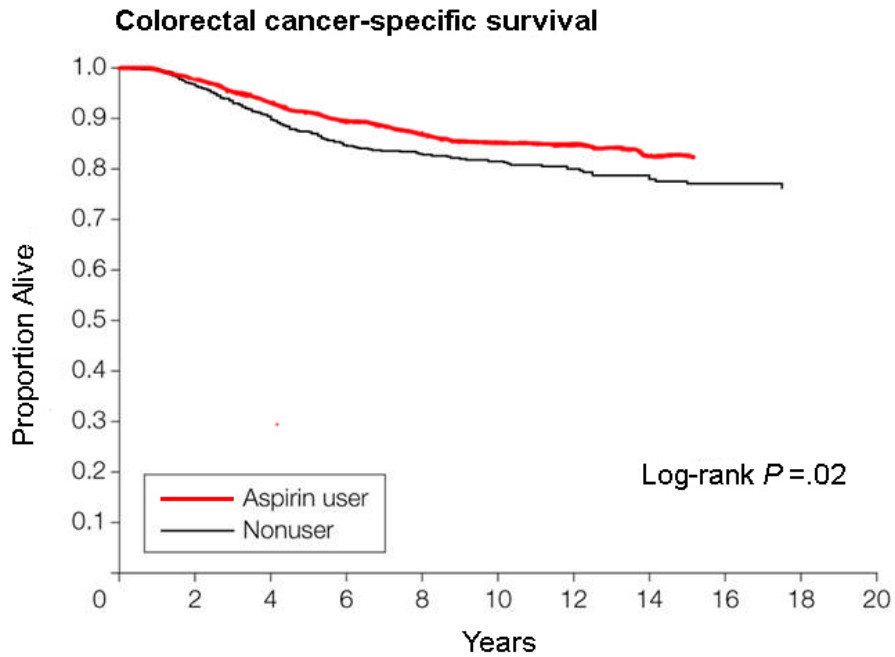


Nurses' Health Study (n=121,700)

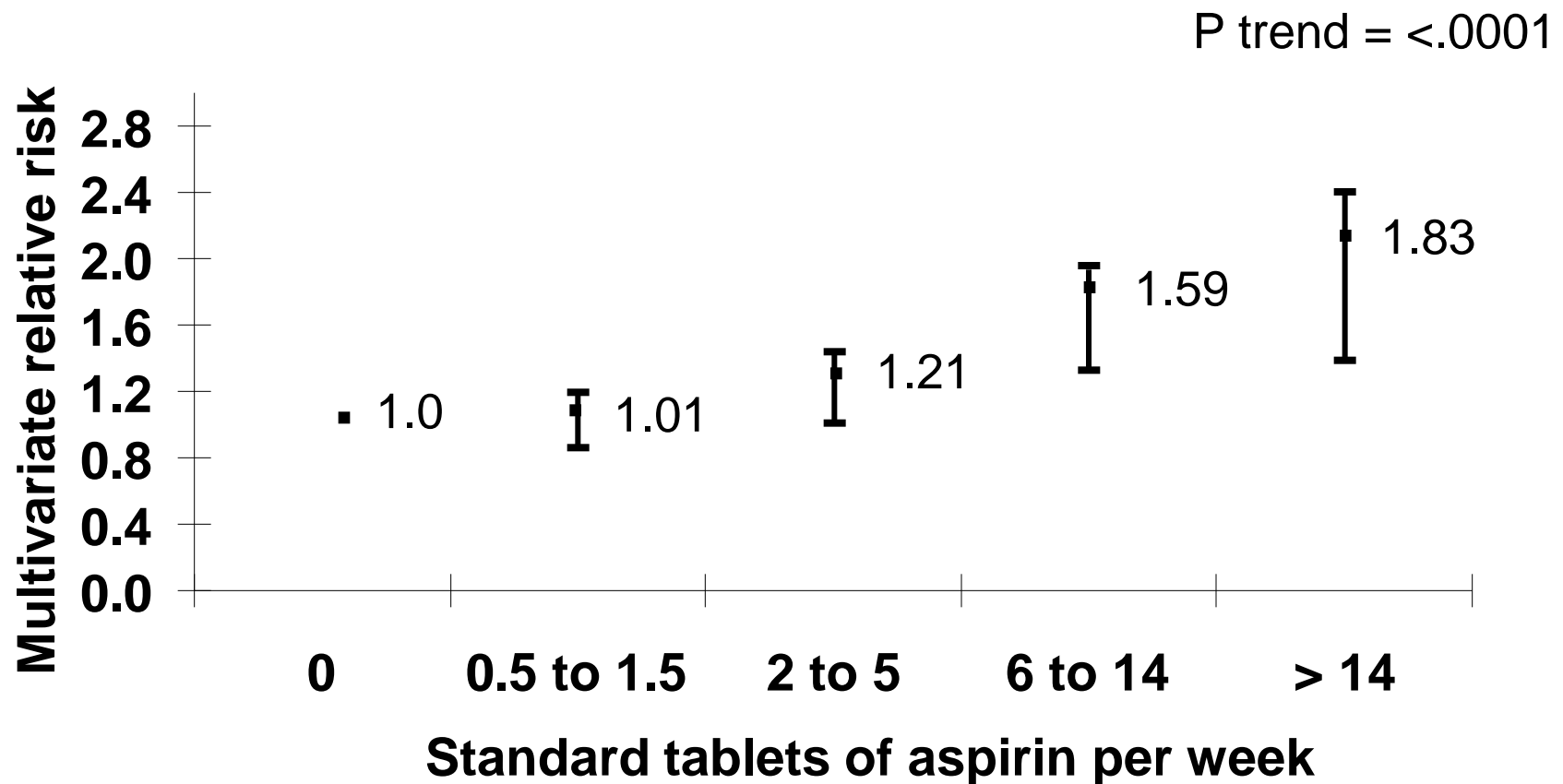


Health Professionals Follow-up Study (n=51,539)

Aspirin use and CRC patient survival



Aspirin and risk of GI bleeding

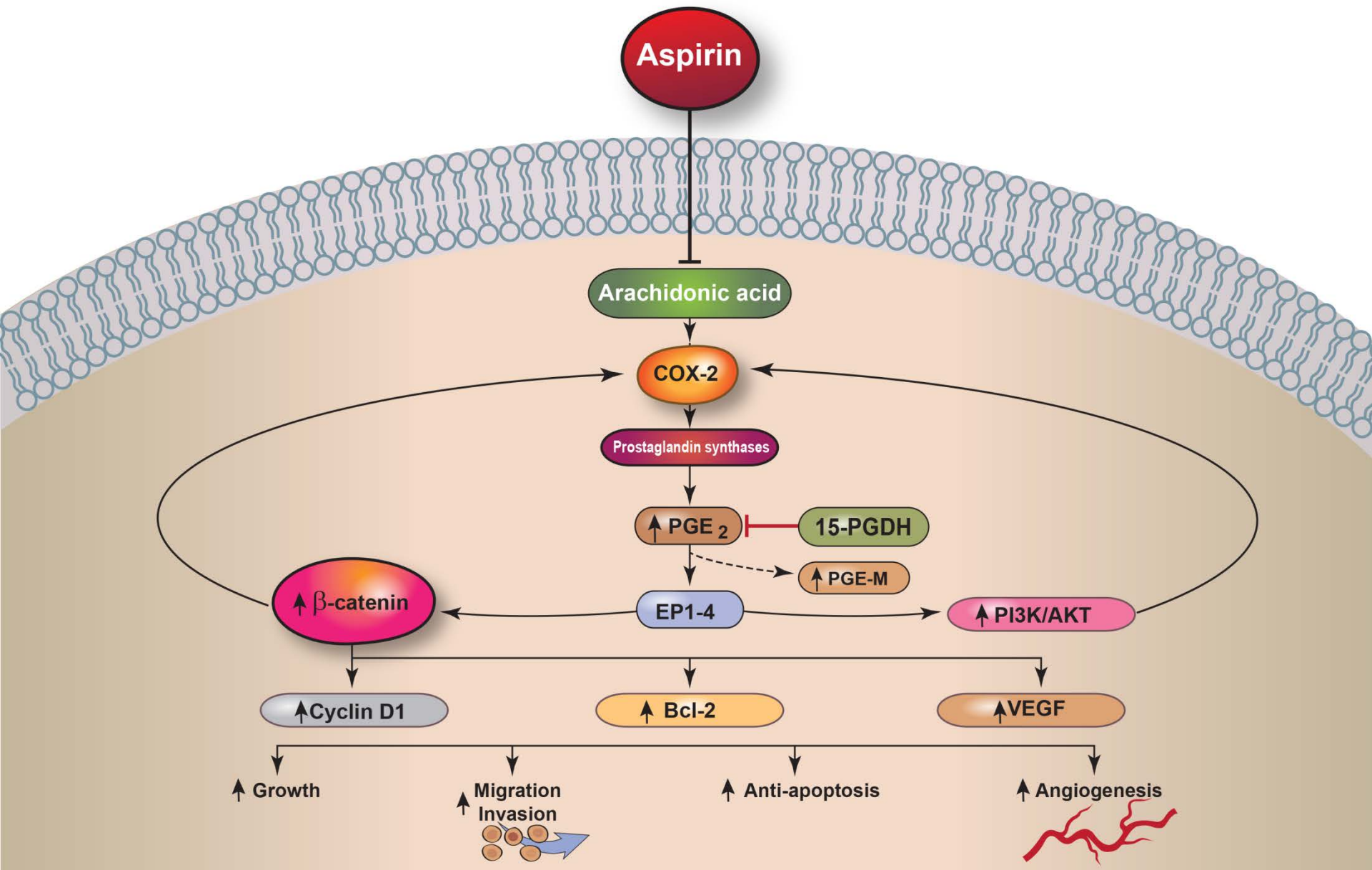


U.S. Preventative Services Task Force 2007

- Recommends against routine use of aspirin or NSAIDs to prevent CRC in average risk individuals
- “Harms outweigh the benefits for the prevention of CRC”

Can we exploit mechanism to personalize chemoprevention?

- Prostaglandin balance
- *Wnt* signaling



Aspirin and risk of CRC by COX-2 expression

	Non-Users	Regular Users
All CRC	1.0	0.73 (0.62-0.86)
COX-2 positive	1.0	0.64 (0.52-0.78)
COX-2 negative	1.0	0.96 (0.73-1.26)

P heterogeneity=0.02

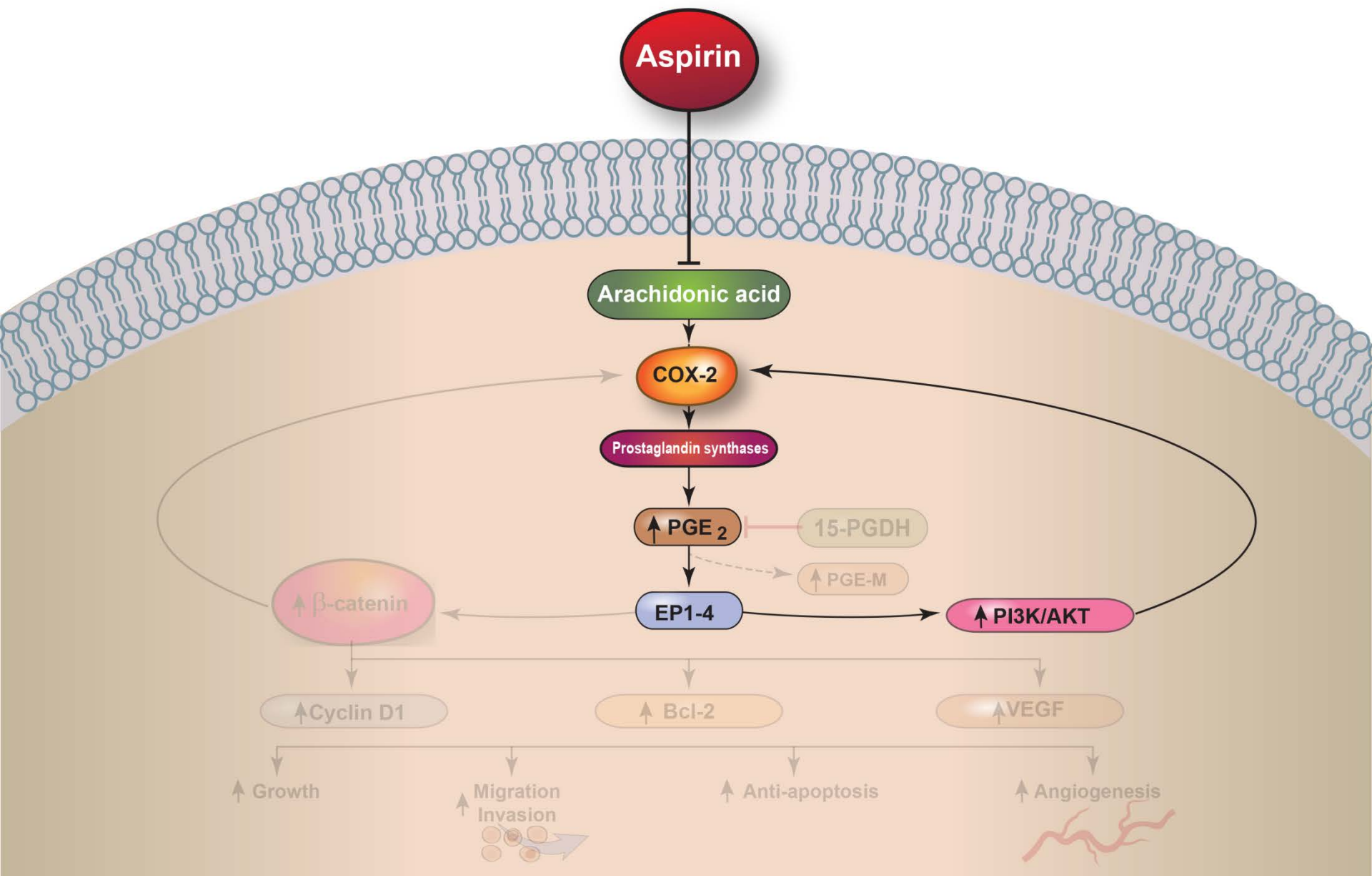
Aspirin and CRC-specific mortality among CRC patients

	Non-Users	Regular Users
All CRC	1.0	0.71 (0.53-0.95)
COX-2 positive CRC	1.0	0.39 (0.20-0.76)
COX-2 negative CRC	1.0	1.22 (0.36-4.18)

P heterogeneity=0.04

Aspirin has greater specificity for COX-2 positive cancers

Aspirin preferentially reduces the risk of CRC and the spread of tumors for which growth depends, at least in part, on COX-2 function



Aspirin and CRC-specific mortality among CRC patients

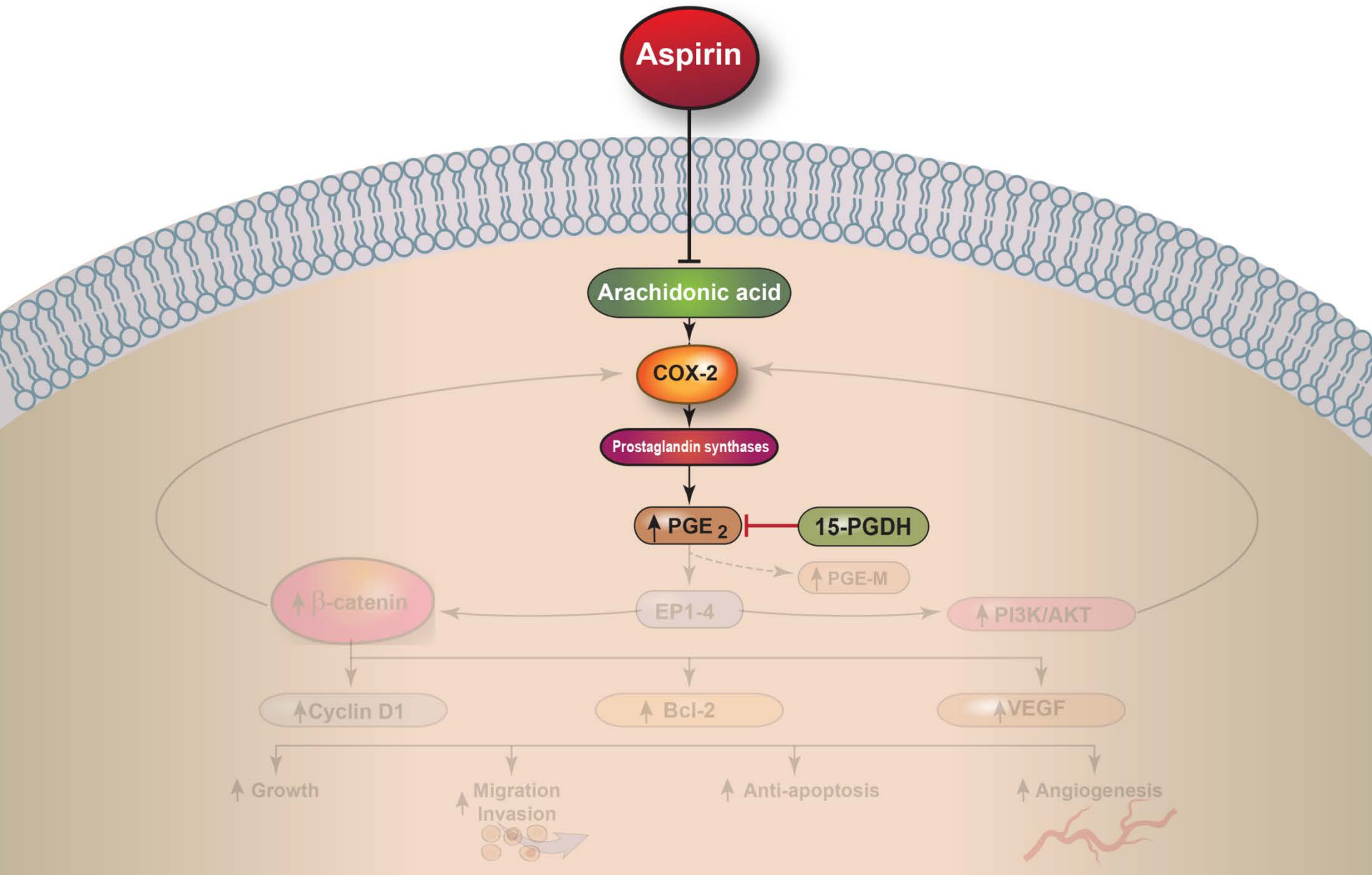
	Non-Users	Regular Users
All CRC	1.0	0.71 (0.53-0.95)
<i>PIK3CA</i> mutant CRC	1.0	0.18 (0.05-0.60)
<i>PIK3CA</i> wildtype CRC	1.0	0.93 (0.68-1.28)

P heterogeneity=0.01

Aspirin and recurrence-free survival among CRC patients in VICTOR

	Non-Users	Regular Users
All CRC	1.0	0.71 (0.53-0.95)
<i>PIK3CA</i> mutant CRC	1.0	0.11 (0.01-0.83)
<i>PIK3CA</i> wildtype CRC	1.0	0.94 (0.59-1.24)

P heterogeneity=0.02



15-Hydroxyprostaglandin dehydrogenase and CRC

- Ubiquitously downregulated in CRC
- Knockout of 15-PGDH in mice
 - ↑PGE-2, ↑ colon tumors, resistance to anti-tumor effect of celecoxib
- Pilot study in APC Trial
 - ↓15-PGDH in normal colon = ↑ resistance to anti-adenoma effect of celecoxib

Assessment of 15-PGDH in normal colon mucosa

- RNA extracted from normal colon in CRC resections
- RT-PCR to quantitate 15-PGDH mRNA expression

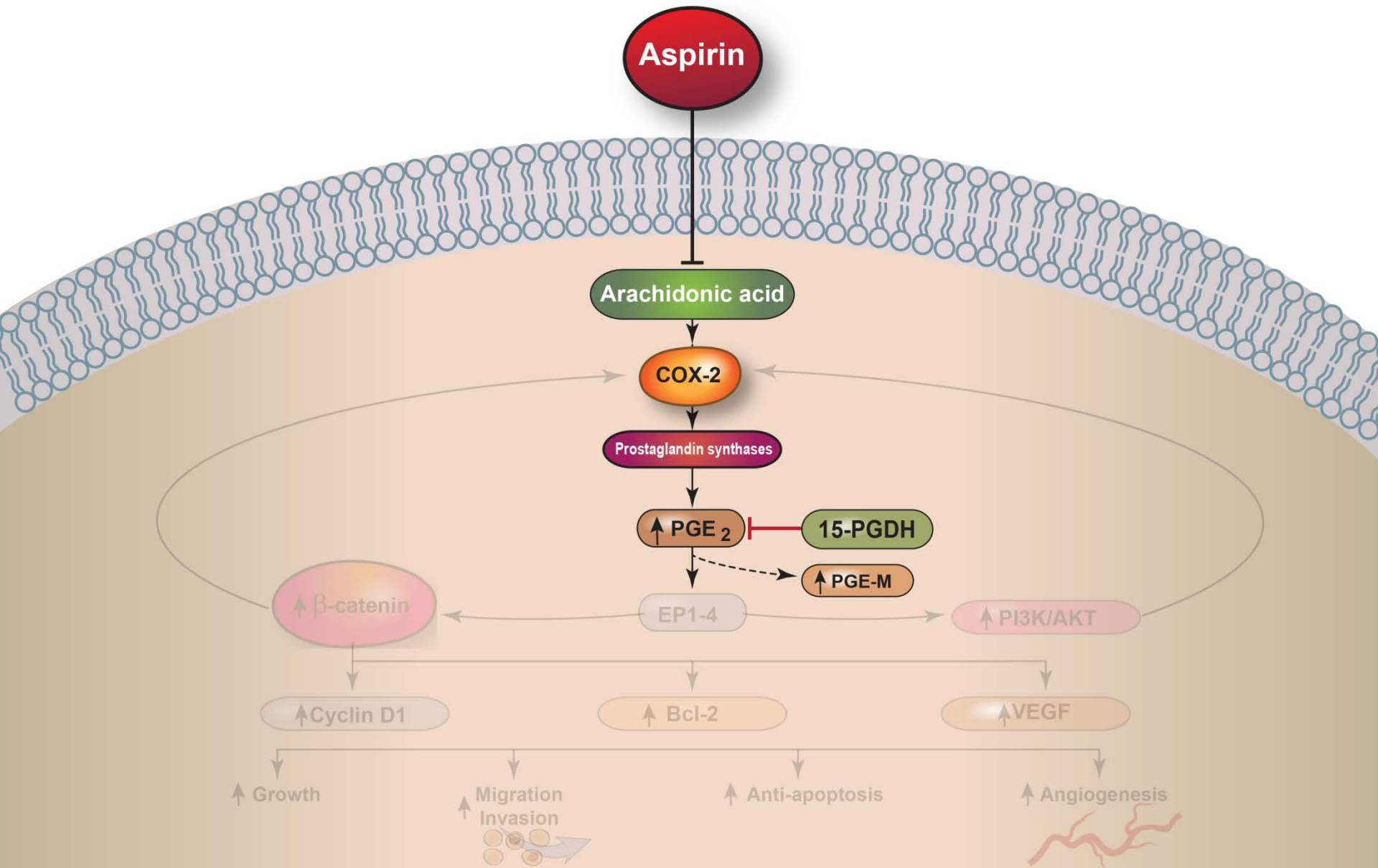
Aspirin and risk of CRC by 15-PGDH in normal colon

	Non-Users	Regular Users
All CRC	1.0	0.73 (0.62-0.86)
High 15-PGDH	1.0	0.49 (0.34-0.71)
Low 15-PGDH	1.0	0.90 (0.63-1.27)

P heterogeneity=0.02

15-PGDH risk-stratifies individuals for aspirin chemoprevention

Aspirin may preferentially reduce the risk of CRC among individuals with sufficient colonic 15-PGDH

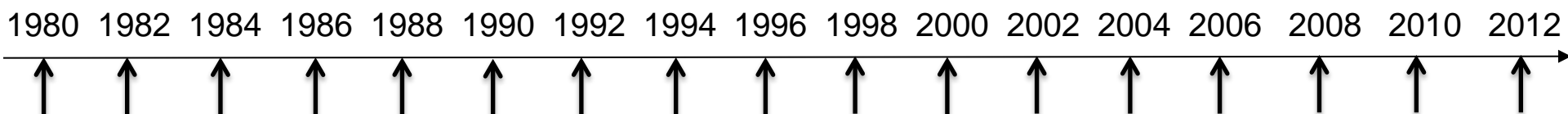


Urinary PGE-M

- Urinary metabolites (PGE-M) accurately reflect systemic prostaglandin balance
- PGE-M previously associated with CRC and adenoma

Study population

Nurses' Health Study (N=121,700)



Diet
Aspirin

Urine collection
N=18,743

Matching factors

- 1) Age
- 2) Date of urine
- 3) Year of endoscopy
- 4) Reason for endoscopy

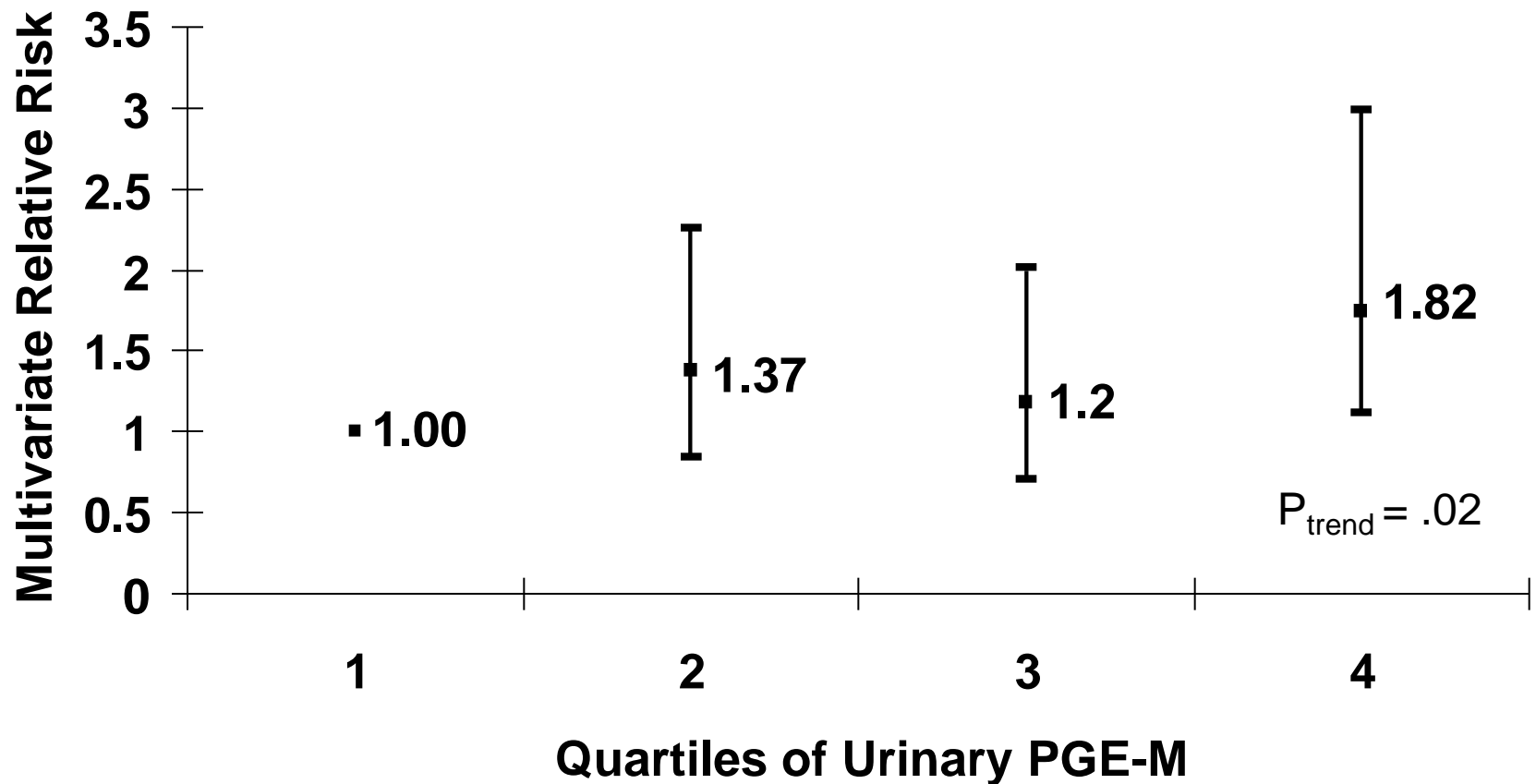
Controls
N=420

Adenoma
N=420

Exclusions

- 1) Prior cancer
- 2) IBD
- 3) Polyposis

Risk of advanced adenoma by urine PGE-M



Aspirin/NSAID use and risk of advanced adenoma by urine PGE-M

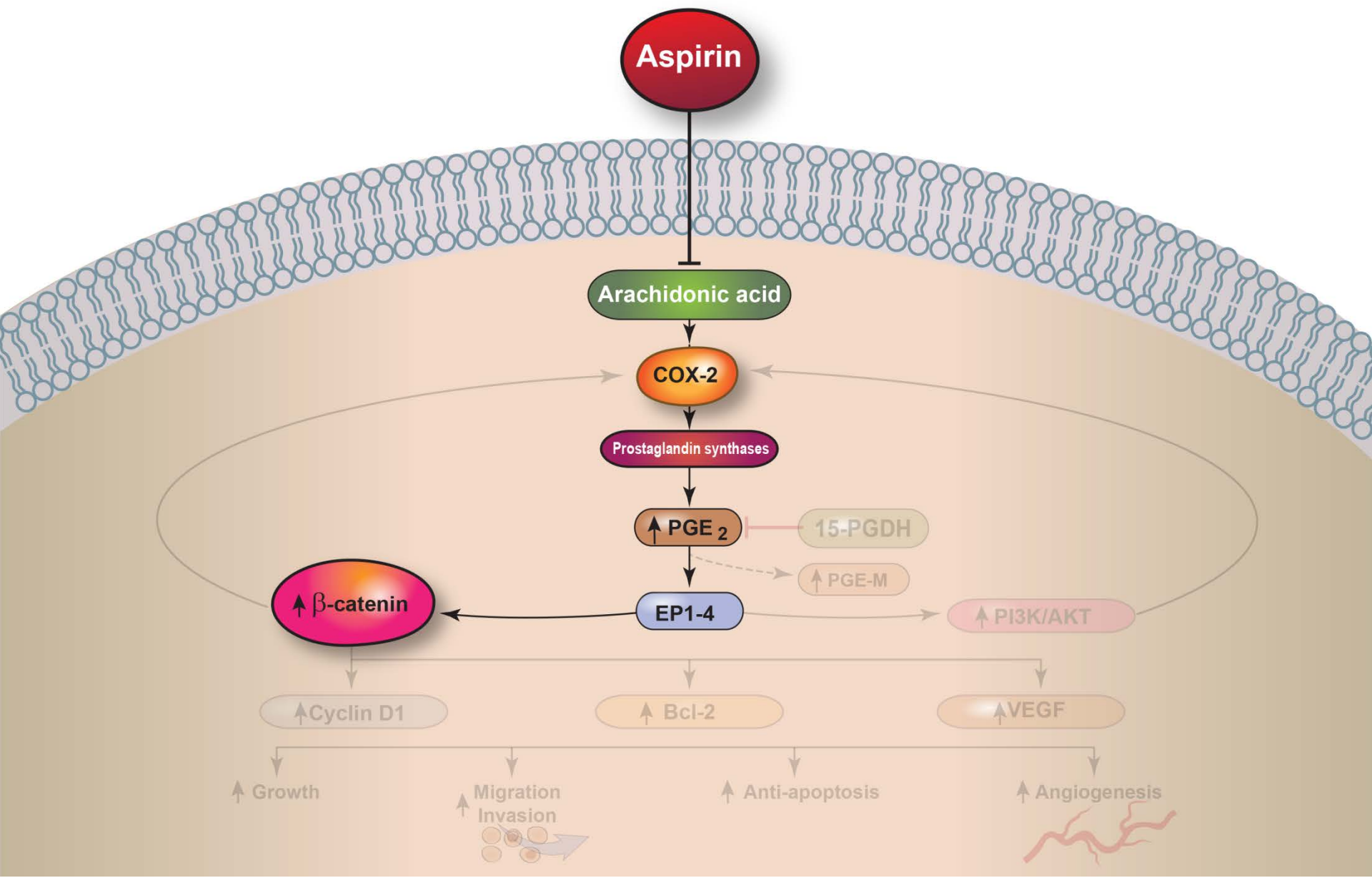
	Non-Users	Regular Users
Any PGE-M	1.0	0.76 (0.53-0.99)
High PGE-M (Q 2,3,4)	1.0	0.65 (0.45-0.94)
Low PGE-M (Q1)	1.0	1.31 (0.62-2.76)

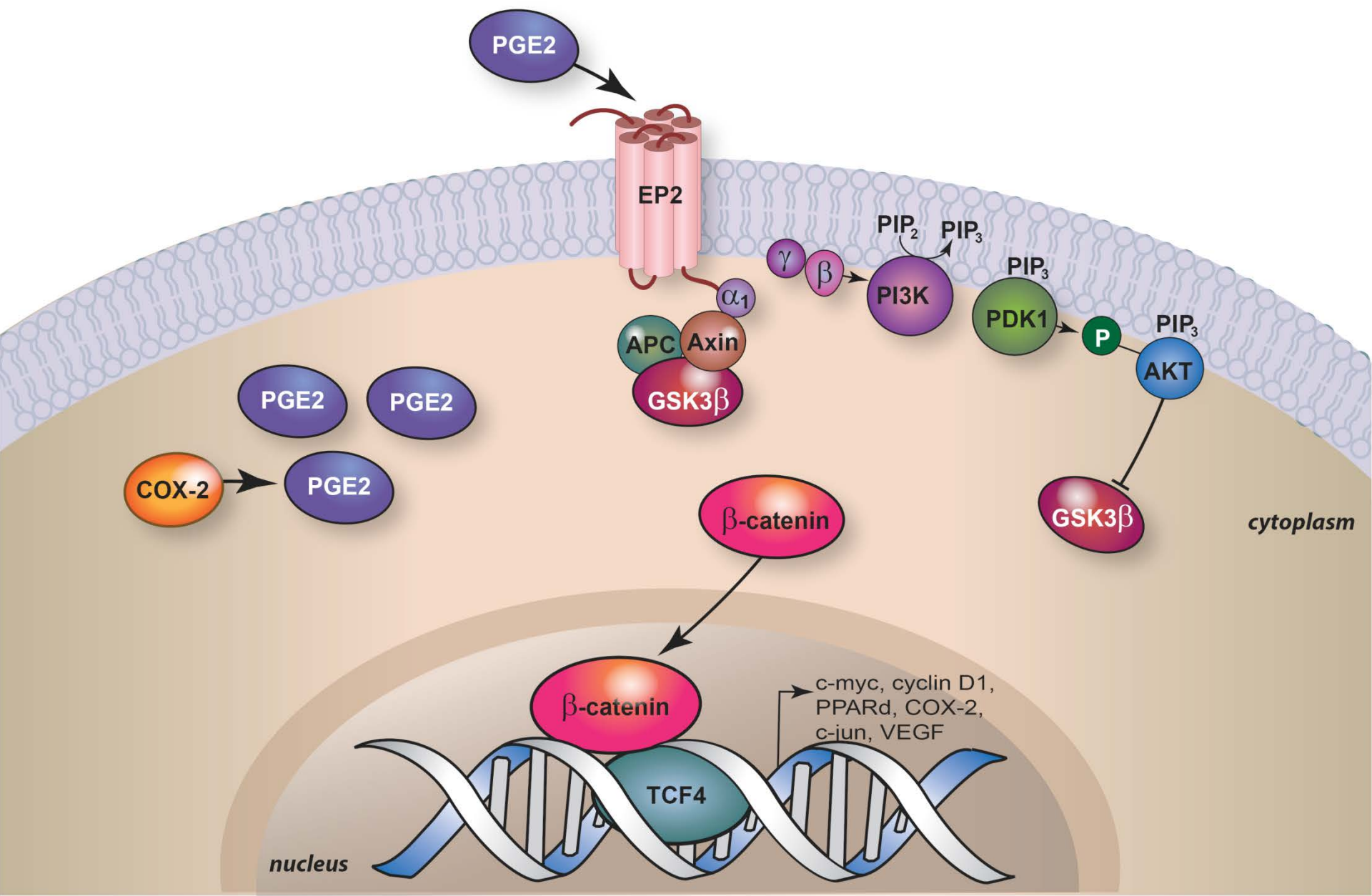
PGE-M risk-stratifies for aspirin chemoprevention

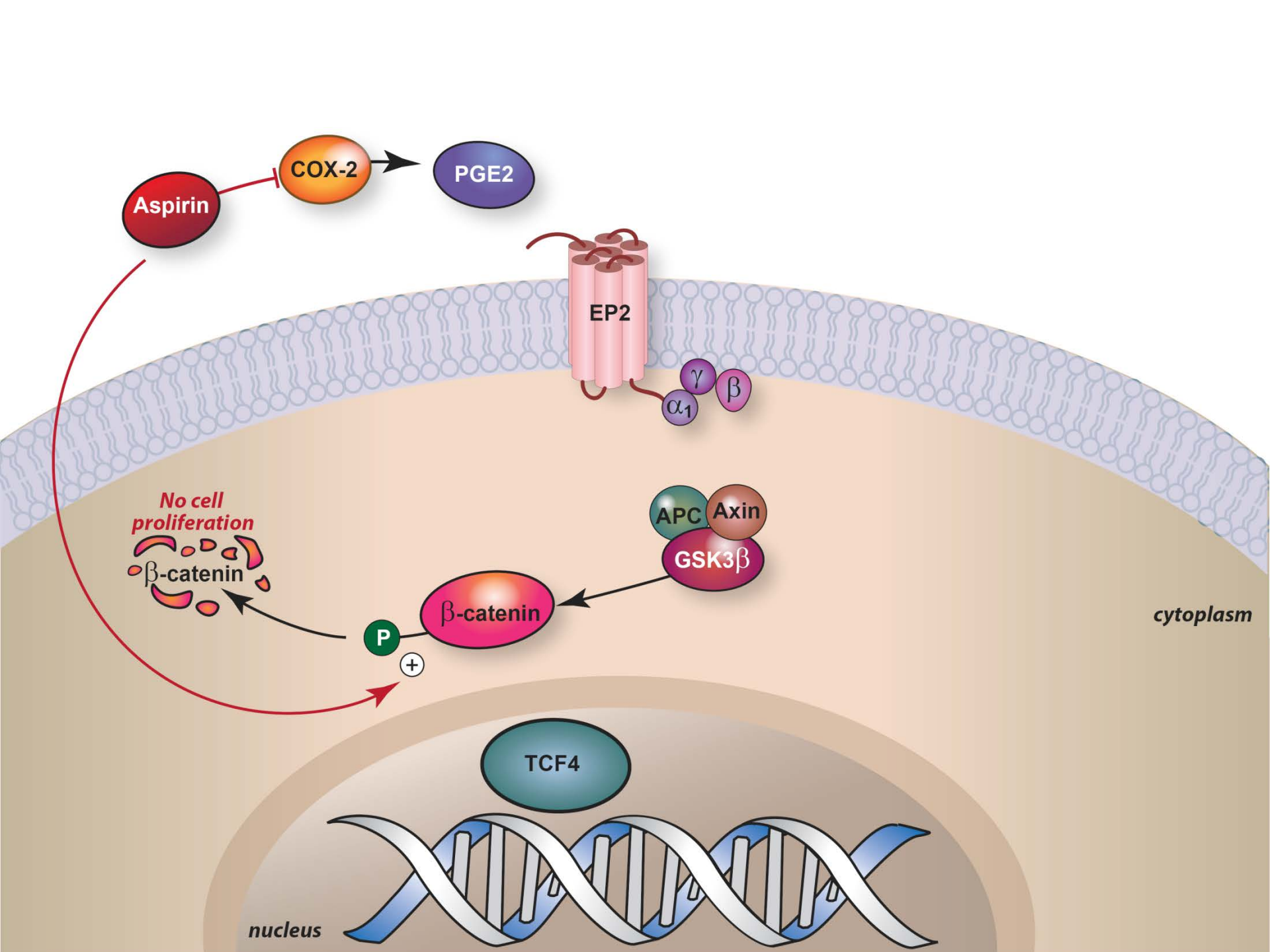
Aspirin/NSAIDs primarily ↓ risk of advanced adenoma in those with ↑ urine PGE-M

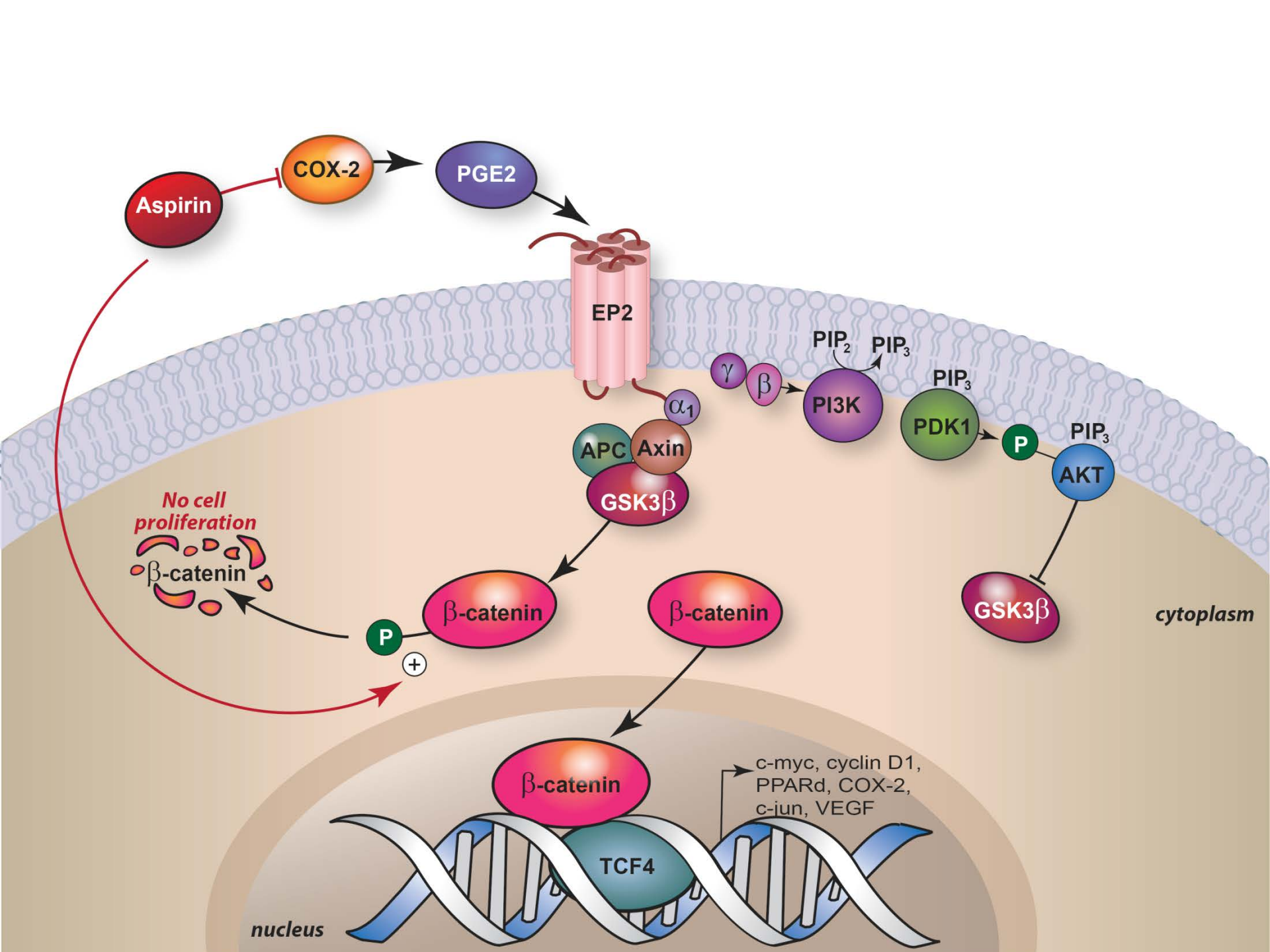
Can we exploit mechanism to personalize chemoprevention?

- Prostaglandin balance
- *Wnt* signaling





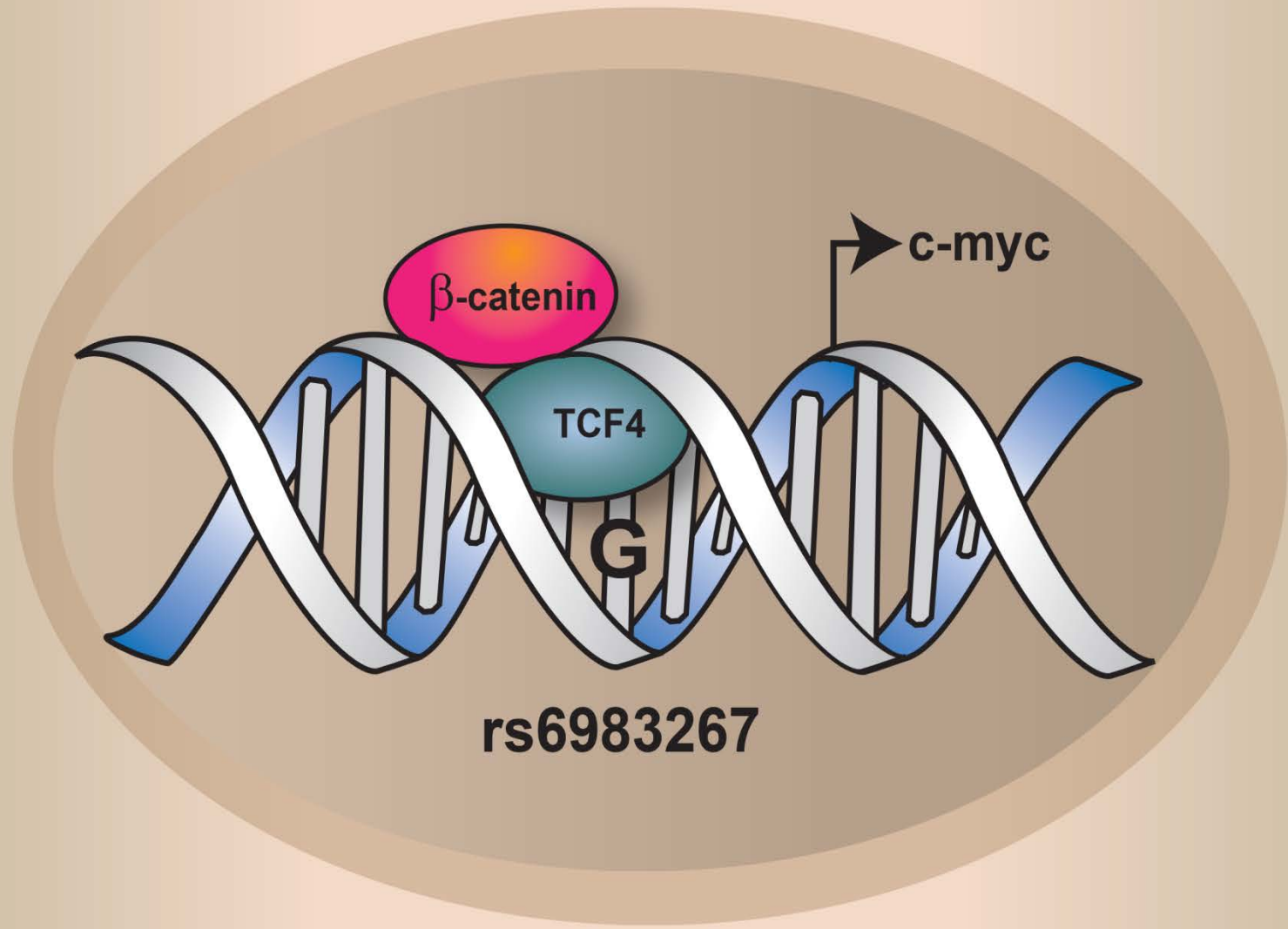


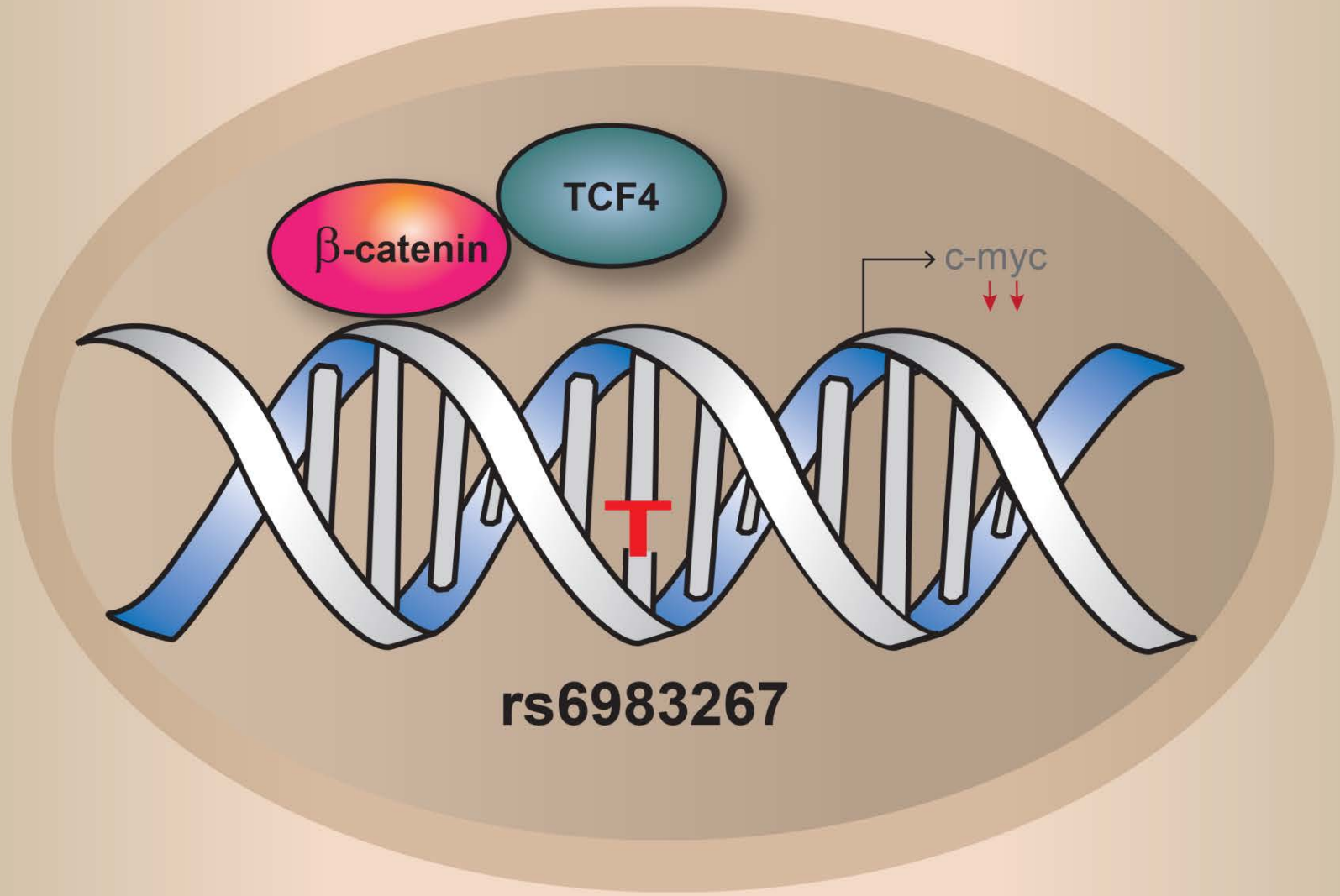


GWAS hits for CRC

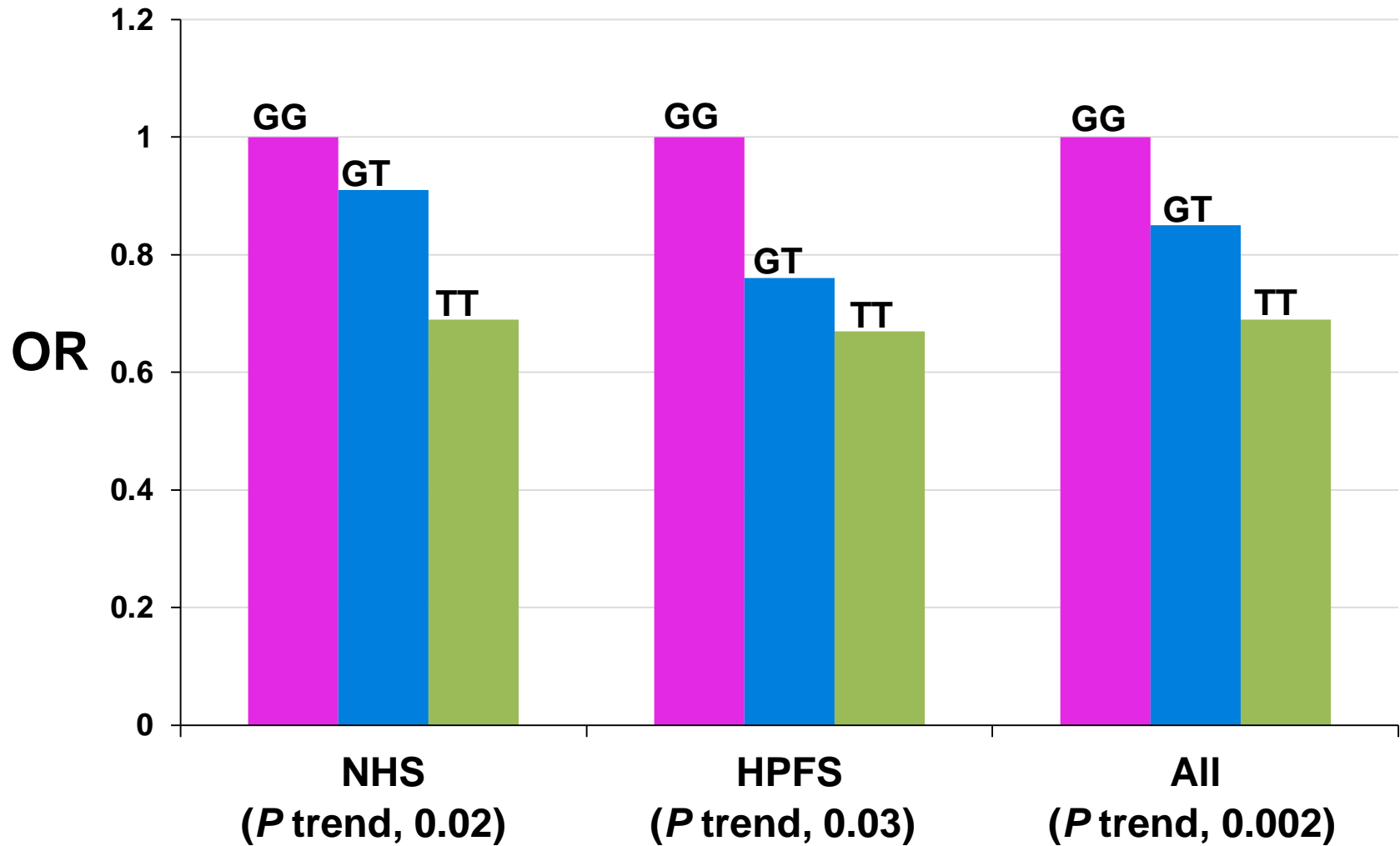
Position/Gene	rs#	Minor Allele	MAF	OR (95%CI)	P-value
8q24	rs6983267	T	0.50	0.83 (0.81-0.85)	7x10⁻³⁰
18q21/ <i>SMAD7</i>	rs4939827	T	0.49	0.85 (0.81-0.89)	1x10 ⁻²⁸
15q13/ <i>CRAC1</i> (<i>HMPS</i>)	rs4779584 rs10318	T	0.18	1.26 (1.19-1.34)	4x10 ⁻¹⁴
10p14	rs10795668	A	0.33	1.25 (1.19-1.32)	3x10 ⁻¹³
8q23.3/ <i>EIF3H</i>	rs16892766	C	0.07	0.89 (0.86-0.91)	3x10 ⁻¹⁸
+ > 30 more					

Tomlinson *et al*, Nat Gen 2007, 2008; Zanke *et al*, Nat Gen 2007; Tenesa *et al*, Nat Gen 2008; Broderick *et al*, Nat Gen 2007; Cogent *et al*, Nat Gen 2008; Houlston *et al*, Nat Gen 2010

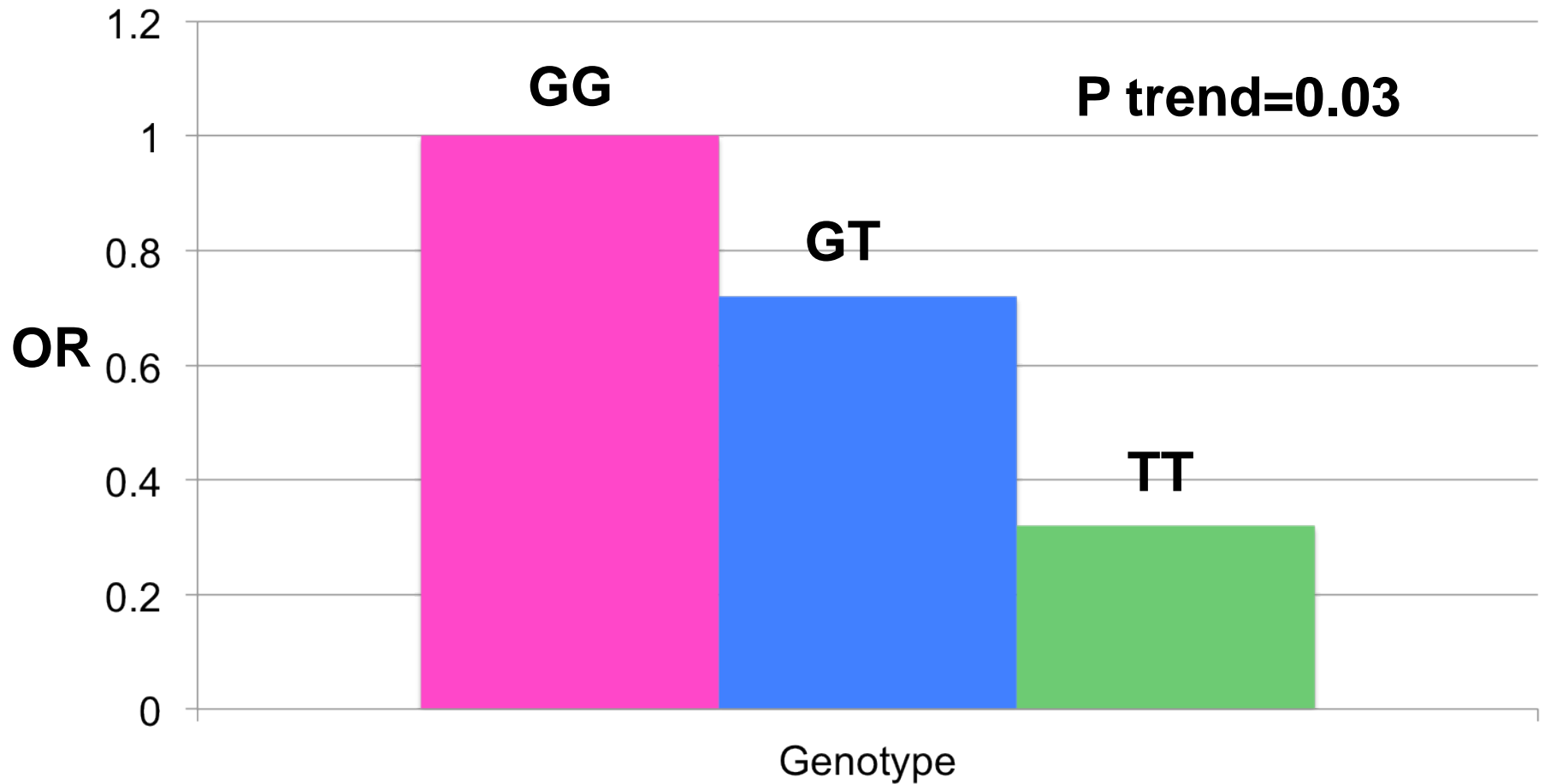




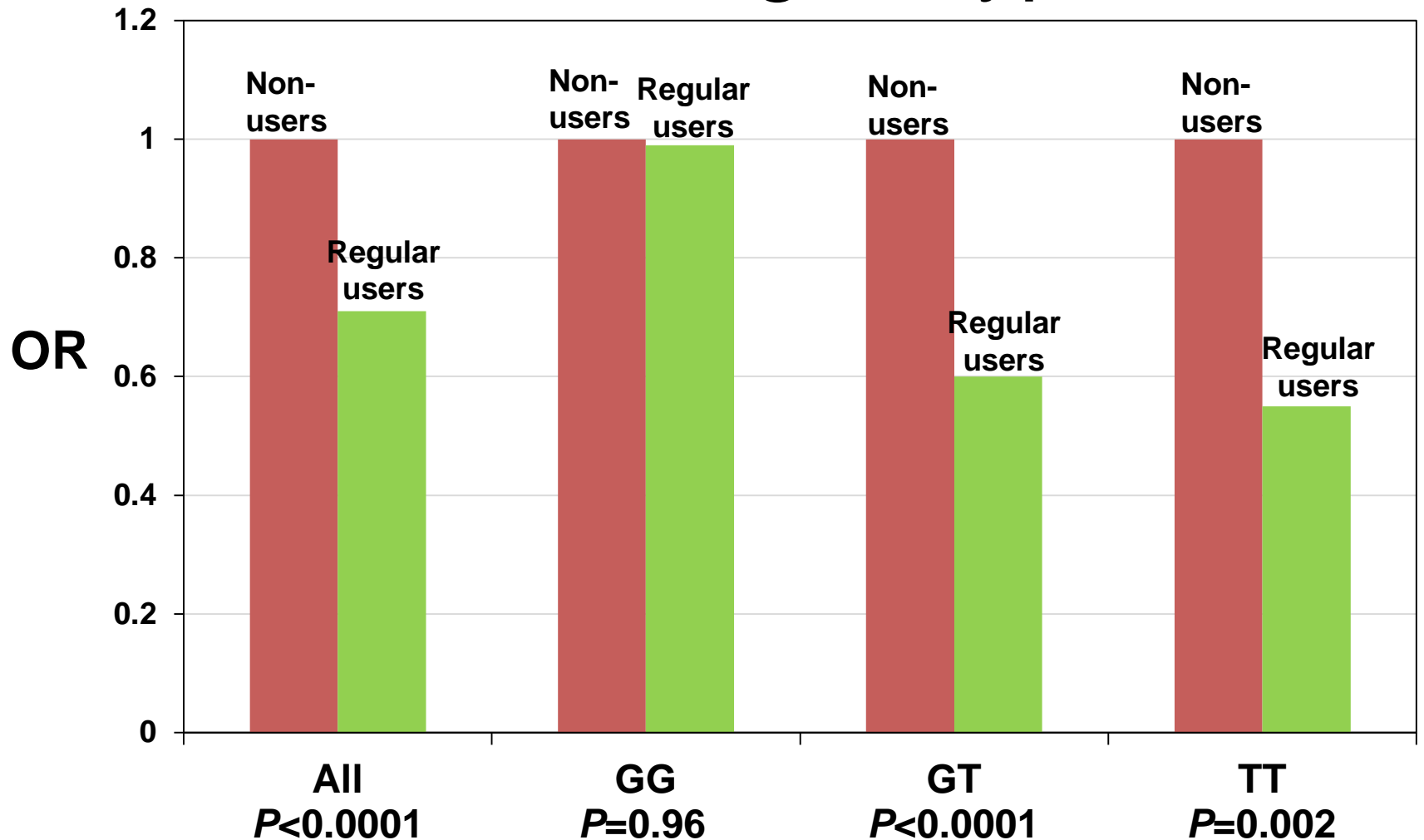
rs6983267 and risk of CRC



rs6983267 and *MYC* expression

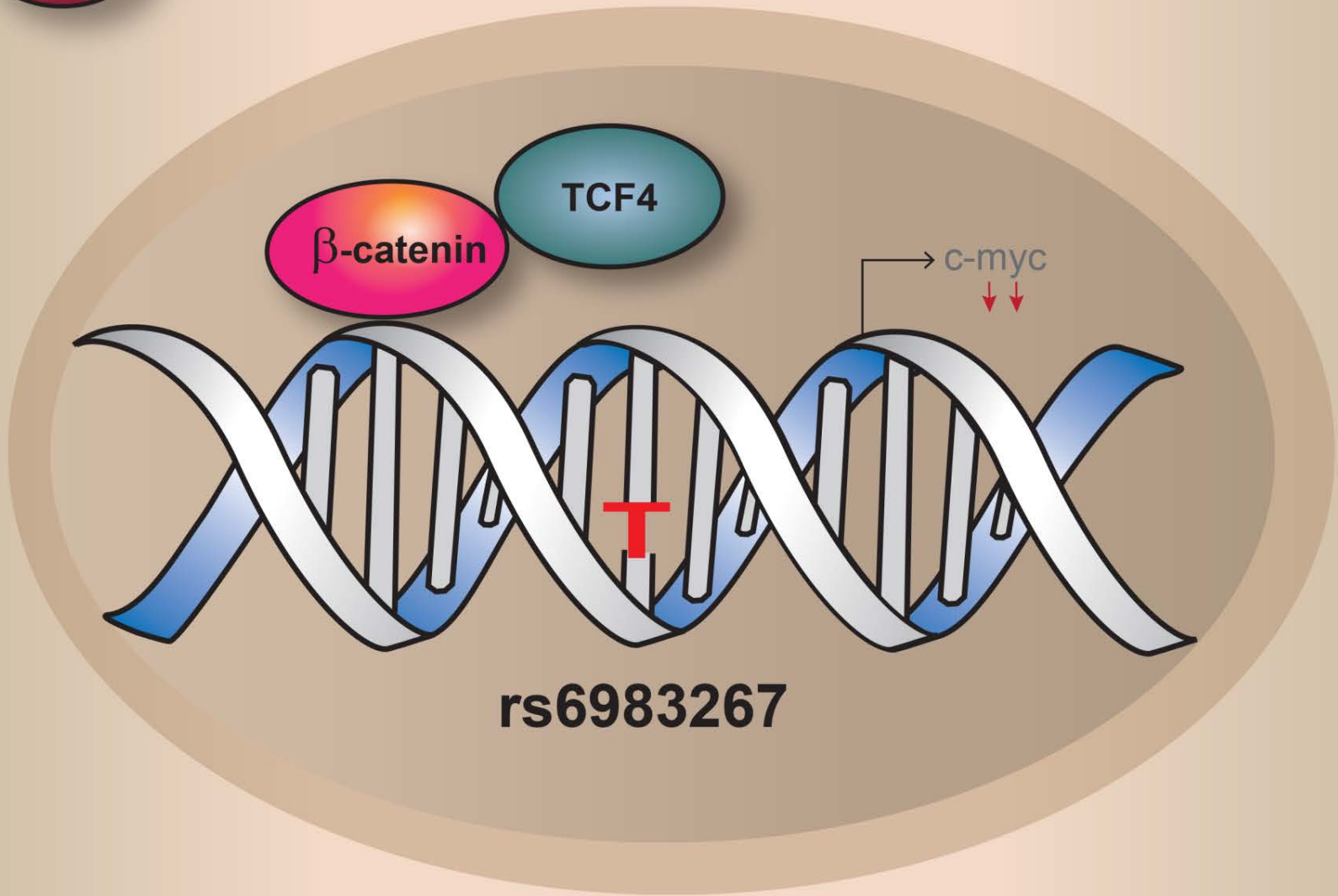


Aspirin and risk of CRC risk by rs6983267 genotype



P for interaction=0.01

Aspirin



Rs6983267 risk stratifies for aspirin chemoprevention

- T allele ↓ risk of CRC and *MYC* expression
- Benefit of aspirin on CRC appears limited to individuals \geq one T allele

Summary

- Overwhelming evidence supports a benefit of aspirin on CRC development
- Aspirin may improve CRC survival
- Mechanisms by which aspirin prevents cancer can be exploited to risk-stratify for chemoprevention

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