Mechanistic Studies of Aspirin and Prevention of Colorectal Cancer

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National Cancer Institute
Board of Scientific Advisors &
National Cancer Advisory Board
June 23, 2014

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)

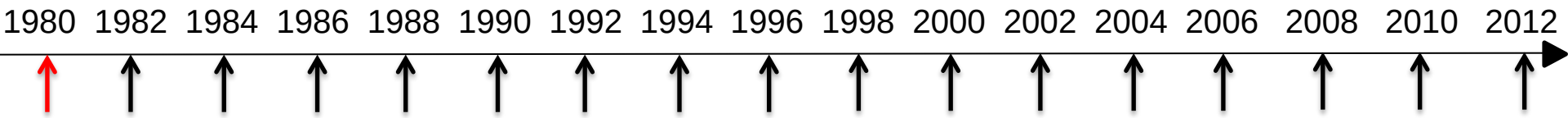
Nishihara *et al*, NEJM 2013

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)

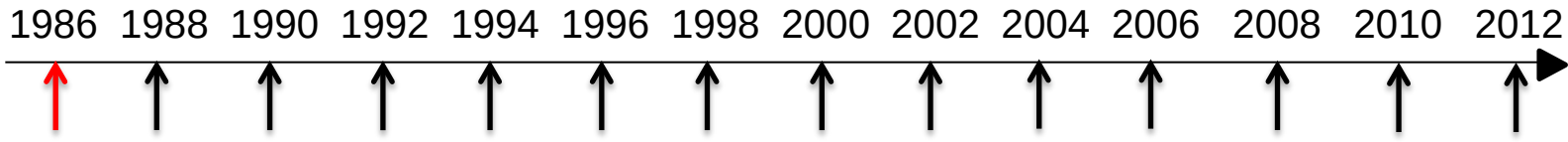
Study population

Nurses' Health Study (n=121,700)



Diet
Aspirin
BMI
Med. Hist.
Tobacco

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



Diet
Aspirin
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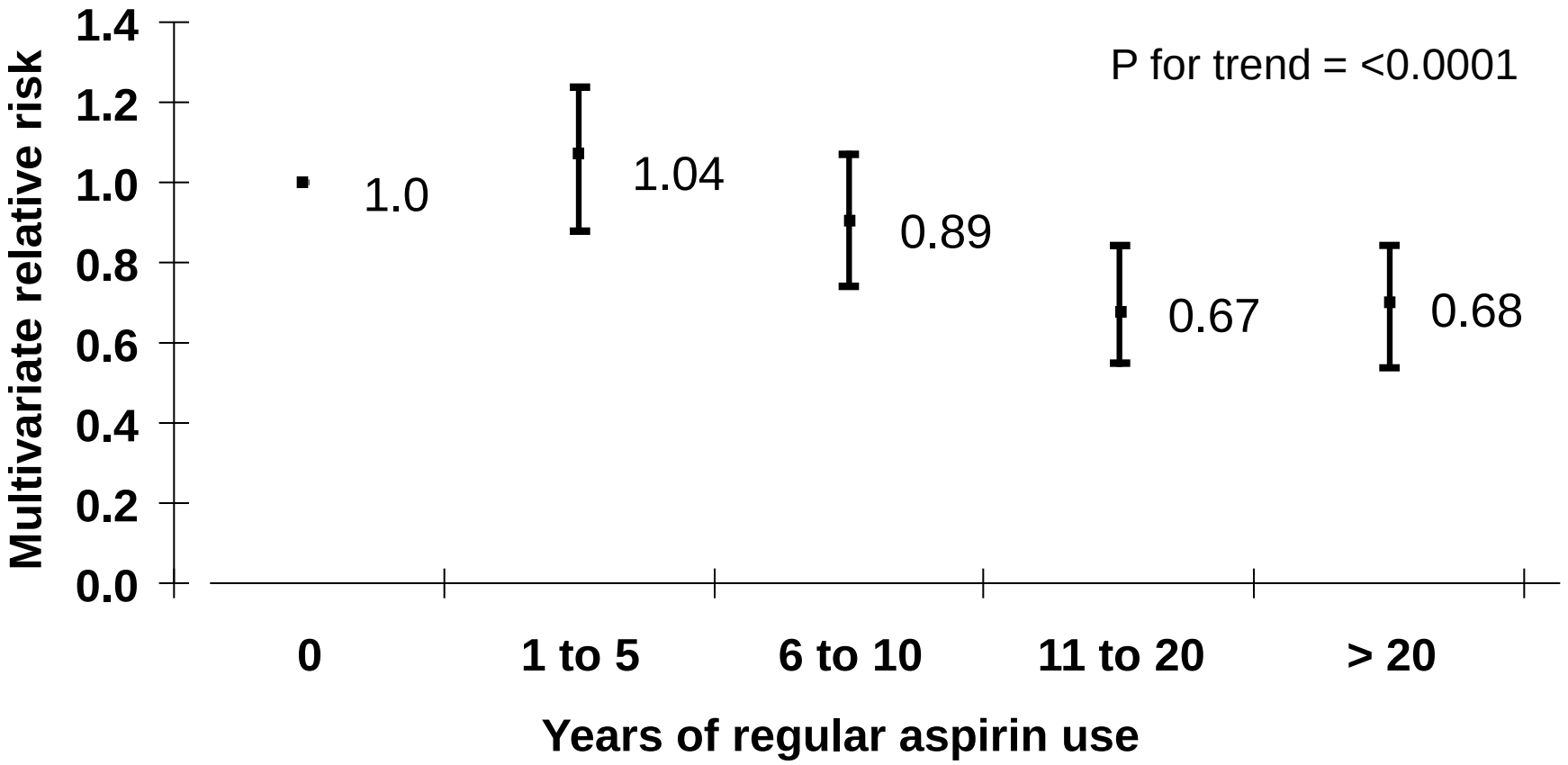
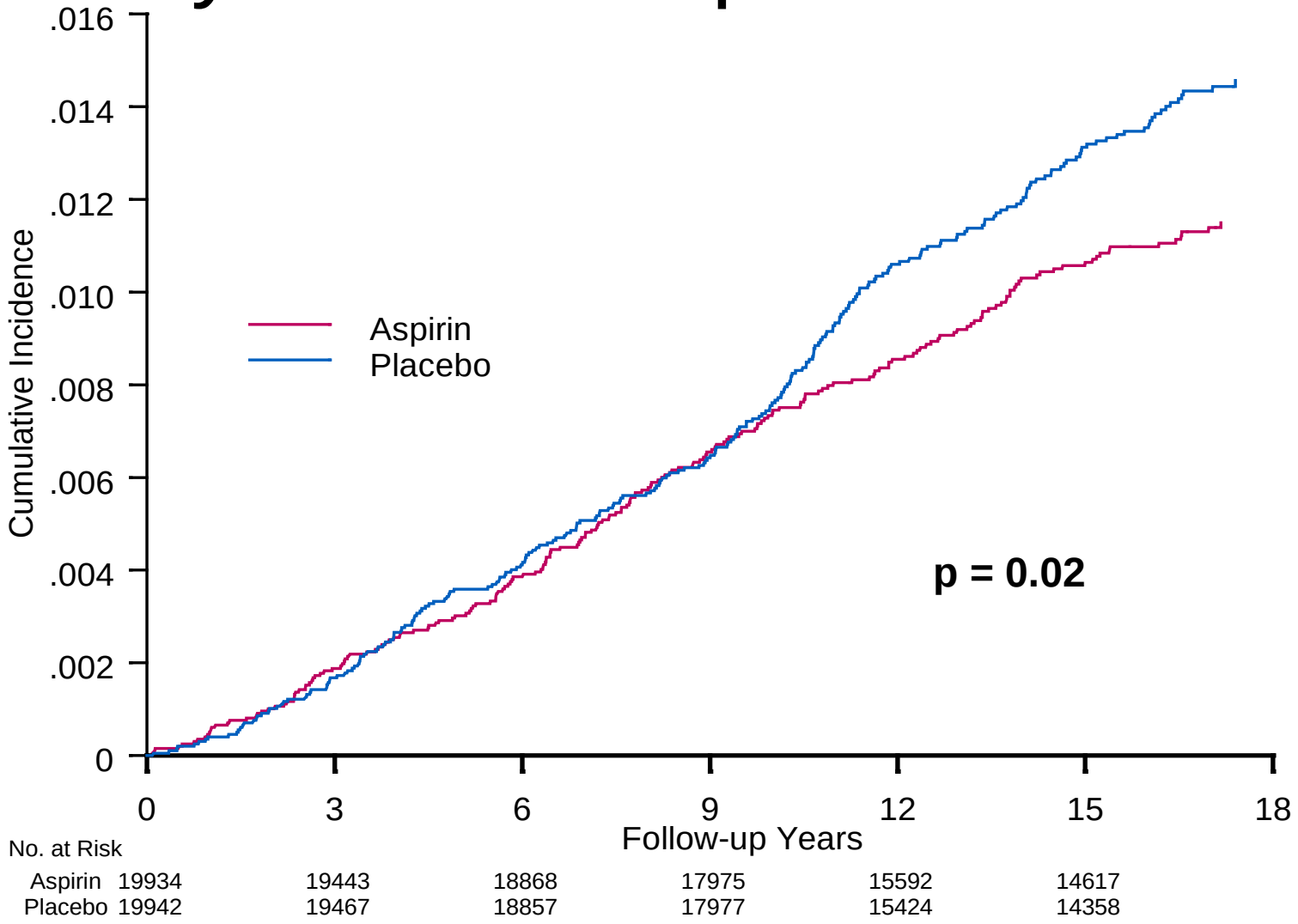
Duration of aspirin use and risk of CRC



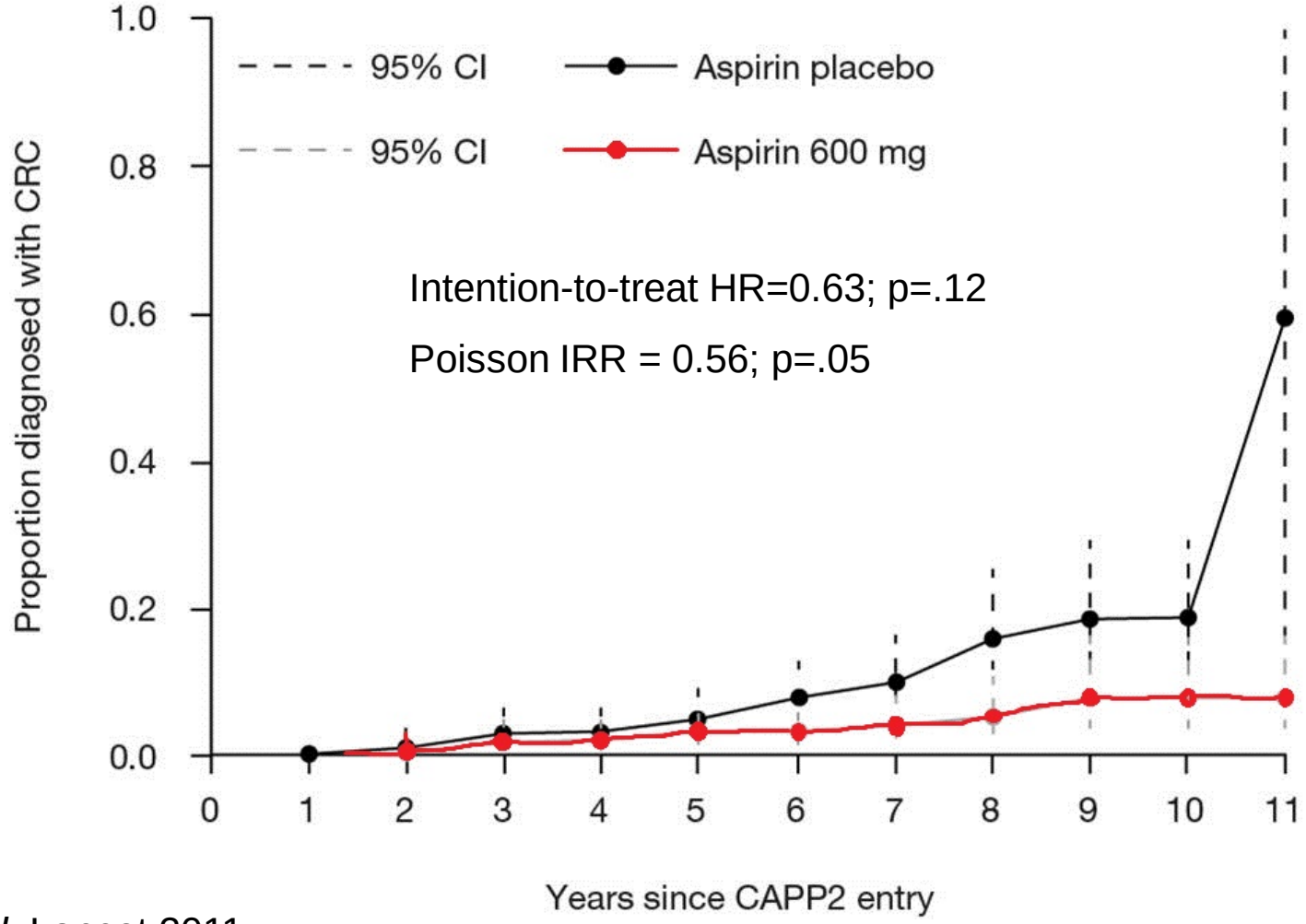
Chan *et al*, JAMA 2005

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



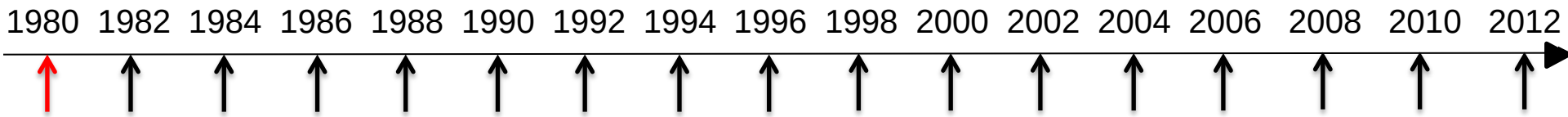
Cook et al, Ann Int Med 2013

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



Burn *et al*, Lancet 2011

Nurses' Health Study (n=121,700)



Diet
Aspirin
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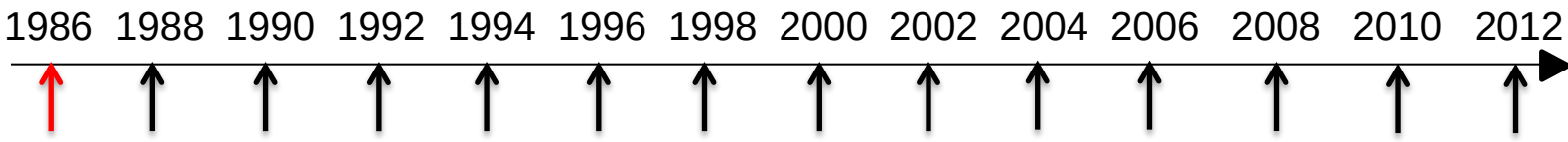
Tobacco

N=1,279 with Stage I, II, III CRC



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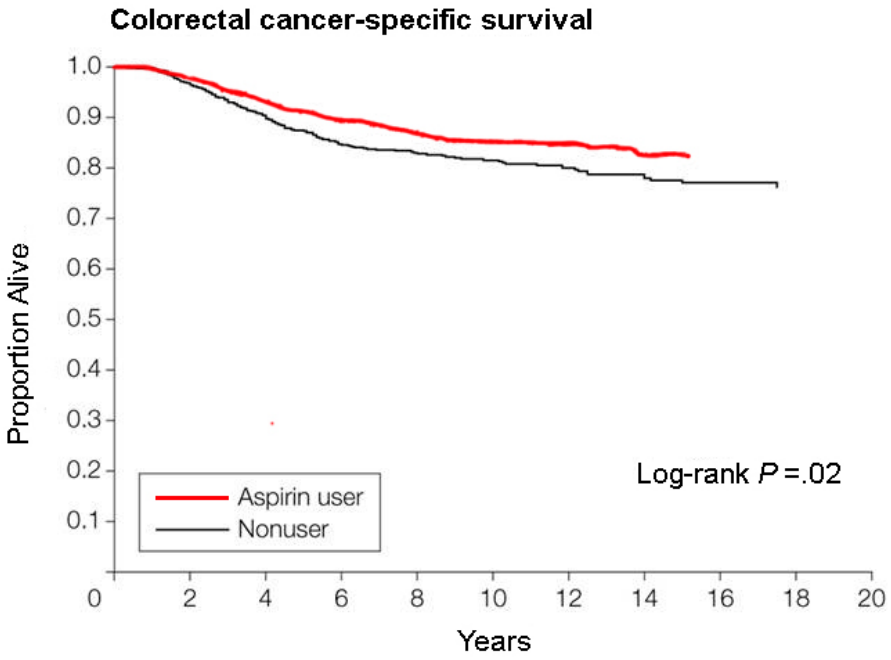
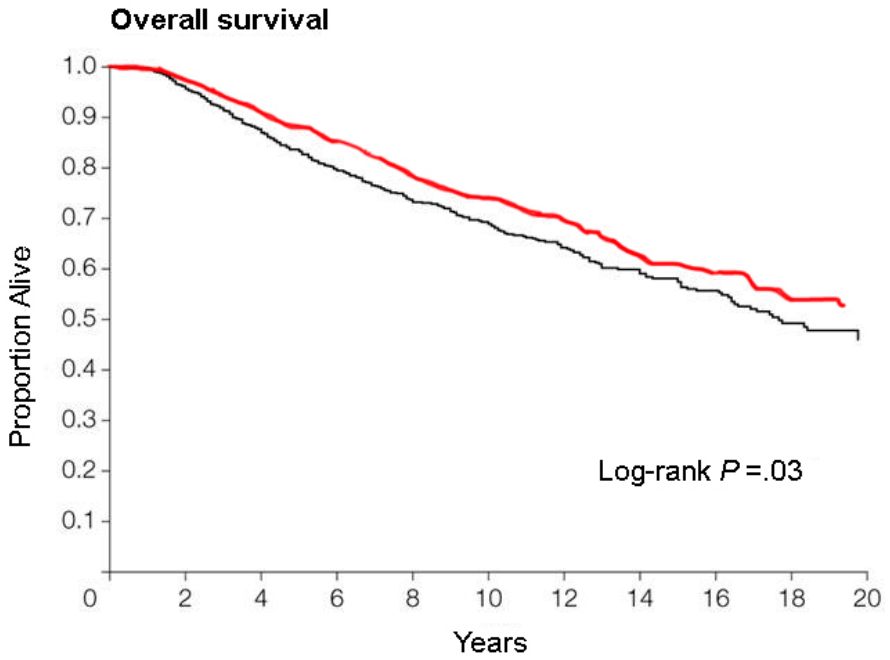
Health Professionals Follow-up Study (n=51,539)

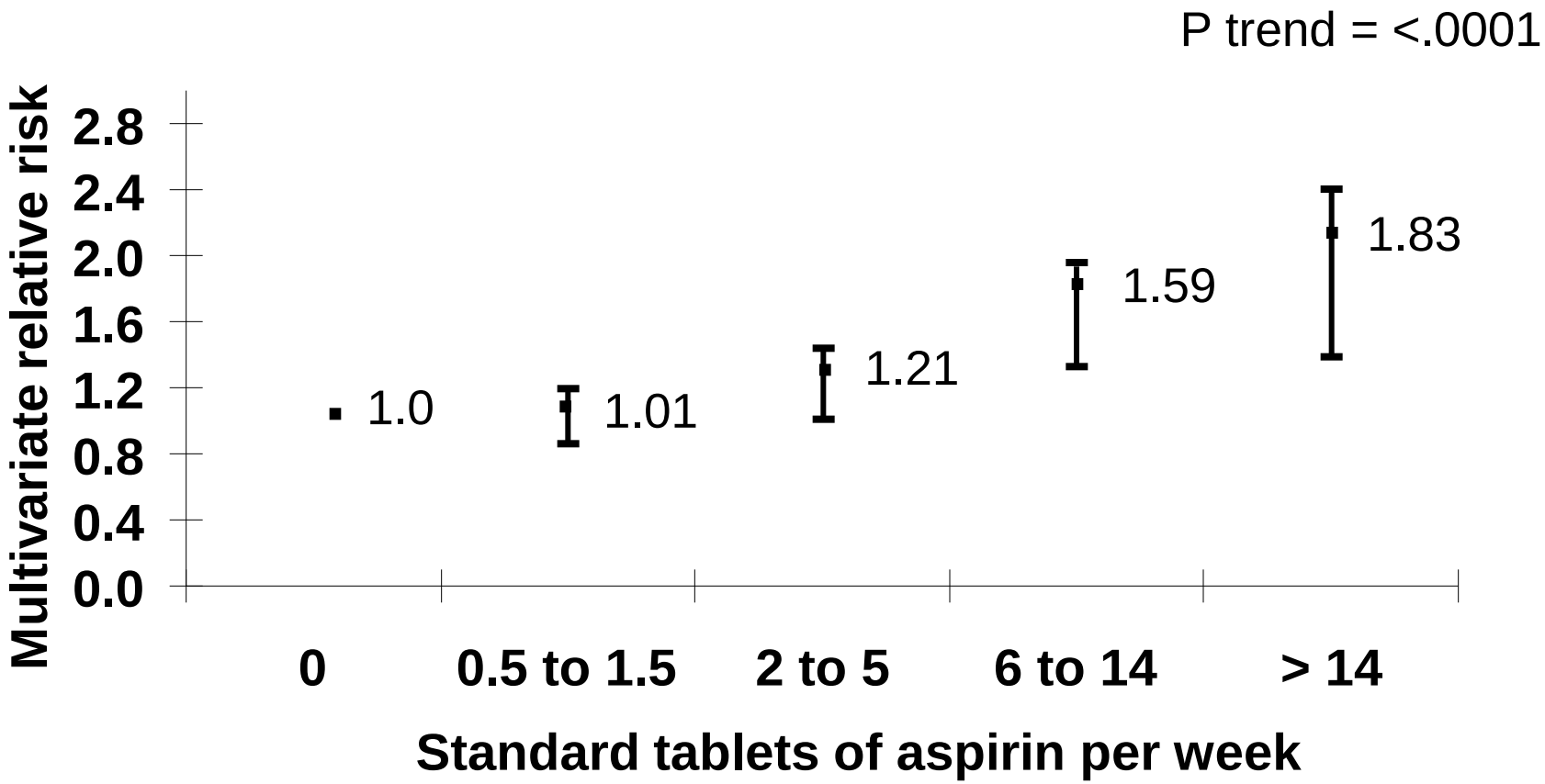
Aspirin use and CRC patient survival





Chan *et al*, JAMA 2009

Aspirin and risk of GI bleeding



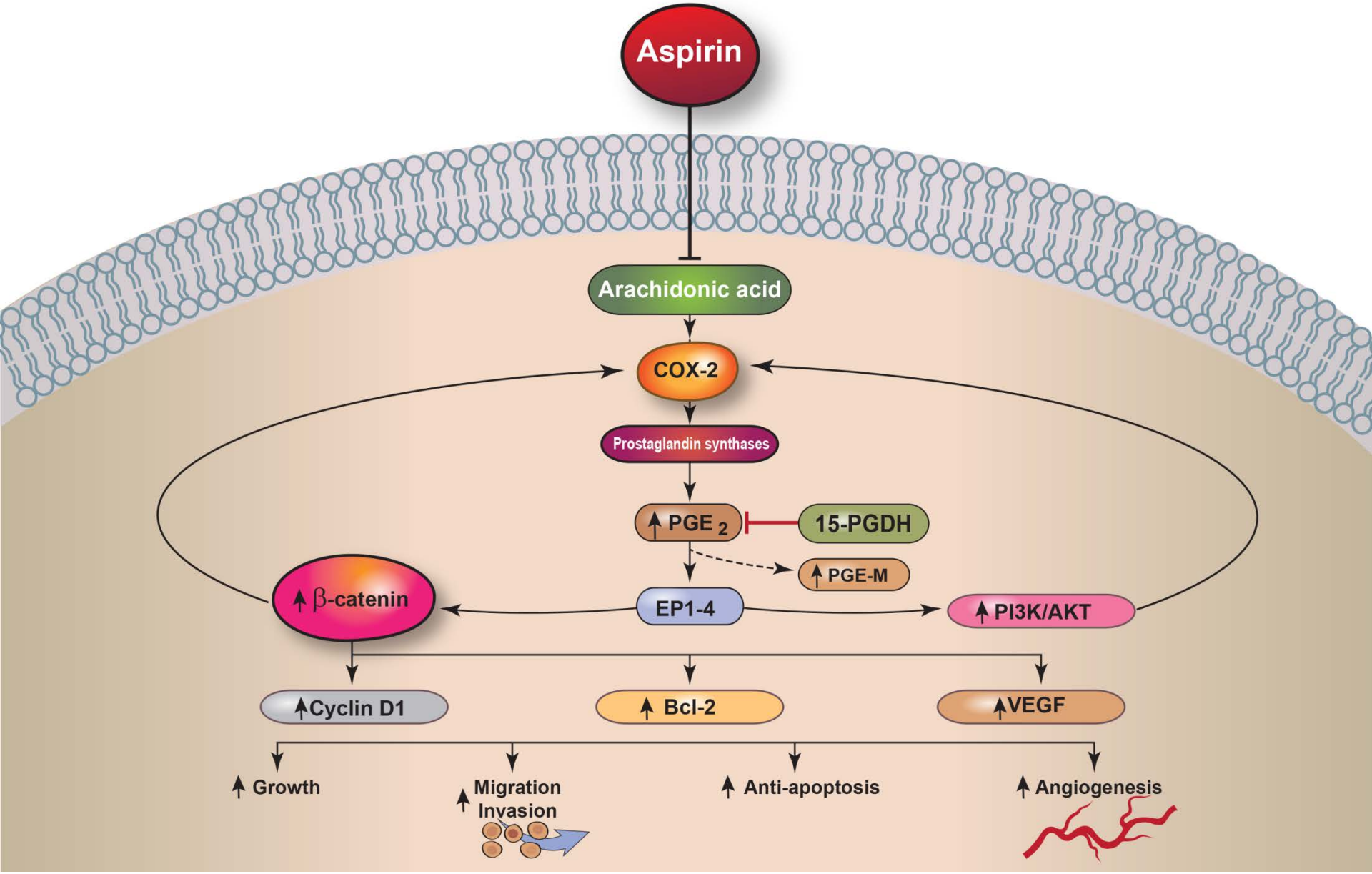
Huang *et al.* Am J. Med 2011.

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
Arachidonic acid
COX-2
Prostaglandin synthases
PGE 2
15-PGDH
PGE-M
β-catenin
EP1-4
PI3K/AKT
Cyclin D1
Bcl-2
VEGF
Growth
Migration
Invasion
Anti-apoptosis
Angiogenesis

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

Chan *et al*, NEJM 2007

Aspirin and CRC-specific mortality among CRC patients

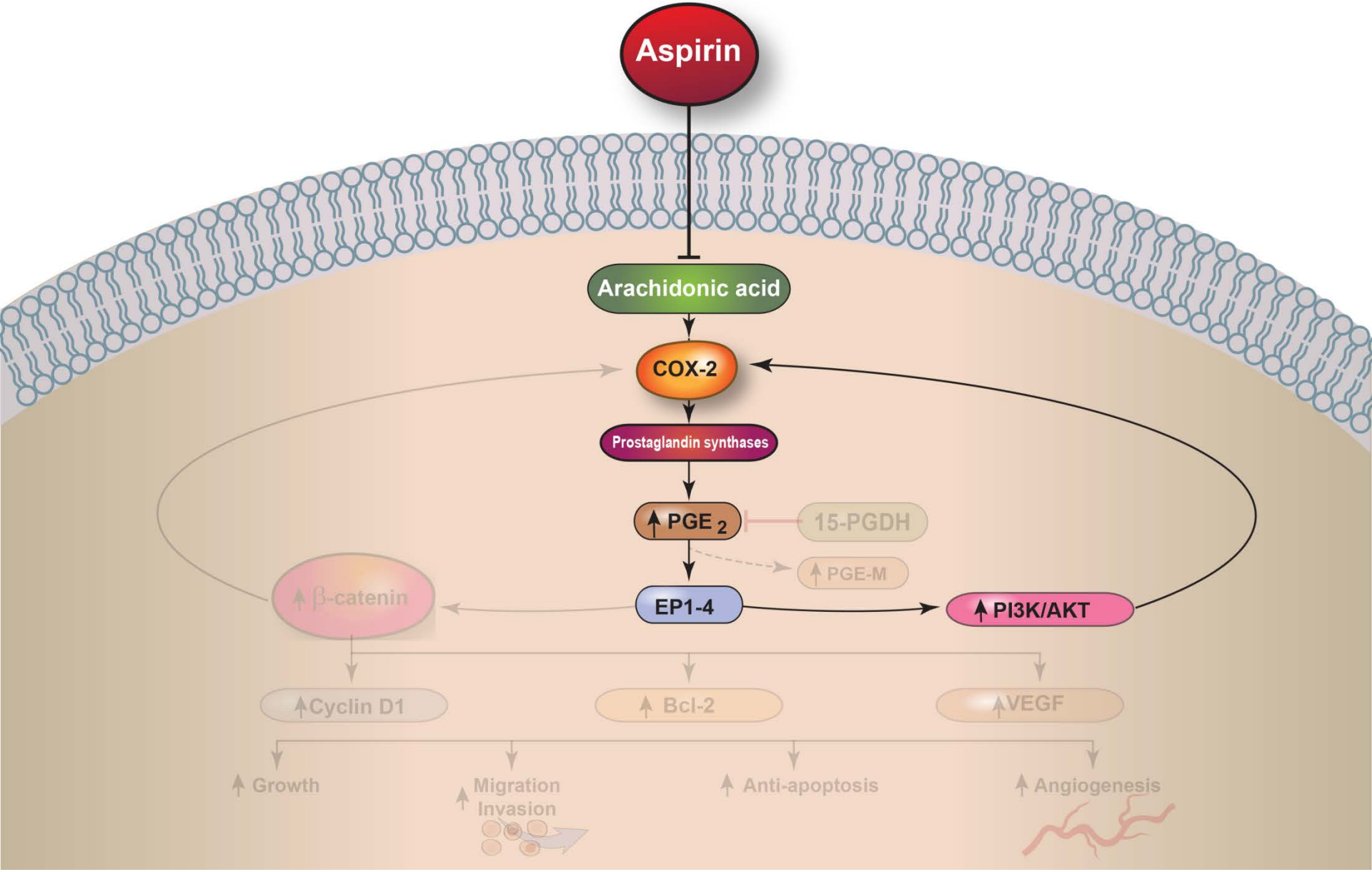
	Non-Users	Regular Users
All CRC	1.0	0.71 (0.53-0.95)
COX-2 positive CRC	1.0	0.39 (0.20-0.76)
COX-2 negative CRC	1.0	1.22 (0.36-4.18)

P heterogeneity=0.04

Chan *et al*, JAMA 2009

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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Prostaglandin synthases
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EP1-4
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Cyclin D1
Bcl-2
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Growth
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Angiogenesis

Aspirin and CRC-specific mortality among CRC patients

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

P heterogeneity=0.01

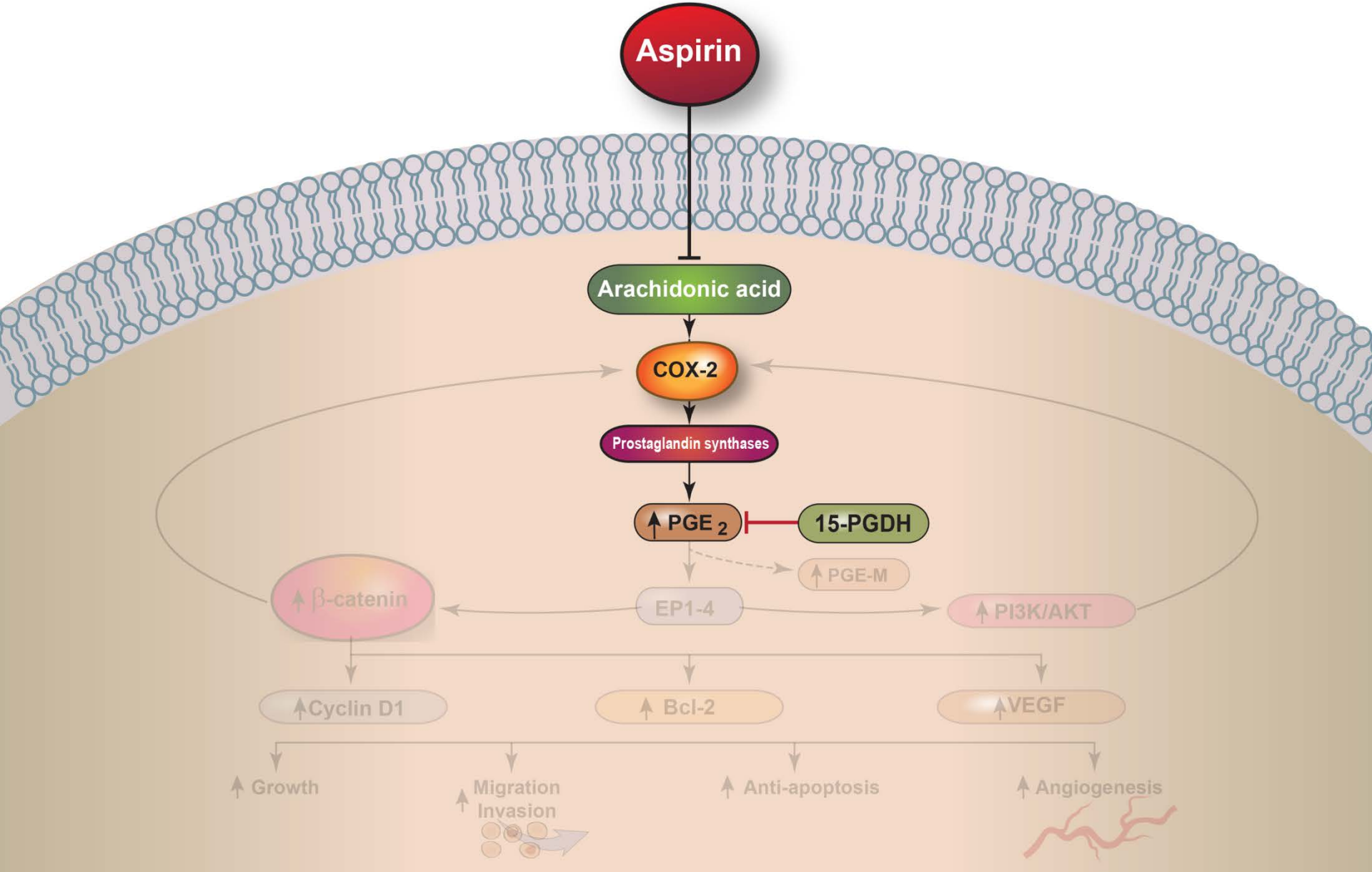
Liao *et al*, NEJM 2012

Aspirin and recurrence-free survival among CRC patients in VICTOR

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

P heterogeneity=0.02

Domingo *et al*, JCO 2013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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

Yan *et al*, PNAS 2004; Yan *et al*, PNAS 2009

Assessment of 15-PGDH in normal colon mucosa

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

Fink *et al*, Dig Dis Sci 2013

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

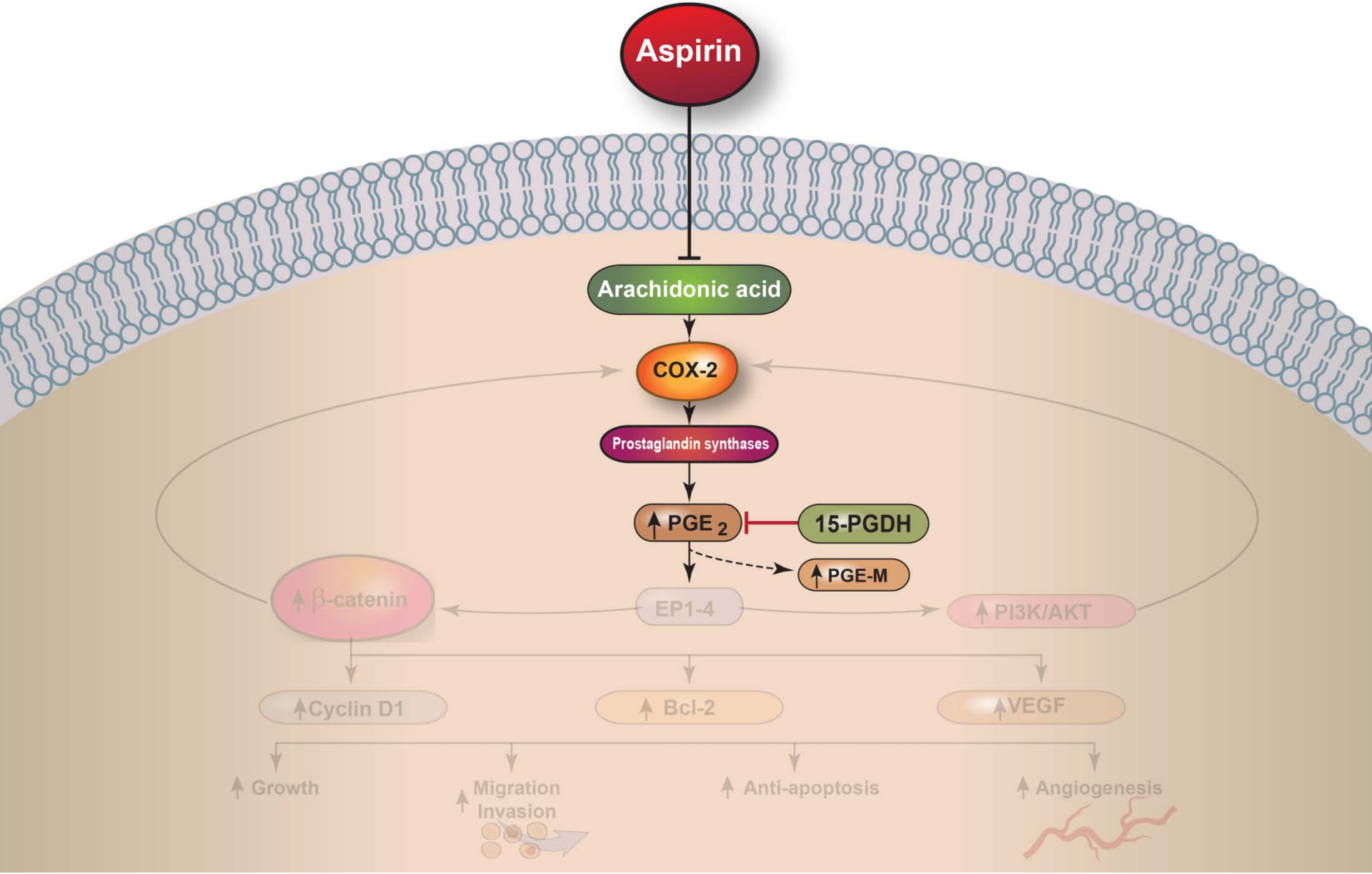
	Non-Users	Regular Users
All CRC	1.0	0.73 (0.62-0.86)
High 15-PGDH	1.0	0.49 (0.34-0.71)
Low 15-PGDH	1.0	0.90 (0.63-1.27)

P heterogeneity=0.02

Fink *et al*, Sci Trans Med 2014

15-PGDH risk-stratifies individuals for aspirin chemoprevention

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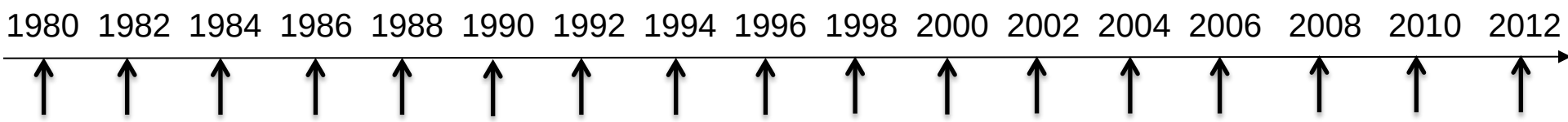
Urinary PGE-M

- 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

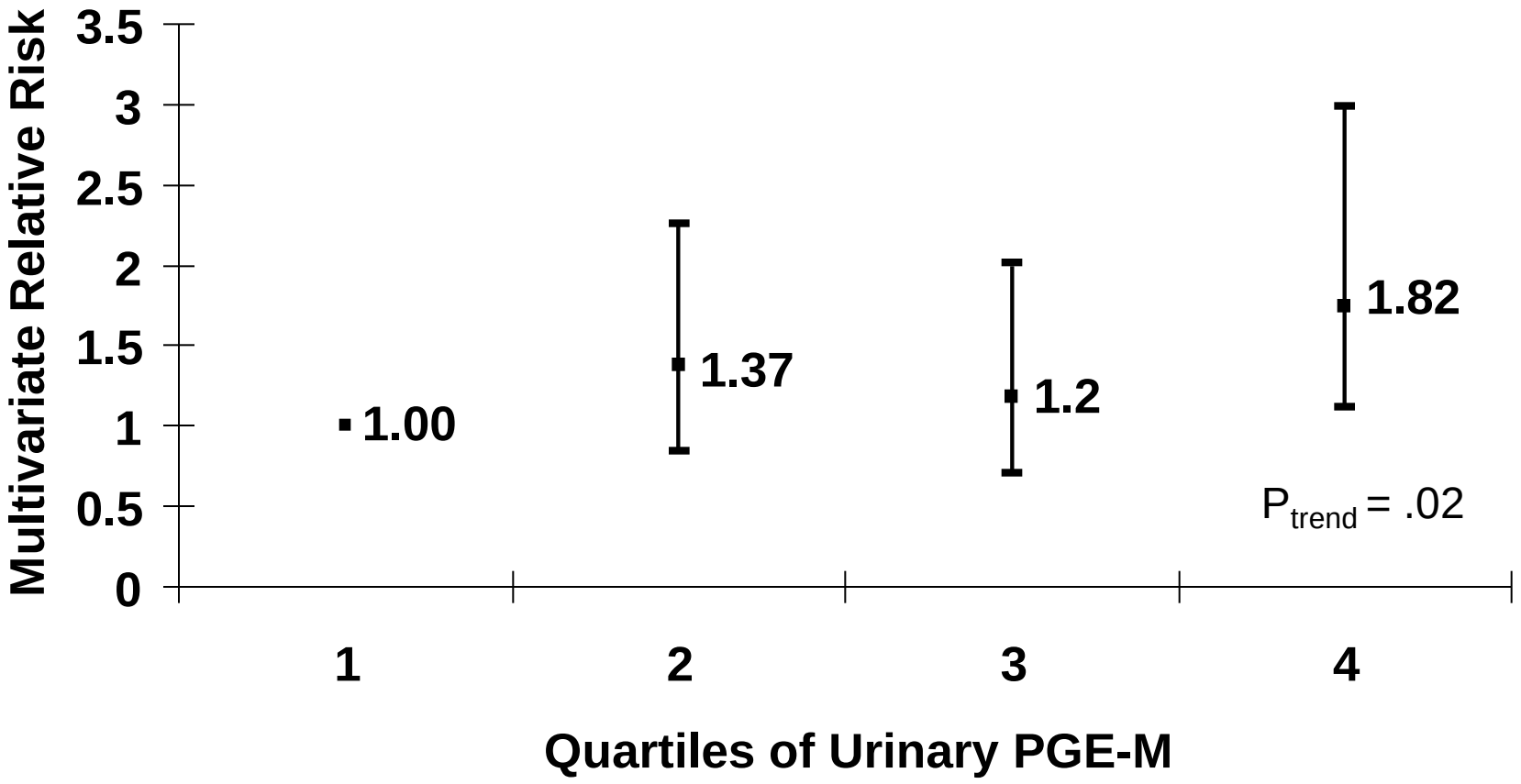
Controls N=420

Adenoma N=420

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

Exclusions
1) Prior cancer
2) IBD
3) Polyposis

Risk of advanced adenoma by urine PGE-M



Bezawada *et al*, Can Prev Res 2014

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)

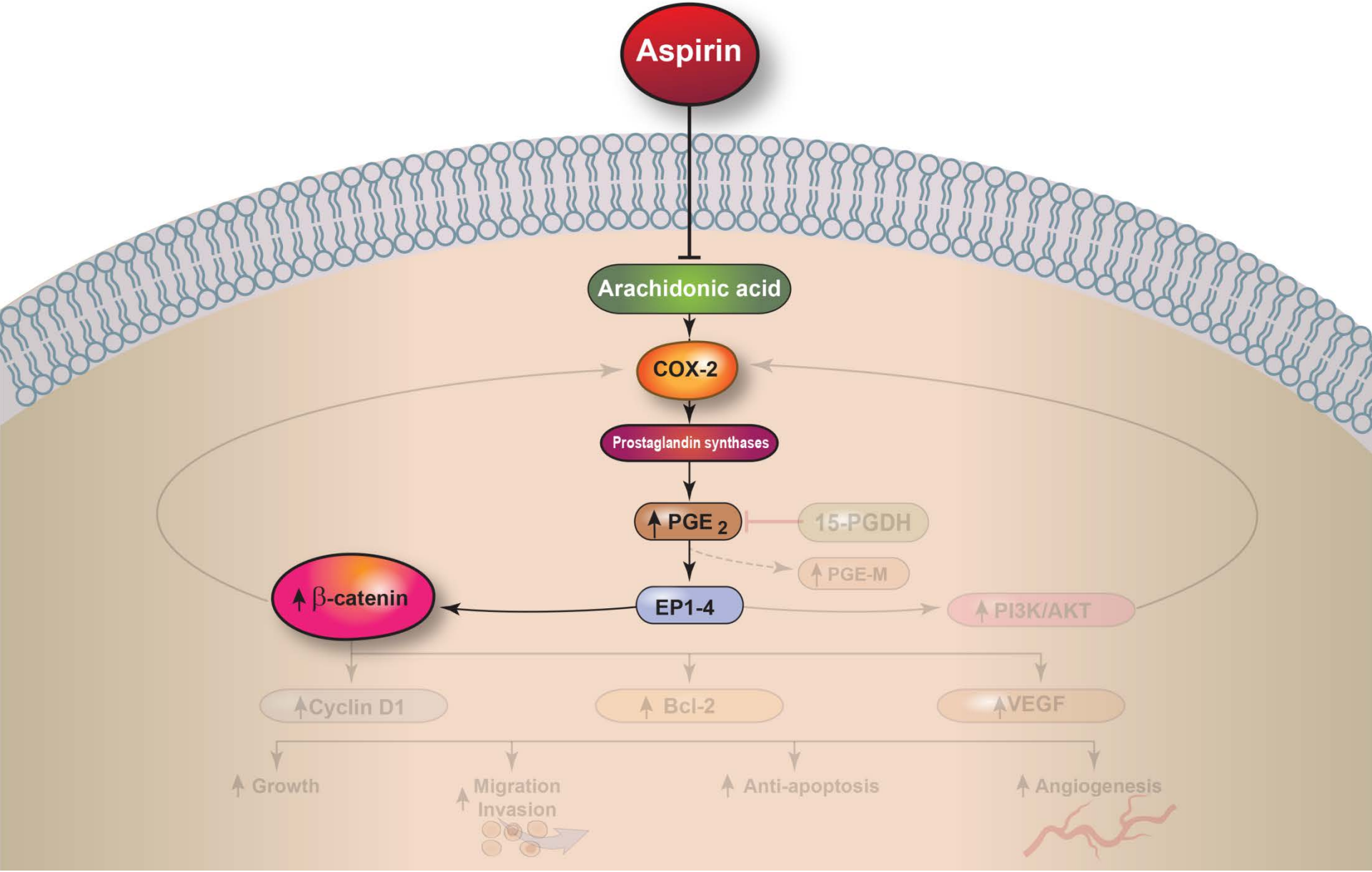
Bezwada *et al*, Can Prev Res 2014

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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VEGF
Growth
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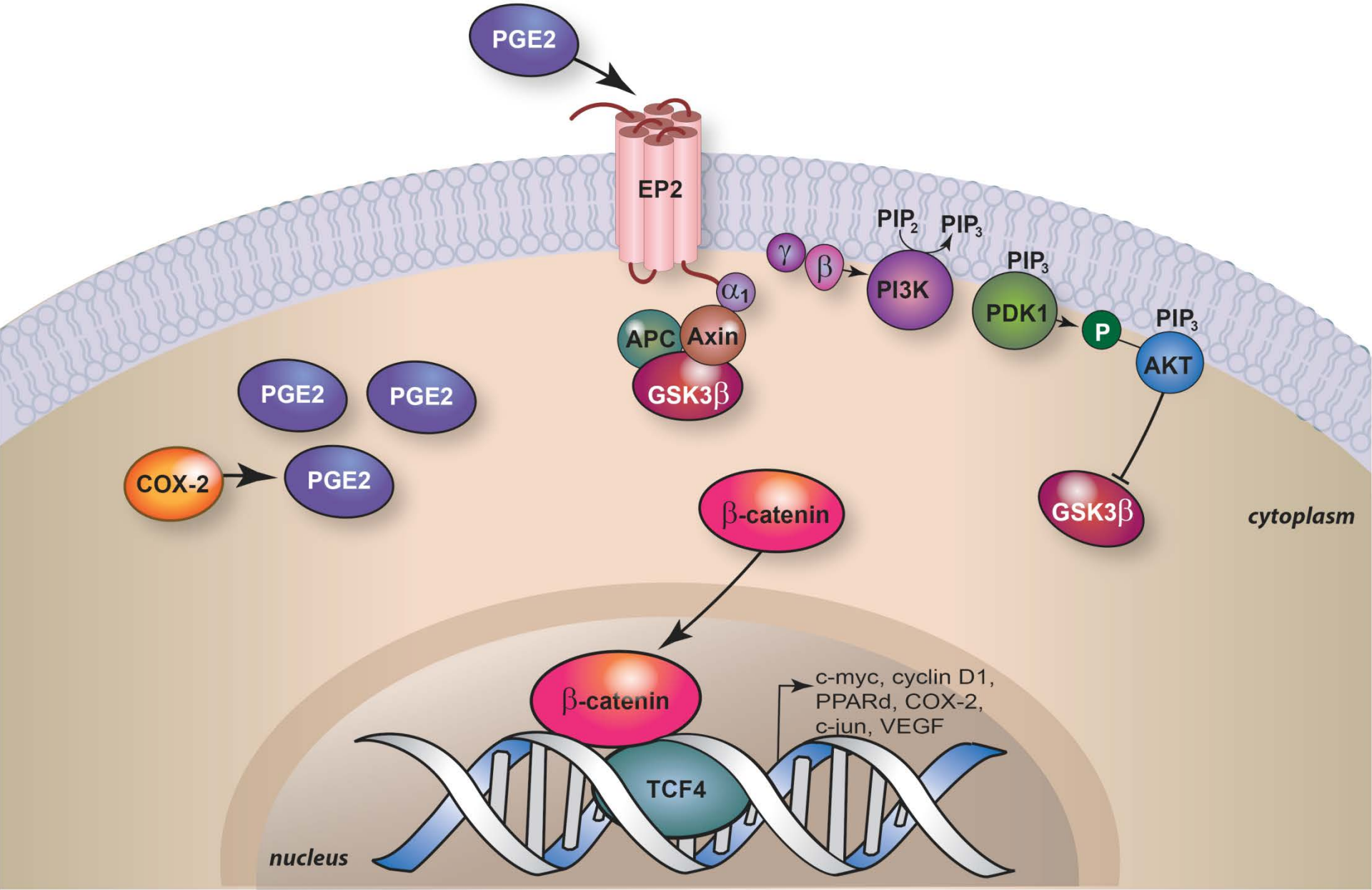
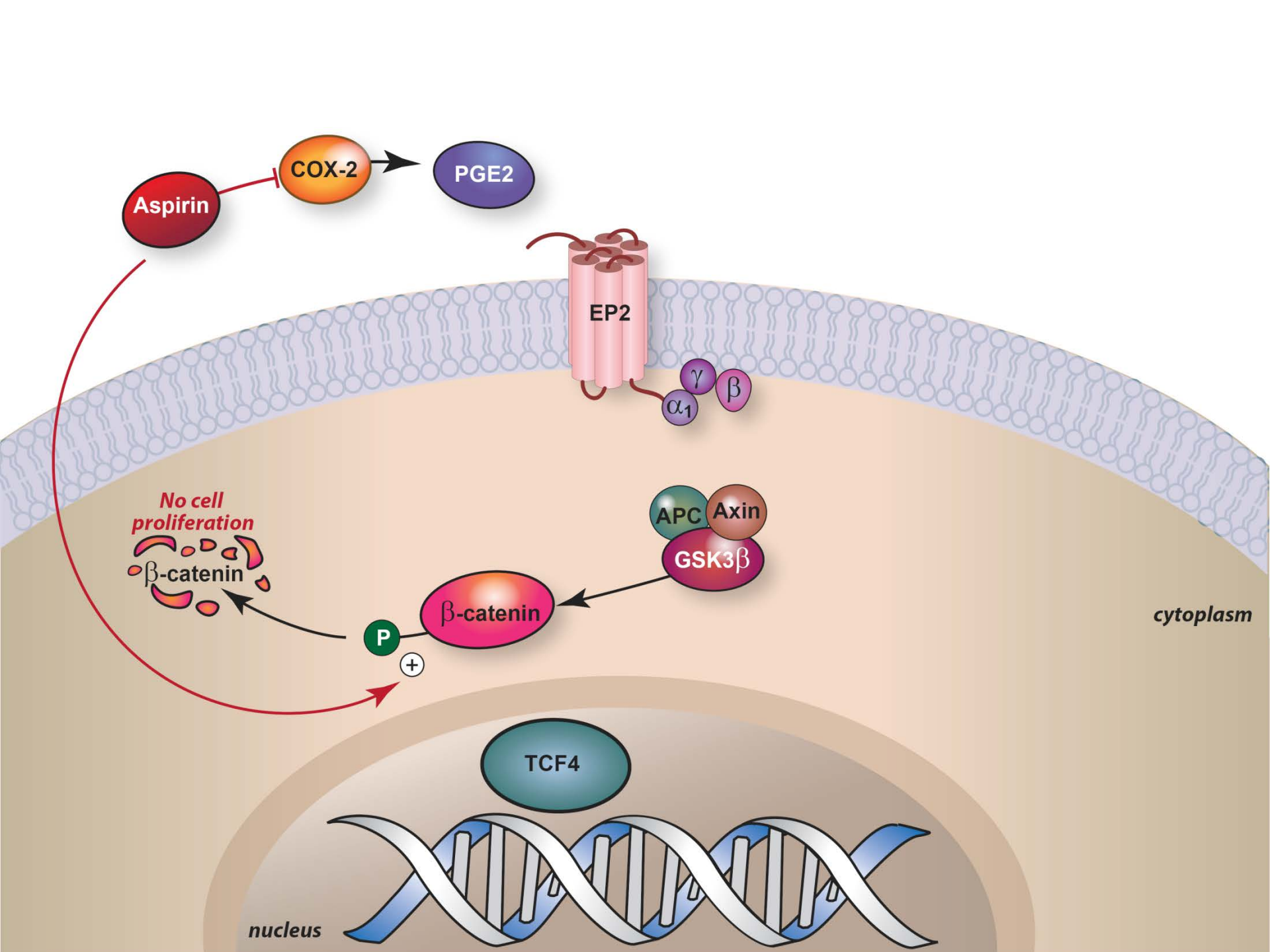
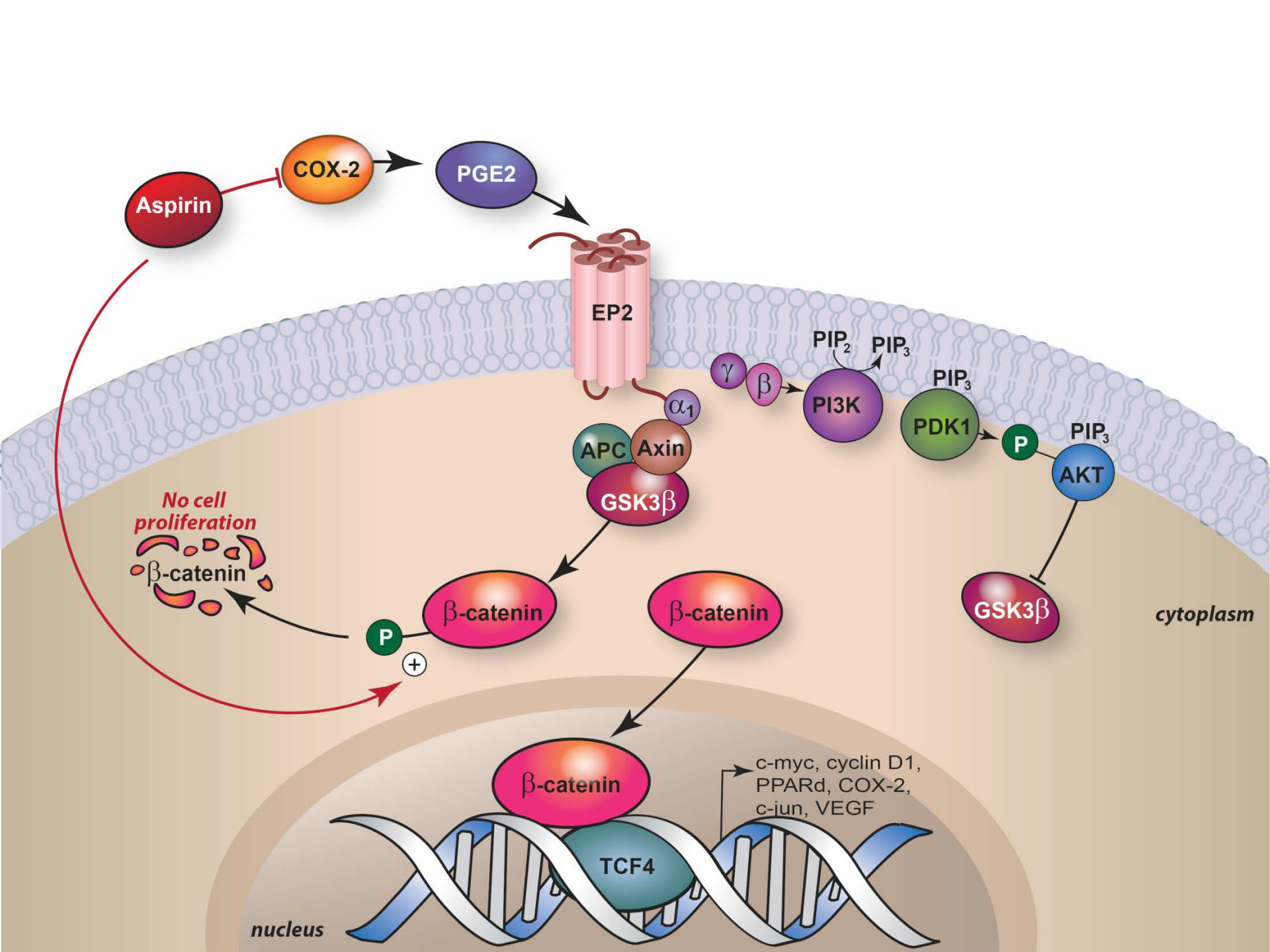
Anti-apoptosis
Angiogenesis


PGE2
EP2
α_1
APC
Axin
GSK3β
γ
β
PI3K
PIP_2
PIP_3
PDK1
PIP_3
P
PIP_3
AKT
GSK3β
PGE2
PGE2
COX-2
PGE2
β-catenin
cytoplasm
β-catenin
TCF4
c-myc, cyclin D1,
PPARd, COX-2,
c-jun, VEGF
nucleus


Aspirin
COX-2
PGE2
EP2
γ
β
α1
No cell proliferation
β-catenin
APC
Axin
GSK3β
β-catenin
P
+
cytoplasm
TCF4
nucleus

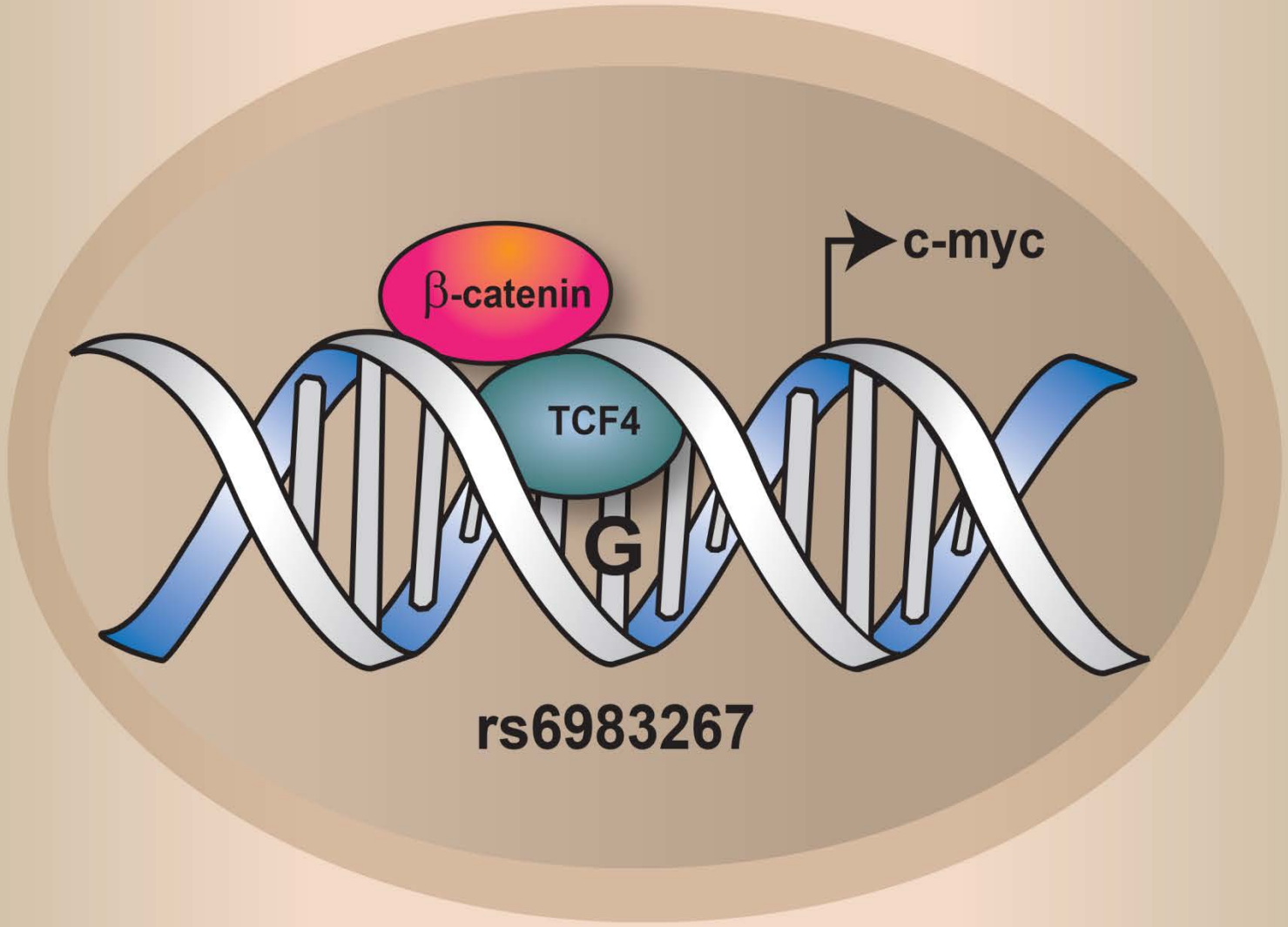

Aspirin
COX-2
PGE2
EP2
α_1
γ
β
PI3K
PIP_2
PIP_3
PDK1
PIP_3
P
AKT
PIP_3
APC
Axin
GSK3β
No cell proliferation
β-catenin
β-catenin
P
+
β-catenin
GSK3β
cytoplasm
β-catenin
TCF4
c-myc, cyclin D1,
PPARd, COX-2,
c-jun, VEGF
nucleus

GWAS hits for CRC

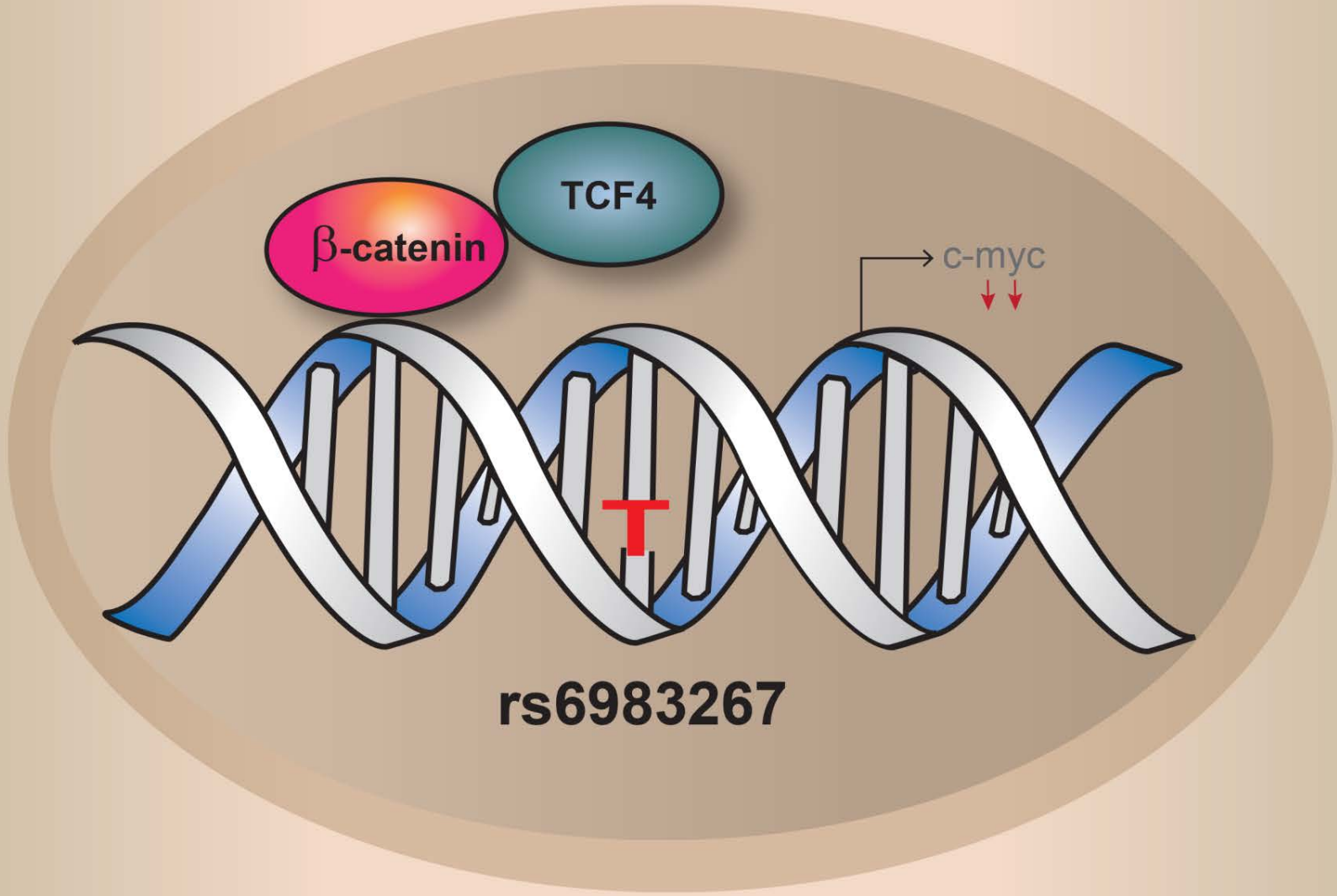
Position/Gene	rs#	Minor Allele	MAF	OR (95%CI)	*P*-value
8q24	rs6983267	T	0.50	0.83 (0.81-0.85)	$7x10^{-30}$
18q21/*SMAD7*	rs4939827	T	0.49	0.85 (0.81-0.89)	$1x10^{-28}$
15q13/*CRAC1 (HMPS)*	rs4779584 rs10318	T	0.18	1.26 (1.19-1.34)	$4x10^{-14}$
10p14	rs10795668	A	0.33	1.25 (1.19-1.32)	$3x10^{-13}$
8q23.3/*EIF3H*	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

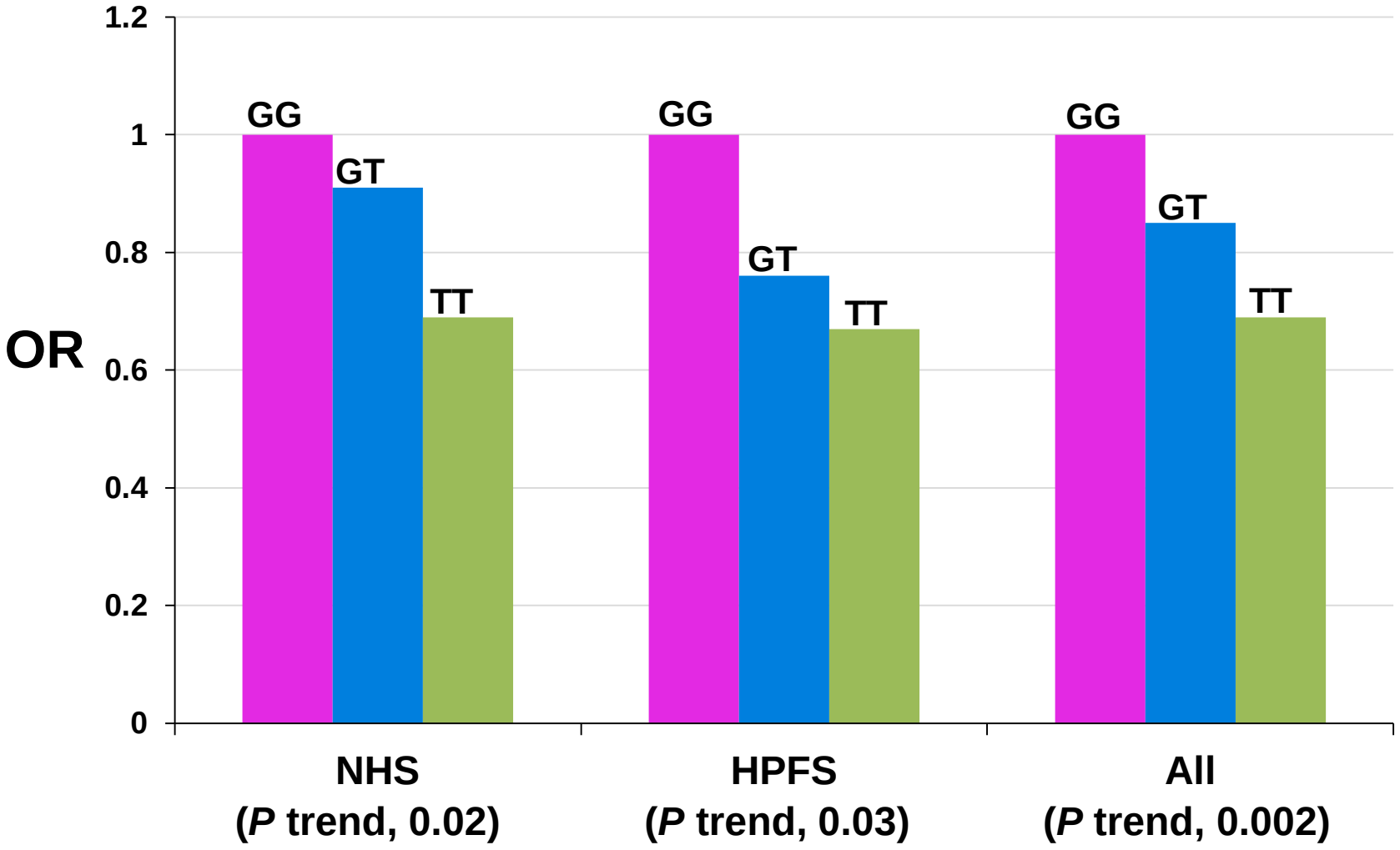


Pomerantz *et al*, Nat Genet 2009; Tuupanen *et al*, Nat Genet 2009



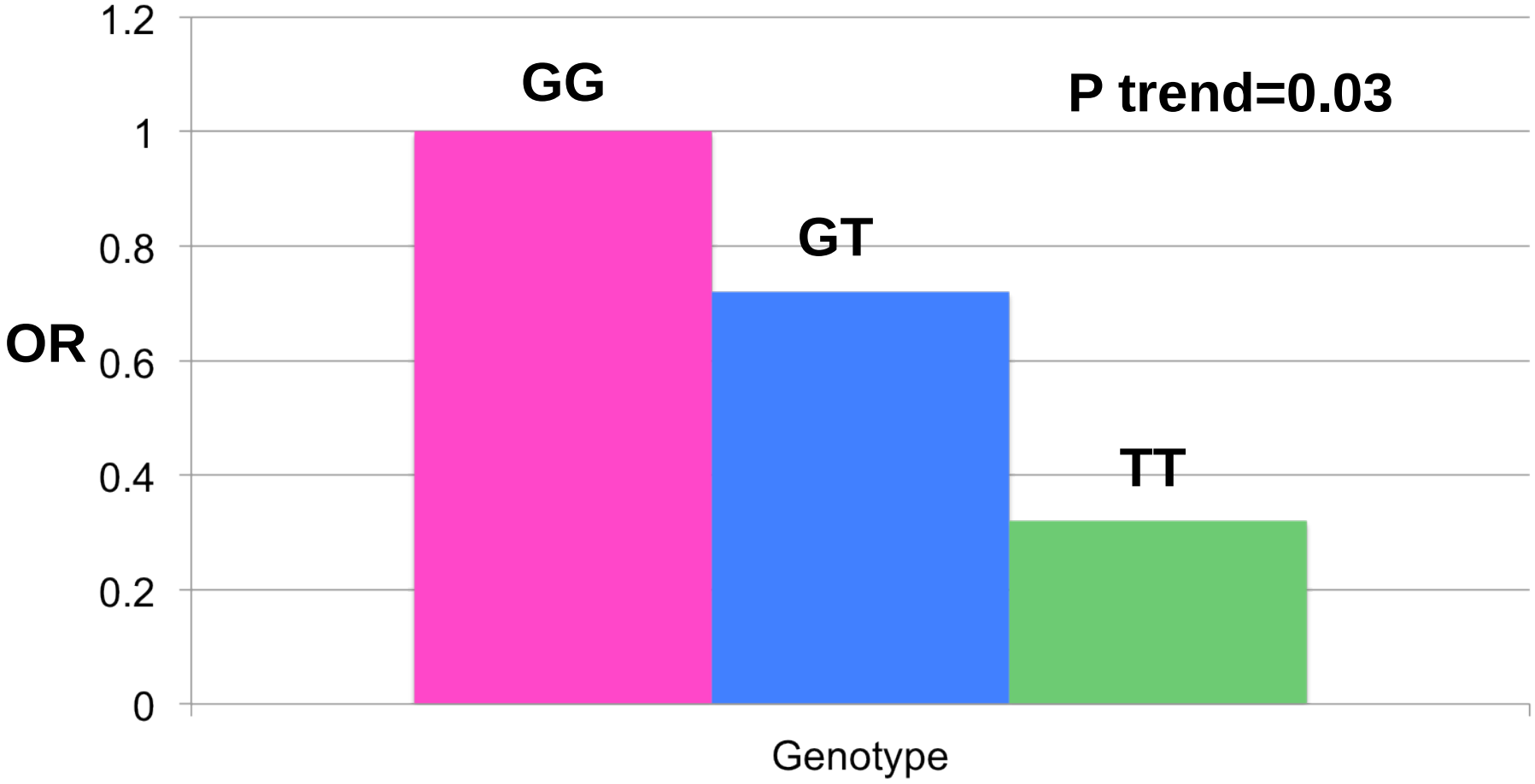
Pomerantz *et al*, Nat Genet 2009; Tuupanen *et al*, Nat Genet 2009

rs6983267 and risk of CRC



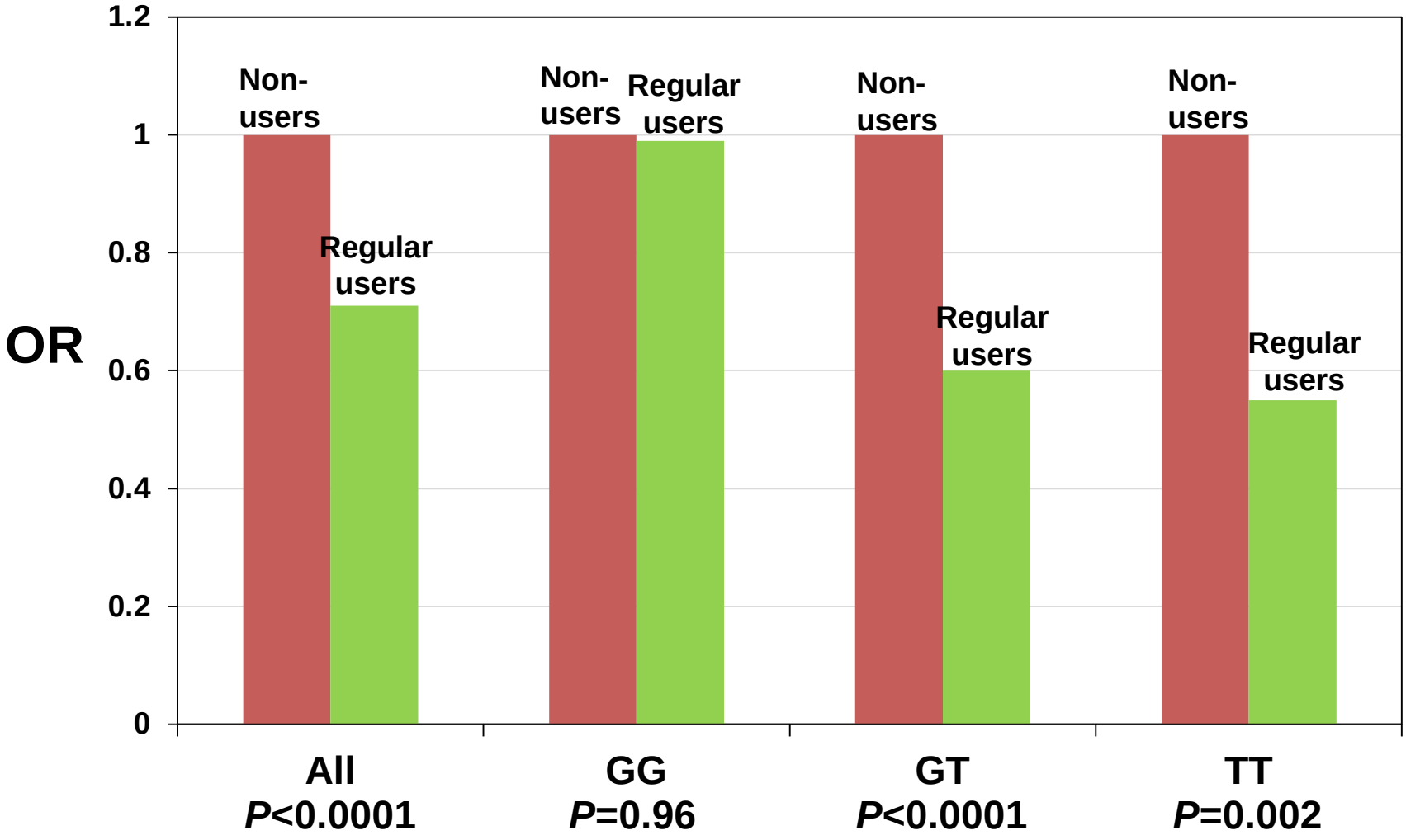
Nan *et al*, JNCI 2013

rs6983267 and *MYC* expression



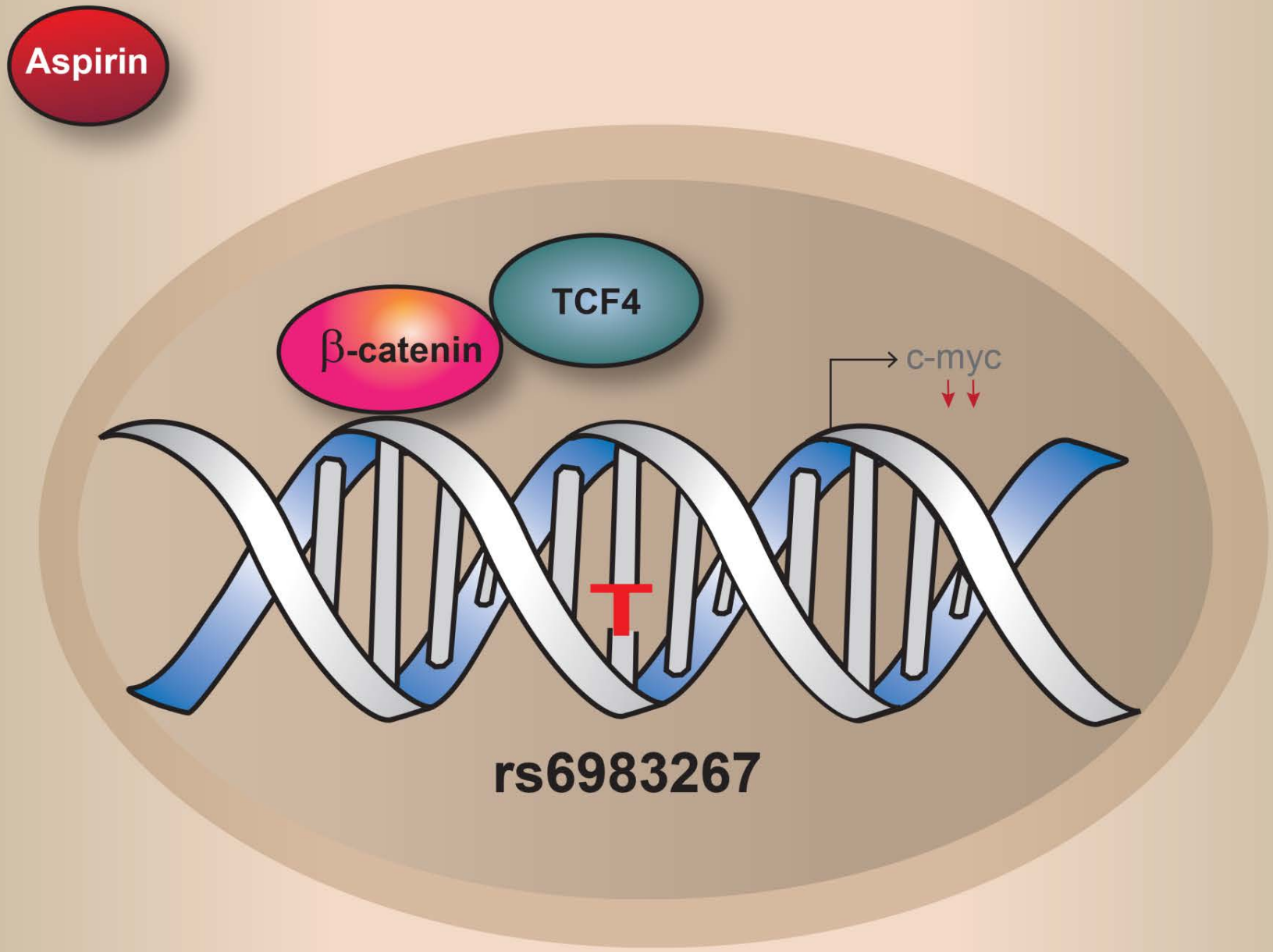
Nan *et al*, JNCI 2013

Aspirin and risk of CRC risk by rs6983267 genotype



Nan *et al*, JNCI 2013

***P* for interaction=0.01**


Aspirin
TCF4
β-catenin
c-myc
T
rs6983267

Rs6983267 risk stratifies for aspirin chemoprevention

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

Acknowledgements

- UM CA167552, P01 CA087969,P50 CA127003, R01 CA137178, K07 CA107412
- Participants of NHS and HPFS
- Co-investigators/Collaborators
  - Shuji Ogino
  - Walter Willett
  - Charlie Fuchs
  - Ed Giovannucci

MGH/DFHCC/HSPH Translational Epidemiology Group

- Faculty – Hongmei Nan, Reiko Nishihara, Manish Gala
- Fellows – Xabier Garcia-de-Albeniz, Linda Hiraki, Ed Huang, Amit Joshi, Hamed Khalili, Xiaomei Liao
- Doctoral students – Mingyang Song
- Medical students – Navya Bezawada, Raaj Mehta