Lynch syndrome and aspirin

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ON BEHALF OF THE CaPP CONSORTIUM

Southampton 1st March 2014

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www.capp3.org

Newcastle University

CaPP3

Cancer Prevention Programme

Genetically Targeted Trials

- **Highly motivated**
- **Homogeneous**
- **Under surveillance**
- **Few needed**

Concerted Action Polyp Prevention

Colorectal Adenoma/carcinoma Prevention Programme

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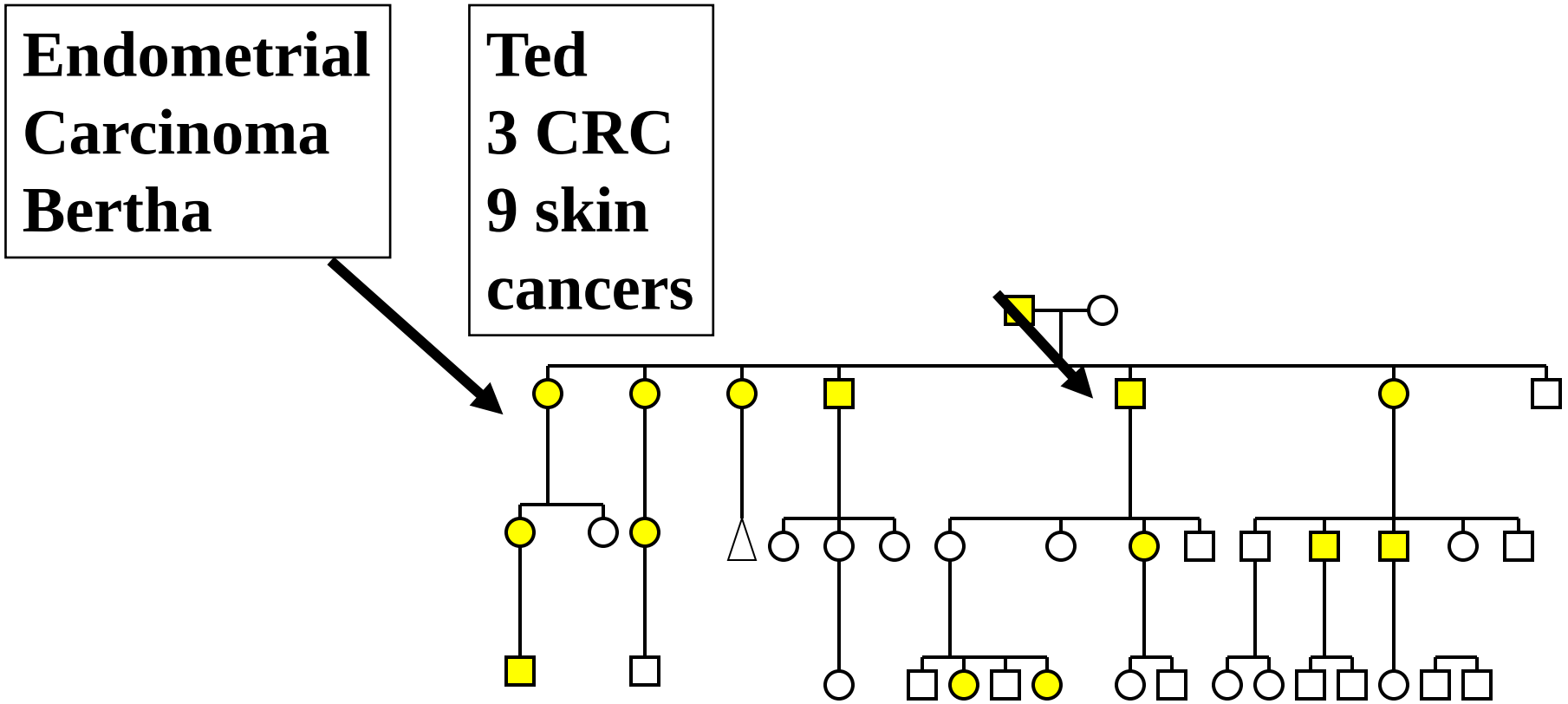

Family from which DNA used to Demonstrate hMSH2 mutation by Kolodner's group 1993: 1st of the MISMATCH REPAIR GENE DEFECTS

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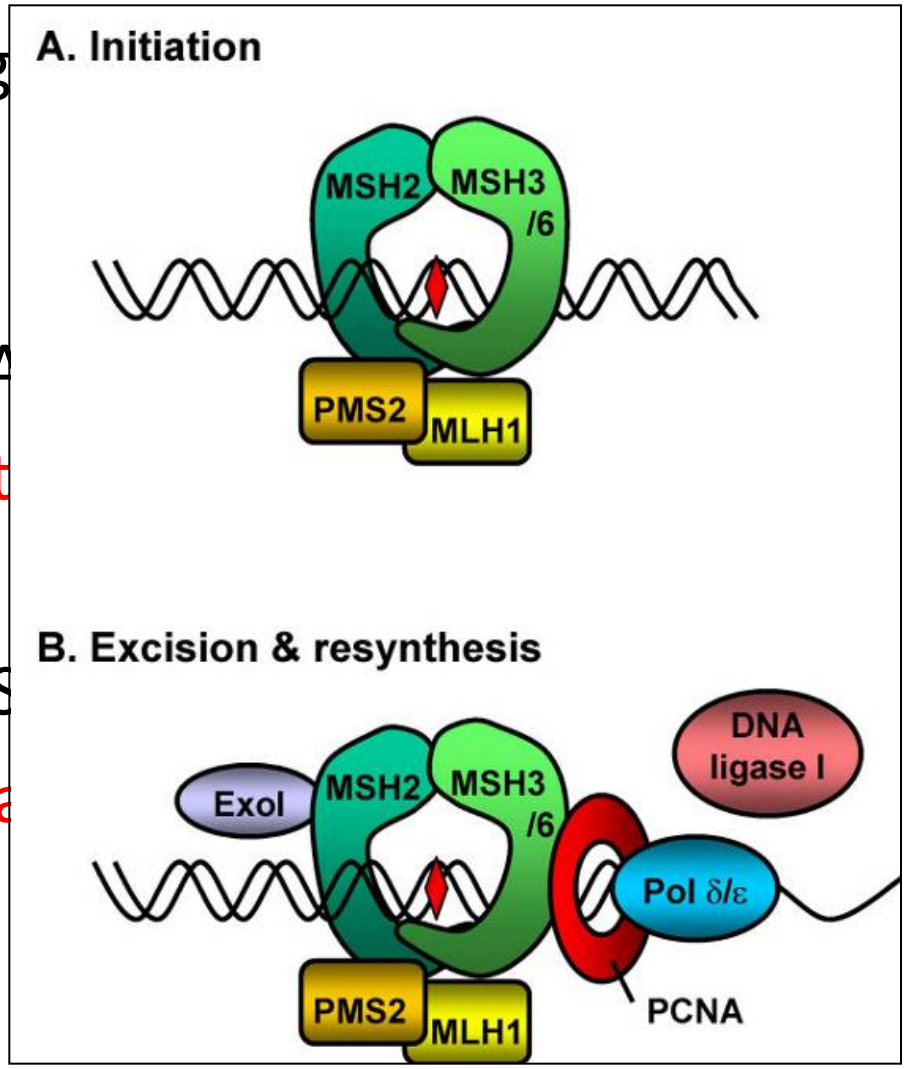
Microsatellites

– Microsatellites are leng
sequences usually

– mononucleotides eg BA
tgttttgttttttgattttttttttttt

– or dinucleotides eg D5S
aatttacacacacacacacacaca



The Genomic Pathogenesis of Colorectal Cancer

FAP

CIN

85 %

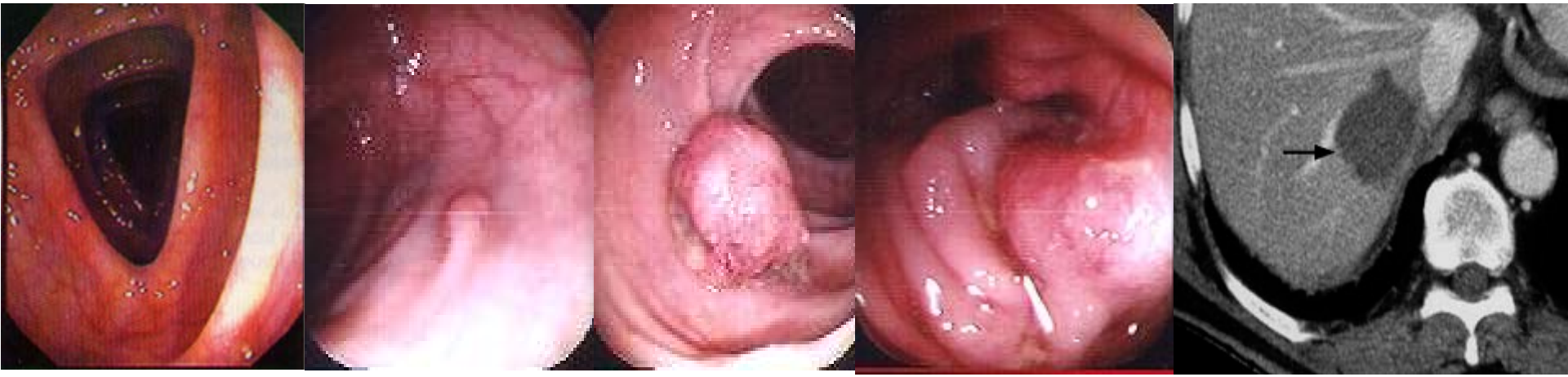
APC, K-ras 12p, DCC 18q, p53 17p, ……..

Normal epithelium

Adenoma

Carcinoma

Metastases



hMLH1, hMSH2, TGF-ß RII, Bax, TCF4, ACVRII, Caspase 5 …….

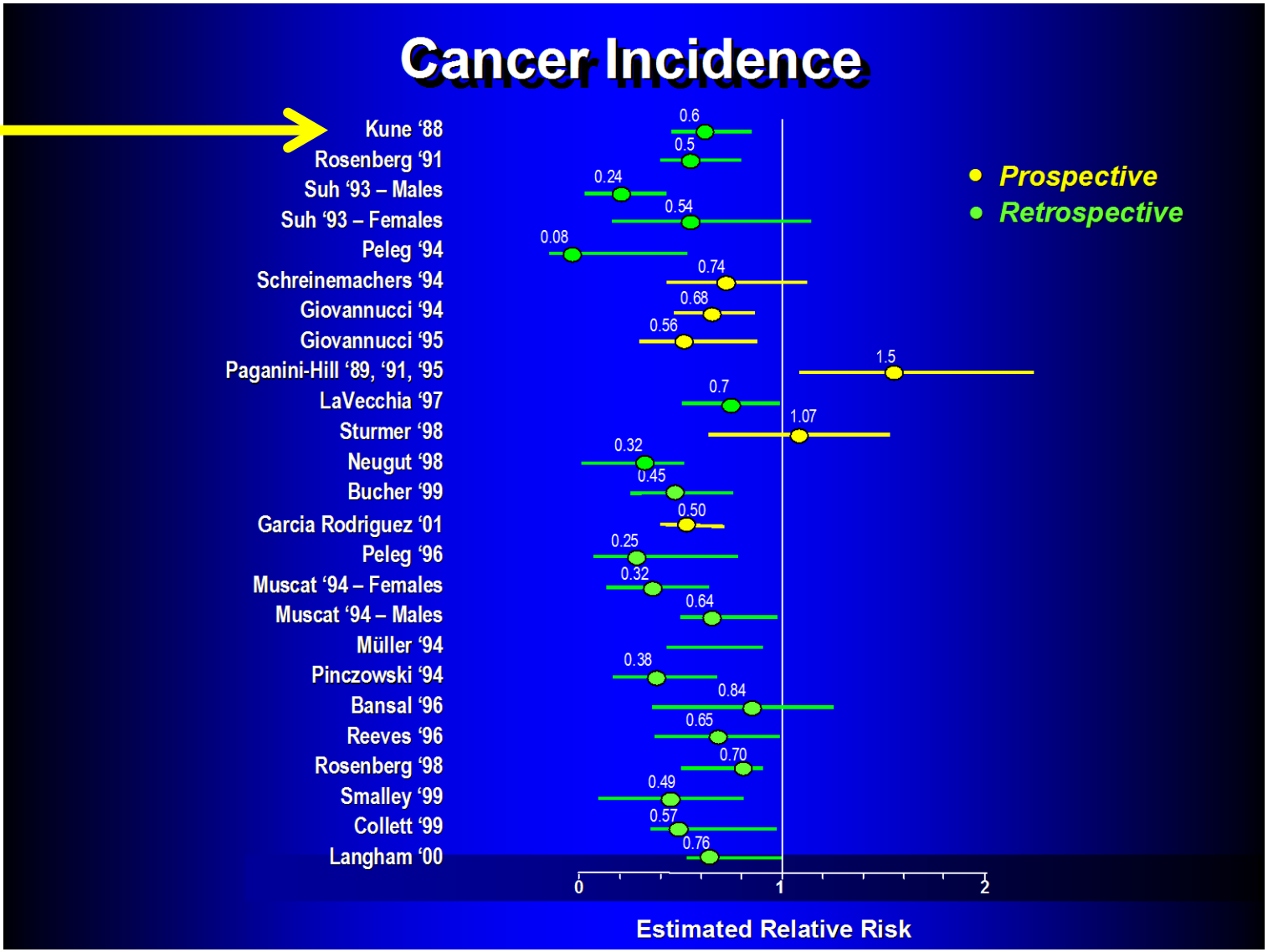
Lynch

MSI

15 %

Gabriel Kune of Melbourne first reported the association of NSAIDs with reduced colorectal cancer risk in 1988

Observational studies of NSAIDs and CRC



Hawk, et al. Epidemiology & Prevention of Colorectal Cancer, 2001

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Timetable

12 years from Helsinki to San Antonio

- Trial proposed ICG-HNPCC in Helsinki 1995
- Structure agreed at Newcastle Workshop 1996
- funding EU/Bayer/National Starch/ICRF 1998
- 1st randomisation 1999
- MRC adoption 2002
- + continued Cancer Research UK support
- Reached target 1000 randomisations 2005
- Closed data file March 2007

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MRC Medical Research Council

CANCER RESEARCH UK

Bayer

National Starch and Chemical Company

A member of the ICI Group

Cancer Prevention Programme

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The CAPP2 consortium

Appendix: CAPP2 has been made possible by all the participants who agreed to be randomised and take daily treatments for up to four years. Special mention must also be given to Kirsi Pylvänäinen, (Jyvaskyla, Finland), Pascale Ives (Melbourne, Australia) and Su Werner (Dusseldorf, Germany) for their exceptional recruitment achievements and to Pam Chapman, the project manager in its early stages. Recruitment has depended on a large number of colleagues from around the world. The study collaborators not listed as authors are: Paul Adamson; Olive Armstrong; Jan Ball; Lauren Baxter; Anne Birkett; Alex Boussioutas, Nicola Bradshaw; Carole Brewer; Mary Broughton; Barbara Bulman; Monica Castiglione; Sue Clarke; Rowena Ching; Carol Chu; Julie Coaker; Susanne Cina; Jackie Cook; Jonathan Coxhead; Gillian Crawford; Carole Cummings; Rhodri Davies; Tadeusz Debniak; Celine de Moncuit; Sarah Drummond; Tony Ellis; Kath Farthing; Paulo Fidalgo; Steve Gallinger; Joanne Gascoyne; Sheila John Gilroy; Goff; Selina Goodman; Chris Harocopos; Shirley Hodgson; Roger Jeffcoat; Lisa Jeffers; Sheila Jordan; Pip Killick; Christian Krauss; Jørgen Kristensen Caroline Langman; Julio Leite; Gunilla Lindgren; Louise Lynagh; Cristina Oliani; Christopher Marks; Julie Miller; Tony Miles; Vicky Murday; Pedro Perez Segura; Elize Pietersen; Ulla Platten; Lynn Reed; Giovanni Rossi; Paola Sala; Julian Sampson; Beverly Schmocker; Joan Shaw; Allan Spigelman; Alfonso Tempesta; Rachel Toes; Mary Velthuizen; Paula Wakelen; Ian Walpole. We are also indebted to: The Trial Steering Committee: David Kerr (Chair); Sarah Perkins – (MRC); Jack Cuzick ; Lynn Faulds Wood; Robert Steele; and the

Data Monitoring Committee: Doug Altman (Chair); Chris Paraskeva; Wendy Atkin; Mark Hull;

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CAPP Factorial Design

R. Starch + Aspirin	Placebo + Aspirin
R. Starch + Placebo	Placebo only

2x300mg aspirin per day (Bayer Corp.)
Hylon VII/potato starch in CAPPI , Novelose CAPP2 (National Starch and Chemical Co, NJ)

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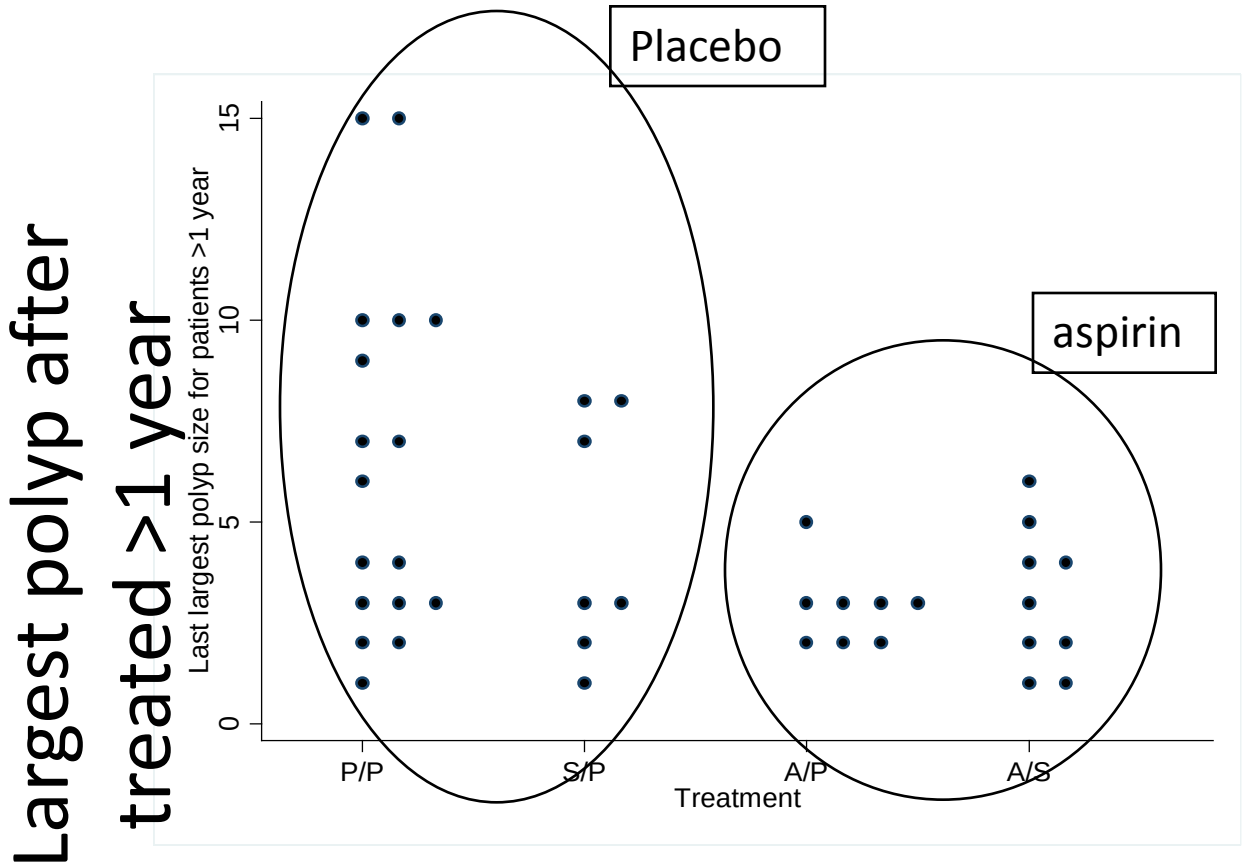
Aspirin reduced the size of the largest polyp in a RCT in 200 FAP carriers

Burn et al Cancer Prevention Research 2011



(CAPP1)

P=0.02

Placebo	**Placebo**	**Aspirin**	**Aspirin**
placebo	**starch**	**Placebo**	**starch**

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UK

Aberdeen, Edinburgh, Glasgow, Newcastle, Leeds Sheffield, Manchester, Liverpool, Birmingham, Cardiff, Belfast,Oxford, Bristol, St Marks, St Georges, Guys-London Southampton, Exeter, Guildford, Worthing,

Rest of Europe

Finland, Sweden, Denmark, Germany, Belgium, Poland, Netherlands, France, Hungary, Switzerland,Portugal, Spain, Italy

Australia

Melbourne
Brisbane
Newcastle
Perth

Status		No.	Placebo/placebo	Starch/placebo aspirin	Aspirin/placebo starch	Aspirin/ starch
Ineligible		62	15	13	15	19
Withdrawn		192	43	61	44	44
Did not start		72	18	20	19	15
Completed (N=745)	**<21 mths**	121	33	31	27	30
	21-27 mths	346	81	80	92	93
	>27 mths	278	78	63	69	68
Total		1071	**268**	**268**	**266**	**269**

Factorial design using **600mg enteric coated aspirin (Bayer)**
And 30g Novelose (a resistant maize starch)

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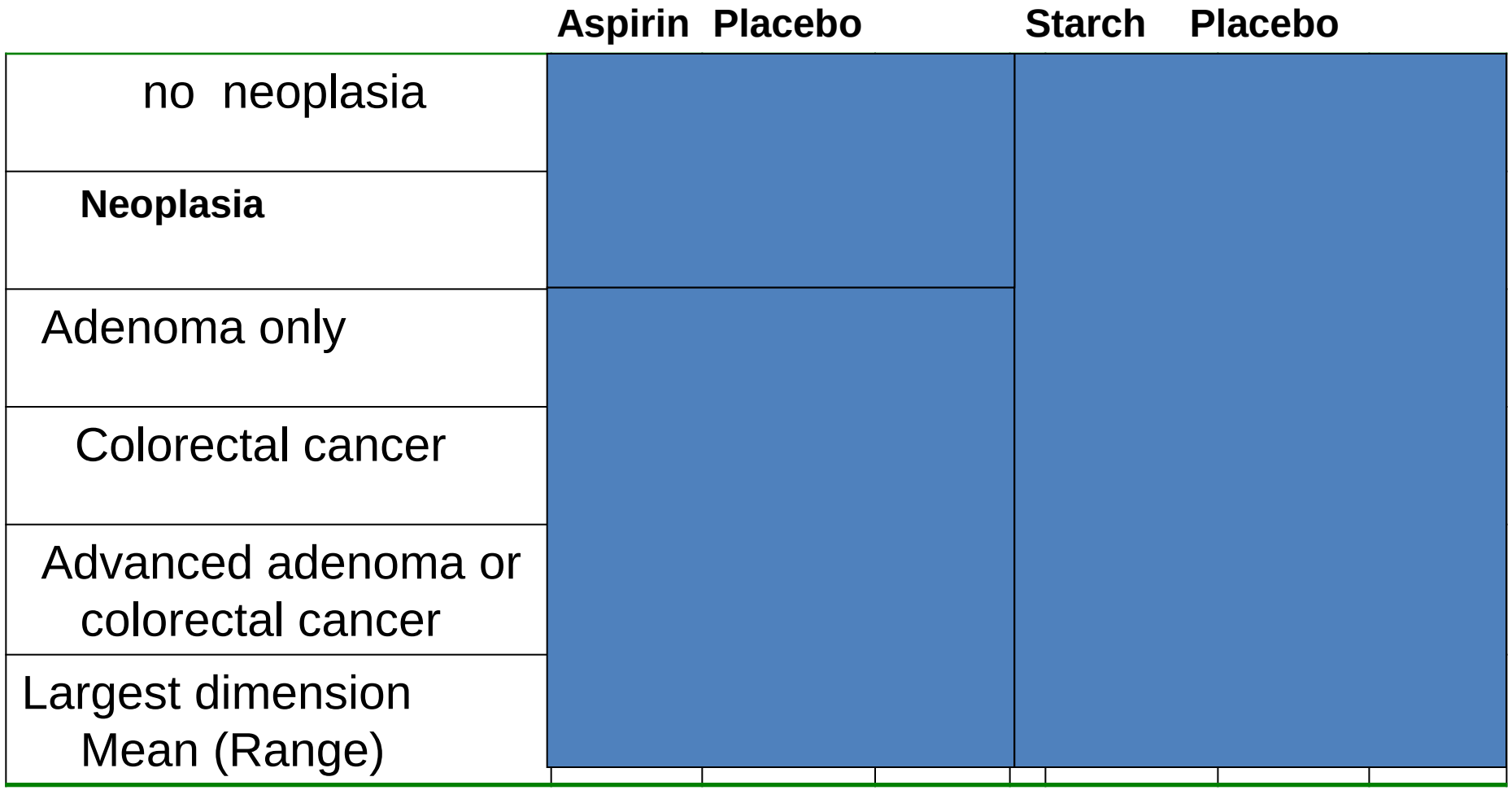

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	Aspirin	Placebo			Starch	Placebo	
no neoplasia	**283**	**278**	P value		**291**	**300**	P value
Neoplasia	**66** (18.9)	**65** (19.0)	**0.8**		**67** (18.7)	**68** (18.5)	**0.9**
Adenoma only	**56** (16.5)	**55** (16.5)	**0.8**		**57** (16.4)	**56** (15.7)	**0.9**
Colorectal cancer	**10** (3.4)	**10** (3.6)	-		**10** (3.4)	**12** (4.0)	-
Advanced adenoma or colorectal cancer	**25** (8.1)	**34** (10.9)	**0.4**		**31** (9.6)	**34** (10.2)	**0.7**
Largest dimension Mean (Range)	**10.5** 0.4-68	**11.1** 1-71	**0.8**		**11.4** 1-71	**11.3** 1-55	**0.9**

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December 11th 2008;359:2567-2578

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Aspirin or Resistant Starch on Colorectal Neoplasia in the Lynch Syndrome

John Burn, M.D., D. Timothy Bishop, Ph.D., Jukka-Pekka Mecklin, M.D., Finlay Macrae, M.D., Gabriela Möslein, M.D., Sylviane Olschwang, Ph.D., Marie-Luise Bisgaard, M.D., Raj Ramesar, Ph.D., Diana Eccles, M.D., Eamonn R. Maher, M.D., Lucio Bertario, M.D., Heikki J. Jarvinen, M.D., Annika Lindblom, M.D., D. Gareth Evans, M.D., Jan Lubinski, M.D., Patrick J. Morrison, M.D., Judy W.C. Ho, M.D., Hans F.A. Vasen, M.D., Lucy Side, M.D., Huw J.W. Thomas, M.D., Rodney J. Scott, Ph.D., Malcolm Dunlop, M.D., Gail Barker, B.A., Faye Elliott, M.Sc., Jeremy R. Jass, M.D., Ricardo Fodde, Ph.D., Henry T. Lynch, M.D., and John C. Mathers, Ph.D., for the CAPP2 Investigators*

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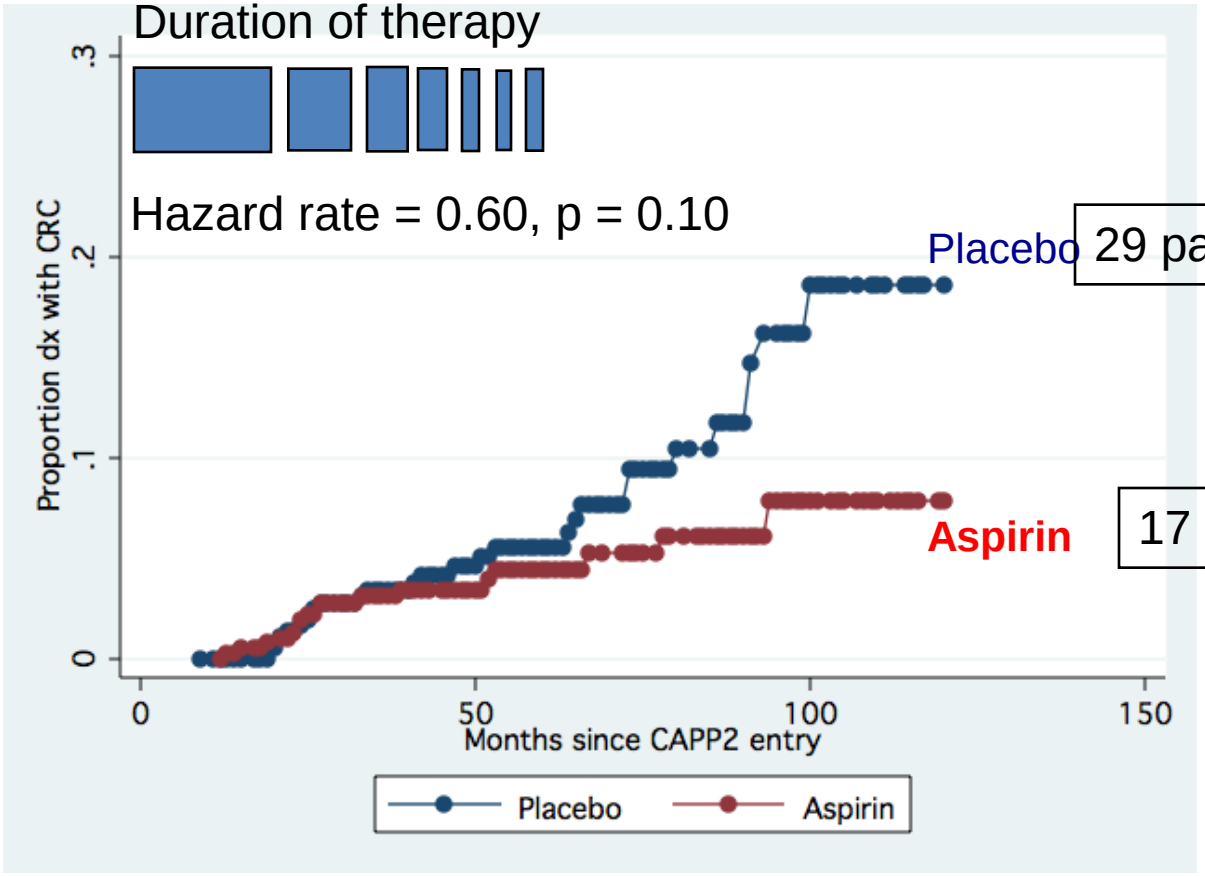
Tim Bishop

Available reports in 2009 showed a trend to reduced CRC in aspirin group



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CAPP2 primary endpoint

" The number, size and stage of colorectal cancers after a minimum of 2 years treatment"

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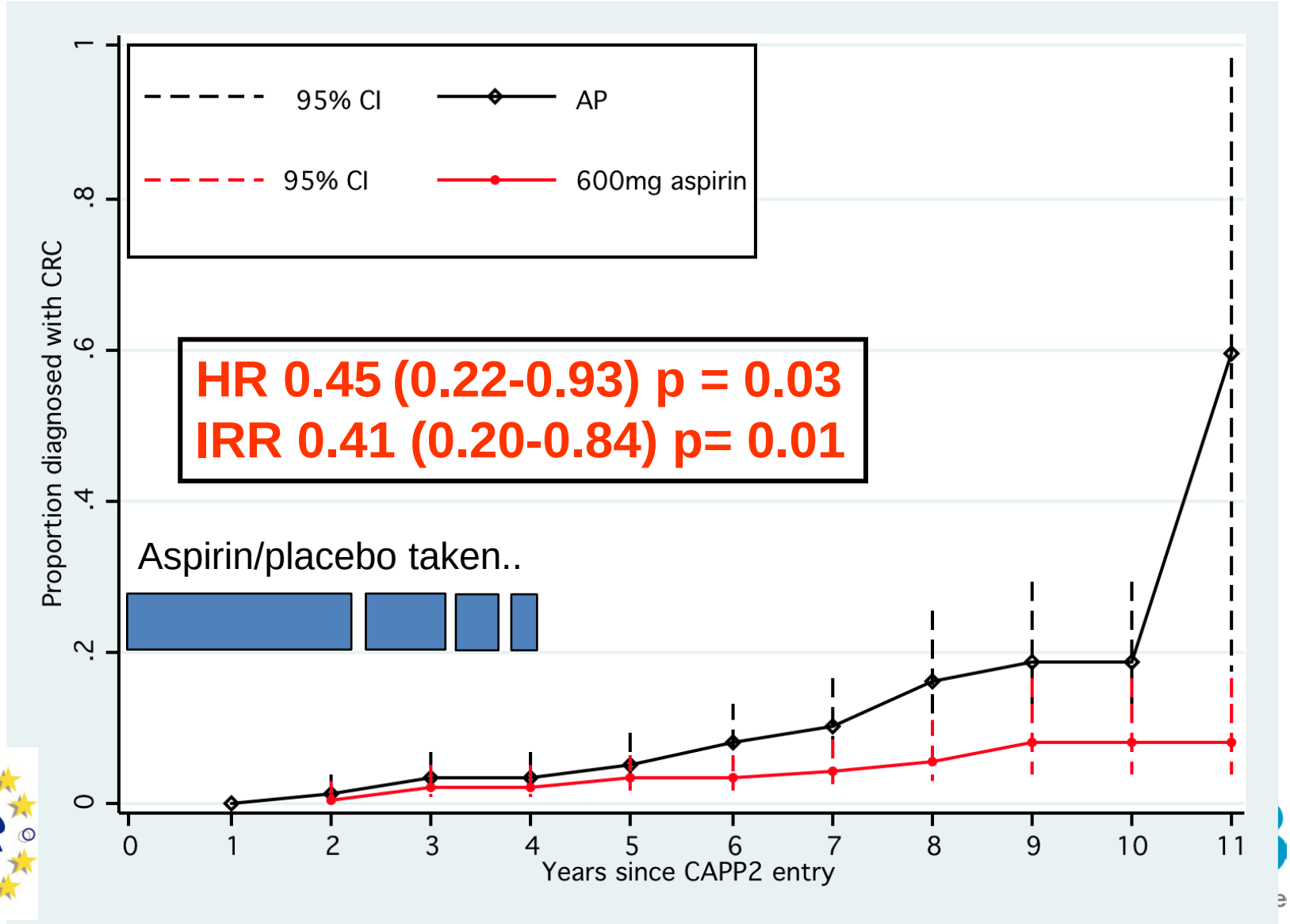
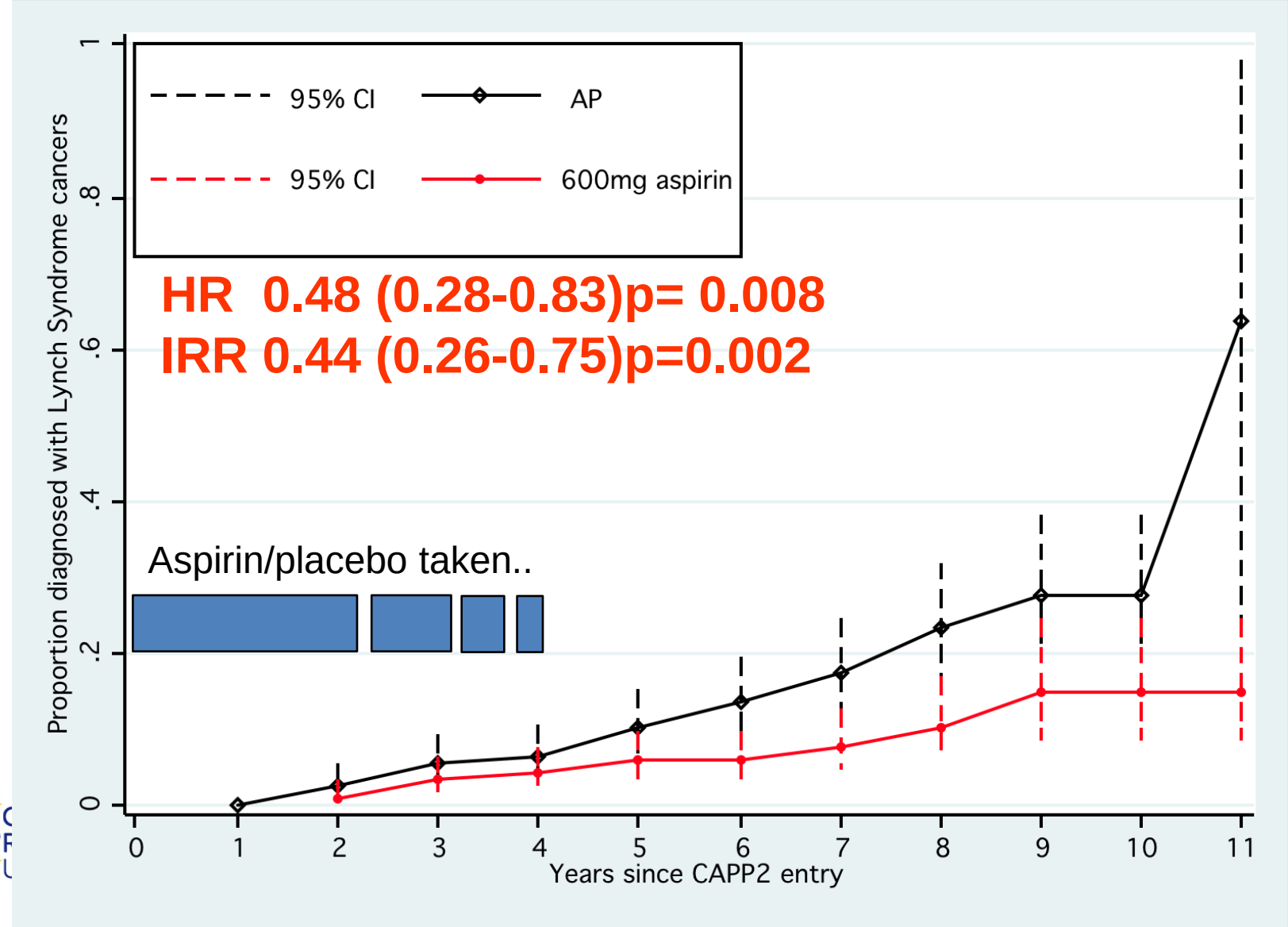
CAPP2: Per protocol analysis (primary endpoint CRC after 2 years treatment) significantly fewer colorectal cancers [paper under review]



CAPP2 per protocol analysis
All Lynch syndrome cancers



600mg aspirin/day for 2 yrs reduced Lynch syndrome cancers at 5 yrs by over 60%

Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial

John Burn, Anne-Marie Gerdes, Finlay Macrae, Jukka-Pekka Mecklin, Gabriela Moeslein, Sylviane Olschwang, Diane Eccles, D Gareth Evans, Eamonn R Maher, Lucio Bertario, Marie-Luise Bisgaard, Malcolm Dunlop, Judy W C Ho, Shirley V Hodgson, Annika Lindblom, Jan Lubinski, Patrick J Morrison, Victoria Murday, Raj Ramesar, Lucy Side, Rodney J Scott, Huw J W Thomas, Hans F Vasen, Gail Barker, Gillian Crawford, Faye Elliott, Mohammad Movahedi, Kirsi Pylvanainen, Juul T Wijnen, Riccardo Fodde, Henry T Lynch, John C Mathers, D Timothy Bishop, on behalf of the CAPP2 Investigators

Lancet volume 378 December 11th 2011

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CAPP2 follow up data May 2013

New colorectal cancers in blinded recruits treated for mean 2.5 yrs with 600mg Aspirin (green) or placebo (red) Unpublished data.

Rothwell et al Lancet 2011
meta-analysis of 8 vascular trials using aspirin
fewer cancer deaths among those randomised to aspirin

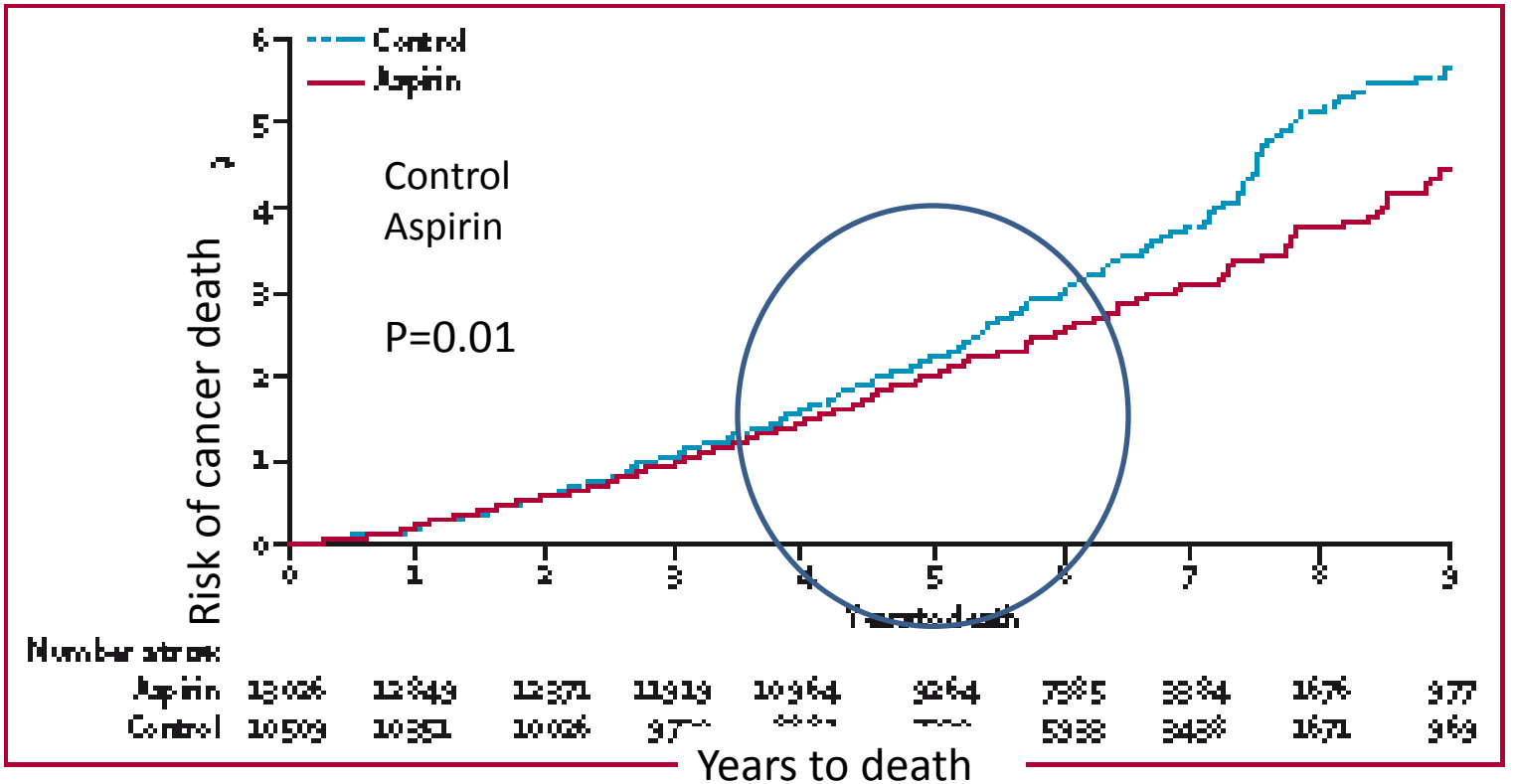

Figure 2: Effect of allocation to aspirin versus control on risk of death due to cancer during the trial treatment periods in a pooled analysis of the 28 535 patients in seven trials

Rothwell PM, Fowkes FGR, Belch JF, Ogawa H, Warlow CP, Meade TW. Effect of aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet 2011;377(9759):31-41.

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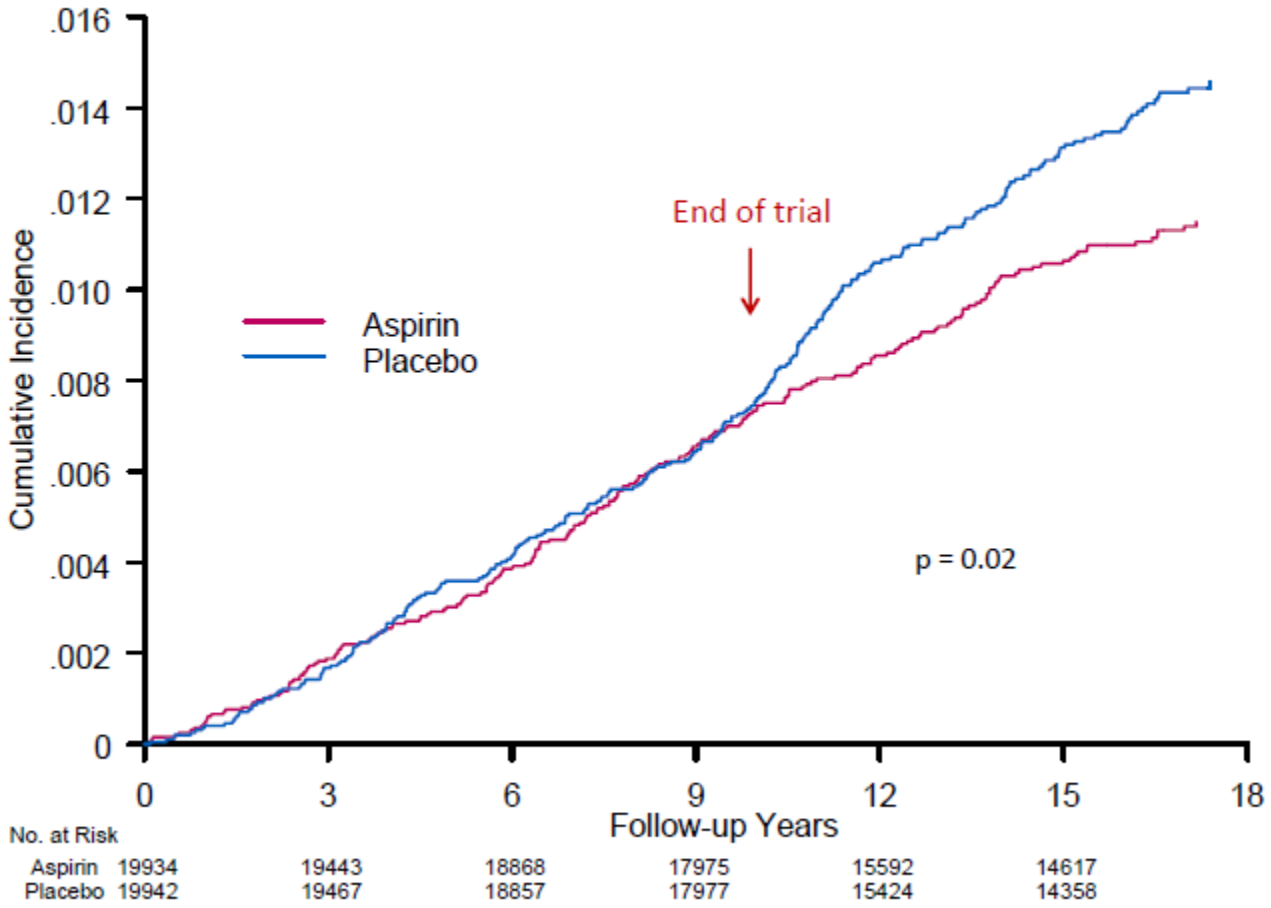
25,570 patients and 674 cancer-related deaths

Any dose associated with 21% fewer deaths

Colorectal Cancer



Cook, Ann Intern Med 2013

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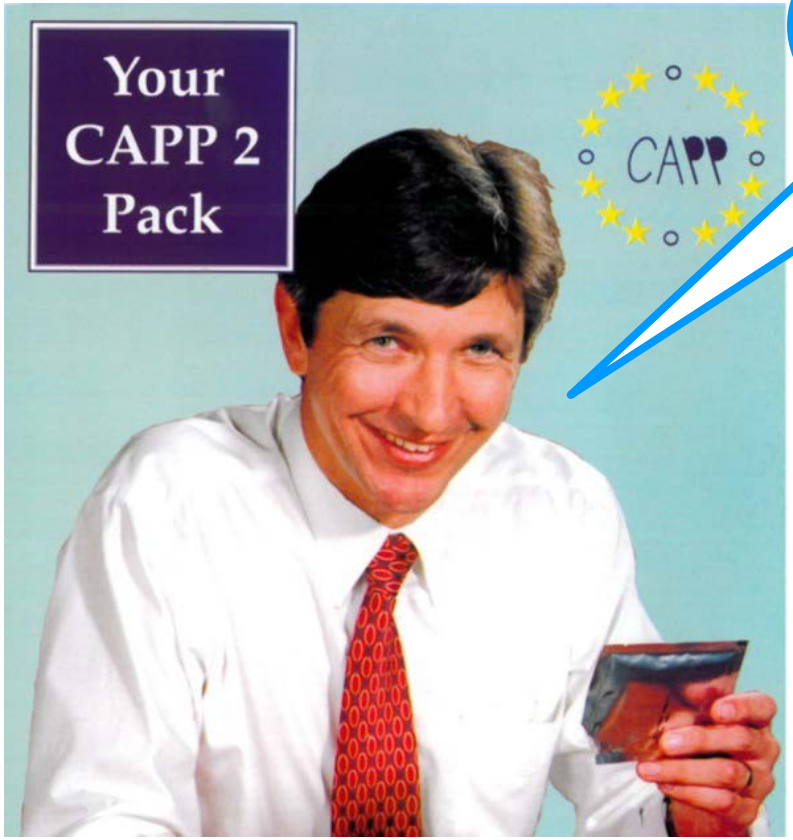
The world has changed

MHRA
Regulating Medicines and Medical Devices

IRAS
INTEGRATED RESEARCH APPLICATION SYSTEM

NHS
National Institute for Health Research
Clinical Research Network



European Commission

Clinical trials Directive

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An update

Funding

- Cancer Research UK CTAAC
- Bayer funds & aspirin

Agreements

- University Research Collaboration Agreement
- Clinical Trial Agreement
- Bayer agreements
- Overseas site agreement
- Insurance cover

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An aspirin dose non-inferiority study in 3000 Lynch syndrome gene carriers

- gene carriers double- blind randomised in 10-patient blocks
  - **4** patients receive **600** mg
  - **3** receive **300** mg
  - **3** receive **100** mg

- 2 years treatment, then low dose open 4 - 5 years

- three comparisons at minimum of 5 years:

  100 mg vs 600mg,
  300 mg vs 600 mg
  100 mg vs 300 mg

- Aspirin will be posted to recruits

- Sites responsible for collection of follow up health & safety data

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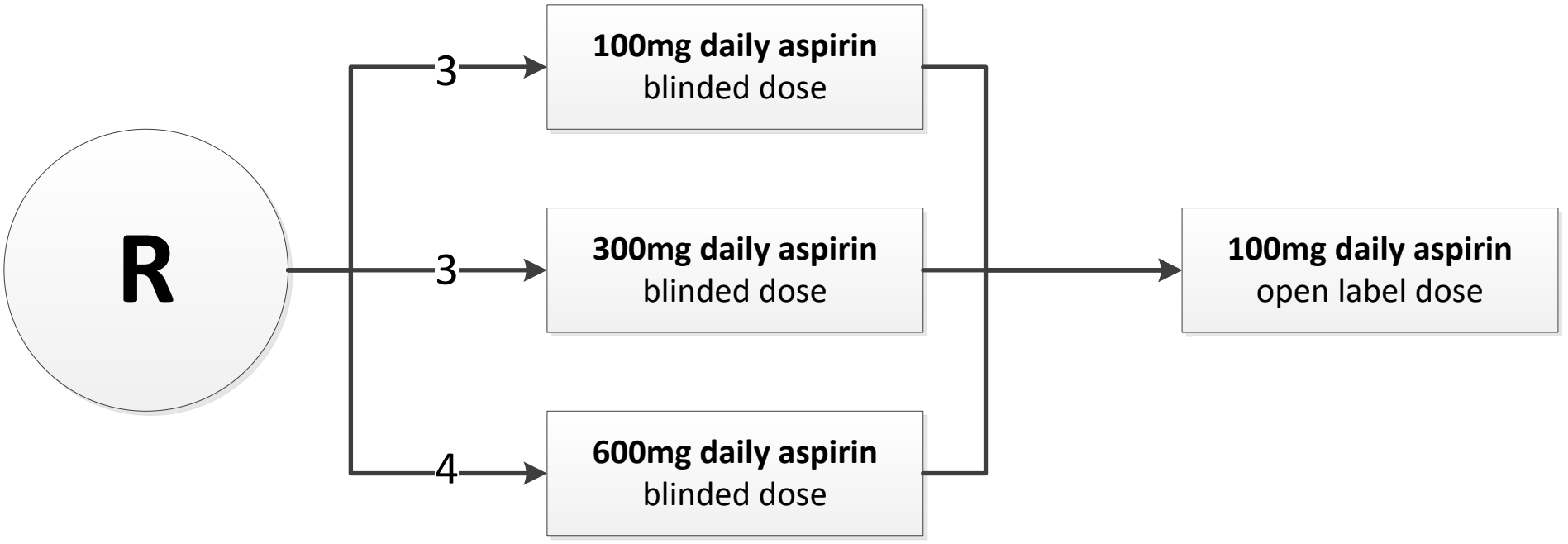
CaPP3: Dose non-inferiority randomised trial



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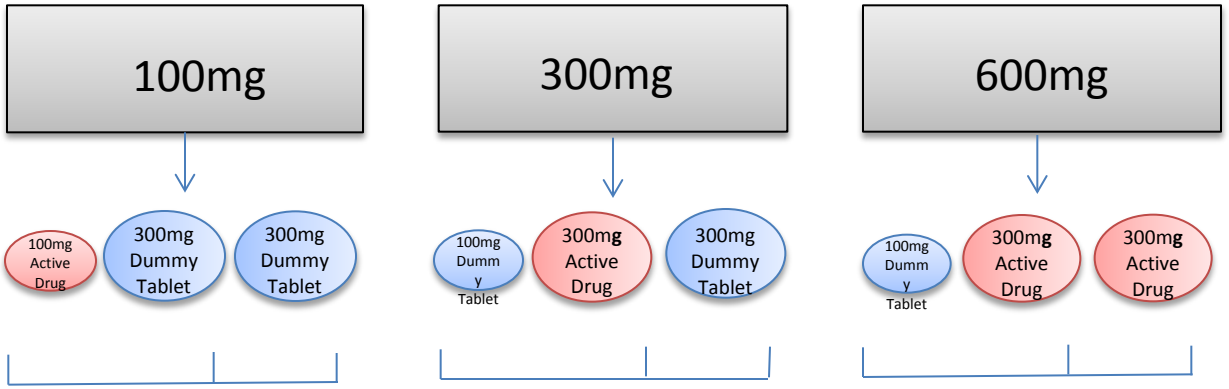
BAYER



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Pharmacogenetics

Cyclooxygenase-2 Polymorphisms, Aspirin Treatment, and Risk for Colorectal Adenoma Recurrence —Data from a Randomized Clinical Trial

Elizabeth L. Barry, Leah B. Sansbury, Maria V. Grau, et al.

CYP2C9 and *UGT1A6* Genotypes Modulate the Protective Effect of Aspirin on Colon Adenoma Risk[1]

Jeannette Bigler,[2] John Whitton, Johanna W. Lampe, Lisa Fosdick, Roberd M. Bostick, and John D. Potter

Ornithine Decarboxylase G316A Genotype Is Prognostic for Colorectal Adenoma Recurrence and Predicts Efficacy of Aspirin Chemoprevention

Richard A. Hubner,[1] Kenneth R. Muir,[2] Jo-Fen Liu,[2] Richard F.A. Logan,[2] Matthew J. Grainge,[2] Richard S. Houlston,[1] and the Members of the UKCAP Consortium

Variants Downstream of the Ornithine Decarboxylase Gene Influence Risk of Colorectal Adenoma and Aspirin Chemoprevention

Elizabeth L. Barry[1], Leila A. Mott[1], Robert S. Sandler[3], Dennis J. Ahnen[4], and John A. Baron[1,2,3]

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Slippage in coding microsatellites generates predictable novel peptides

Dr Magnus von Knebel Doeberitz

repeat length

$(A)_{10}$ TGT . AAA . AAA . AAA . ACG . TGC . TGG . CTA . GCT . GA.....

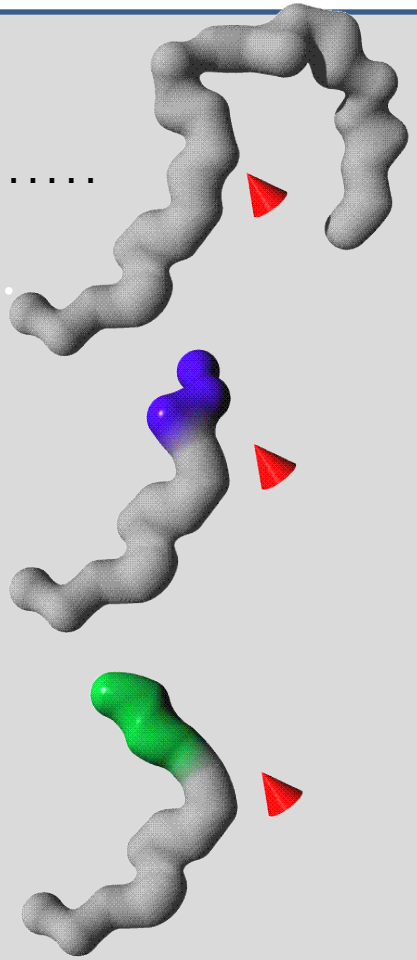
C K K K T C W L A .

$(A)_9$ TGT . AAA . AAA . AAA . CGT . GCT . GGC . TAG . CTG . A.....

C K K K R A G STOP

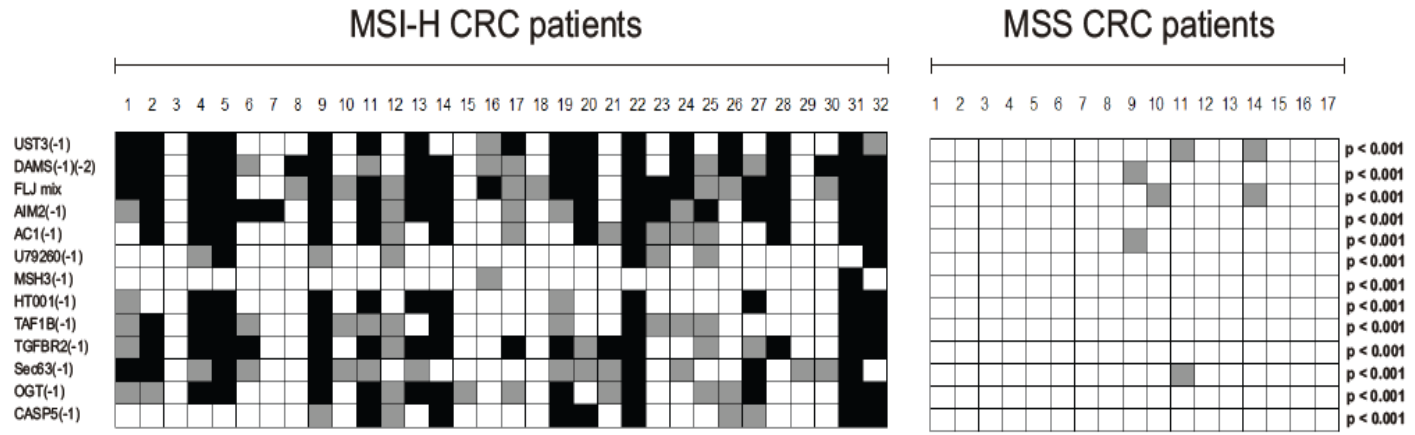
$(A)_8$ TGT . AAA . AAA . AAC . GTG . CTG . GCT . AGC . TGA....

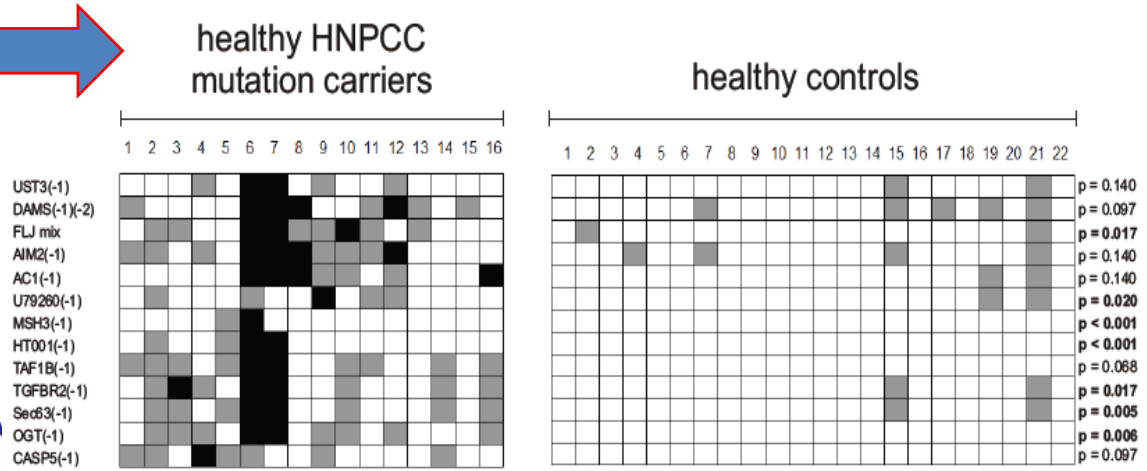
C K K K V L A S STOP



- **loss of function**
- *generation of cancer specific peptides*

Lynch syndrome carriers develop Frameshift peptide antibodies even if they have not had a recognised cancer: is this a chemoprevention biomarker?





Schwitalle et al., Gastroenterology 2008

Recruitment criteria

- Age over 18
- Proven MMR gene carrier

- CAPP2 participants can be recruited
- Willing to take randomised blinded dose (**100, 300, 600mg) of aspirin for 2 years** & self-report numbers of tablets taken

- Agreement for **indefinite clinical follow up** with a minimum of 5 years

- Availability of **MSI** and/or IHC to establish whether any lesions are likely to be Lynch syndrome related, are all non-negotiable

- Consent to Bio-banking (bloods for DNA & serum) and sharing tissue sections to al pharmacogenetic sub-studies, FSP antibody testing & effects of aspirin on molecular tumour phenotype.

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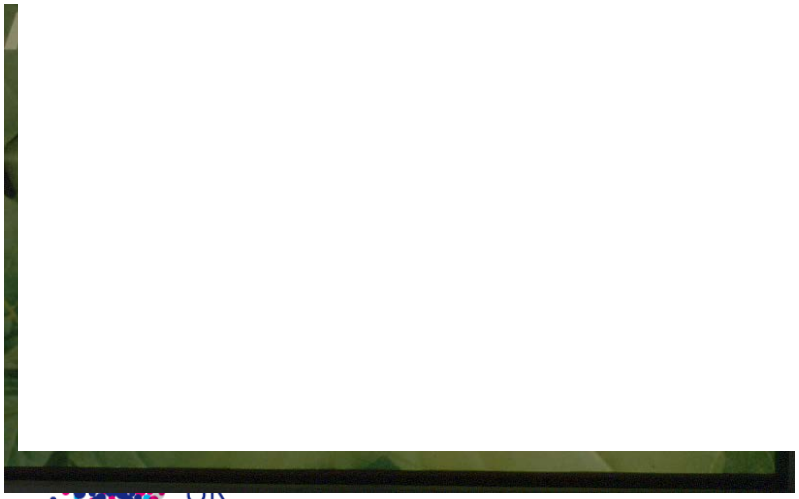
How can aspirin be so effective in so many diseases?

Anti-inflammatory: COX2 inhibition

Anti platelet: exposes metastatic cells to immune attack

Enhances immune response

Is pro apoptotic



FAQs

- 600mg aspirin -high dose isnt it? -
- Side effects are very dangerous? -
- Do we need to go to such trouble?-
- Why do we need so many people?-
- Can I join after cancer?
- Can I join w/out a DNA diagnosis? -
- Can ulcers be avoided/reduced?
- Can cerebral haemorrhage risk ?

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UK Recruitment PIs

ABERDEEN	Zosia Miedzybrodzka
BELFAST	Patrick Morrison
BIRMINGHAM	Emma Woodward
BRISTOL	Alan Donaldson
CAMBRIDGE	Ruth Armstrong
CARDIFF	Mark Rogers
SWANSEA	Alex Murray
RHYL	Emma McCann
DUNDEE	Jonathan Berg
EDINBURGH	Malcolm Dunlop
EXETER	Carole Brewer
GLASGOW	Vicky Murday
LEEDS	Julian Adlard
LEICESTER	Julian Barwell
LIVERPOOL	Lynn Greenhalgh
GOSH	Lucy Side
GUYS	Adam Shaw
ROYAL MARSDEN	Helen Hanson
ST GEORGES	Meriel McEntagart
MANCHESTER	Gareth Evans
NEWCASTLE	John Burn
NORTHWICK PARK	Huw Thomas
NOTTINGHAM	Rachel Harrison
OXFORD	Dorothy Halliday
SHEFFIELD	Jackie Cook
SOUTHAMPTON	Diana Eccles

Overseas sites

Parallel studies & share data

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Other countries: parallel design

- If they share protocol we can pool data
- Offer free randomisation
- Local PI responsible for reliable data collection/ethics/governance/translation
- Need a budget for aspirin distribution
  - Some countries will insist on local prescription, others will accept direct mailing from UK
  - Catalent Ltd will package aspirin

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LynchPiN

The **Lynch** syndrome **P**revent**i**on **N**etwork

Study Team

Lynn Reed, Study Coordinator
Lynne Longstaff, Communications Administrator
Donna Job, Clerical Officer
Chloe Vasseghi CTU Trial Manager
Gill Borthwick, Programme Manager

CaPP3@newcastle.ac.uk

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CAPP2 Paper Released
On October 28th 2011 the CAPP2 paper was published in the Lancet, click to find out more.

HOW TO JOIN?

You would like to participate in the trial.

HOW TO HELP?

Are you a healthcare professional that would like to help?

FIND OUT MORE

The history of the trial and the people involved.

Latest News

28 OCT 2011

CAPP2 Paper Released

posted on Friday, 28th October 2011

Research has finally provided proof that taking a regular dose of aspirin reduces the long-term risk of cancer in people with a family history of the disease by around 60 per cent.

01 SEP 2011

CaPP3 is go!

posted on Thursday, 1st September 2011

Now that we have the result of the CAPP2 study which shows that regular aspirin significantly reduces cancer risk in Lynch syndrome, we now need to try and work out the best dose.

Downloads & Links

CAPP2 Paper October 2011

posted on Thursday, 27th October 2011

Research has finally provided proof that taking a regular dose of aspirin reduces the long-term risk of cancer in people with a family history of the disease by around 60 per cent.

CAPP2 Website

posted on Wednesday, 26th October 2011

Information on the CAPP2 Study (Colorectal Adenoma/carcinoma Prevention Programme).

327
Participants registered interest

5
Countries

48
Healthcare professionals registered interest

Elaine Warburton takes Josephine
to see David Cameron
November 2013

Summary 1

The Cancer Prevention Programme (CaPP) : genetic targeting allows powerful chemopreventive strategies to be tested

The effects of aspirin in FAP were equivocal. Further followup of the cohort is planned
CAPP2 has demonstrated a significant protective effect of aspirin in those with a MMR gene defect

Latest data indicates a strengthening case for use of aspirin in hereditary cancer

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Summary 2

- CaPP3 will test 100 vs 300 vs 600 mg daily in 3000 gene carriers with Lynch syndrome
- Treat blind for 2 years follow up to minimum five yrs on open label 100mg Bayer enteric coated aspirin per day
- Bioresource DNA and serum
    - Frame shift peptide antibody titres will be explored as a biomarker of sub clinical cancer
    - Pharmacogenetic variation will be examined
- GP guidance and young age range should reduce side effects
- Will tweet on @capp3

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ASPIRIN

aPP3
Cancer Prevention Programme

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