CANCER RESEARCH UK

Breakthroughs in genetic medicine and implications for degenerative diseases

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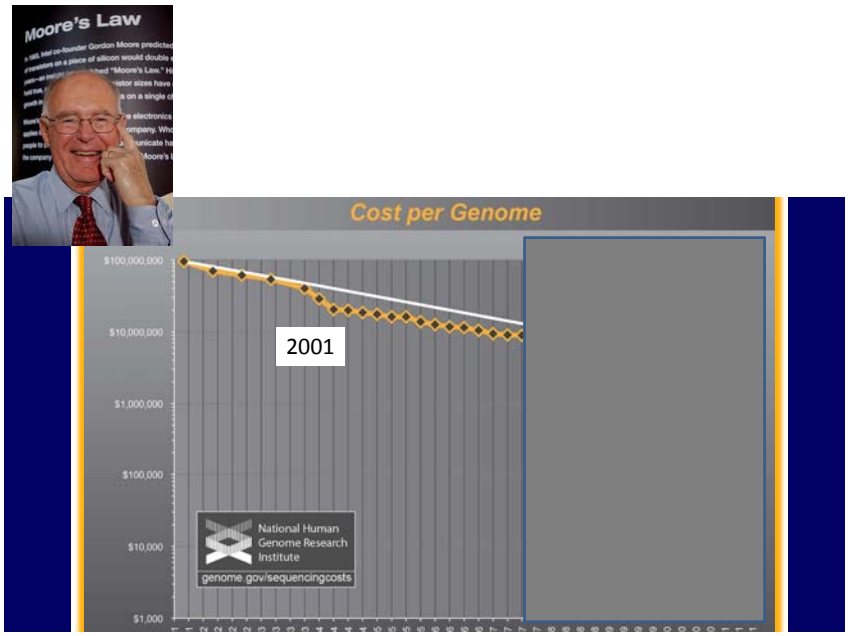
Institute and Faculty of Actuaries
Mortality and Longevity Seminar
London
27th June 2013

Newcastle University



August 2010 China National Highway 110 traffic jam, China, world's worst traffic jam ever….
more than 100 kilometres from August 14 - 26, inc. at least 11 days of total gridlock.

We are heading for the biggest traffic jam in history

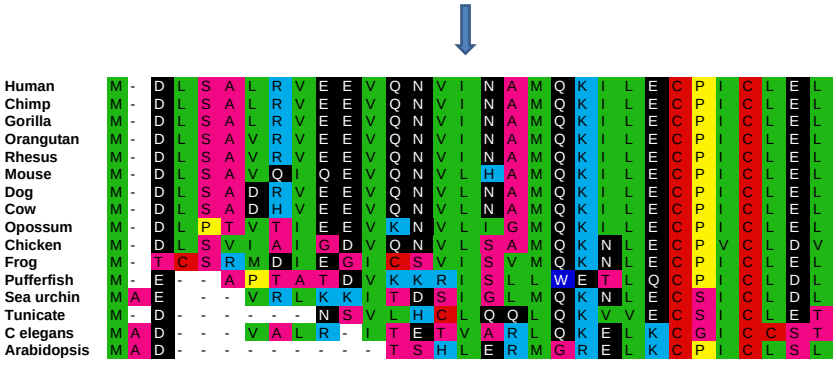
Human Genomics Strategy Group 2011-12

- Government response December 2012
  - 100,000 diagnostic whole genomes
  - £100 million investment
  - NHS Genomics Strategy Board

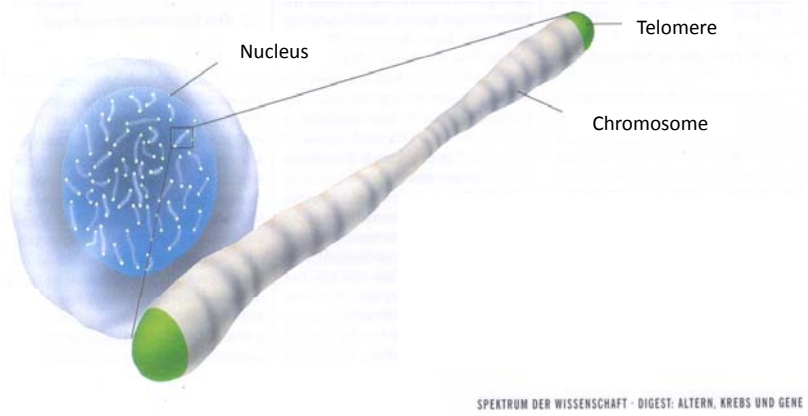
Functional classification of JDW SNPs

SNP Type	Novel SNPs
Missense	2421
Nonsense	5
Synonymous	2261
UTR	7102
Intron	381924

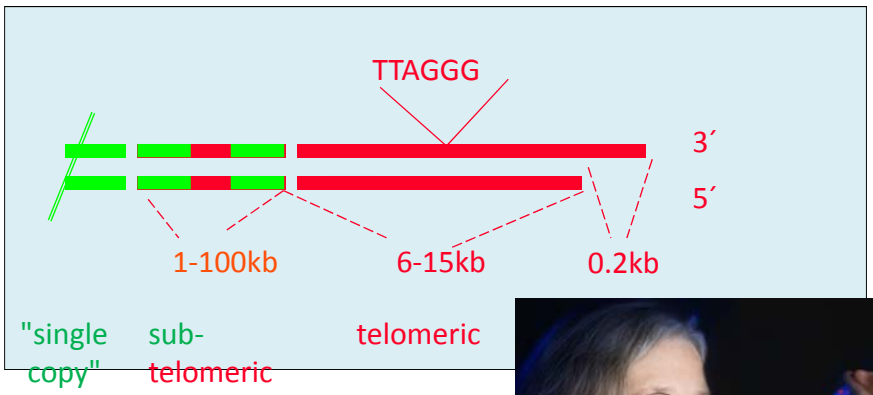
BRCA1 Amino-terminal alignment

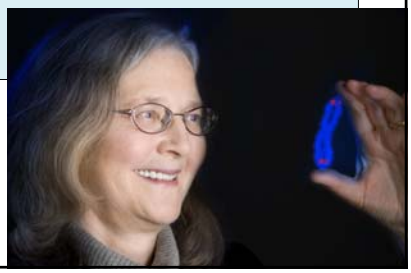


Courtesy of Sean Tavtigian



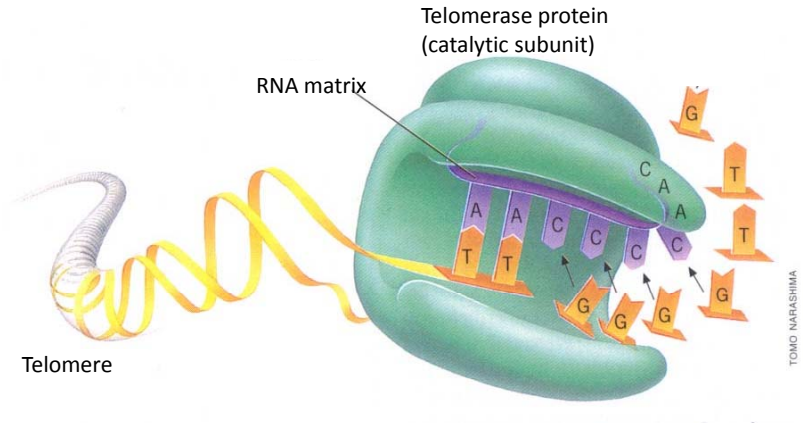
An End Is An End if it´s marked by a telomere





Dr Elizabeth Blackburn

Telomerase counteracts telomere shortening in immortal cells



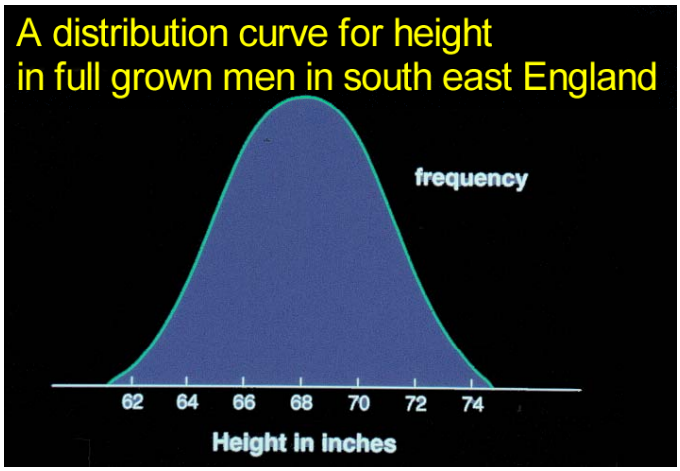
ttaggg

Needham BL, Fernandez JR, Lin J, Epel ES, Blackburn EH.
Soc Sci Med. 2012 Jun;74:1948-51. Epub 2012 Mar 17.

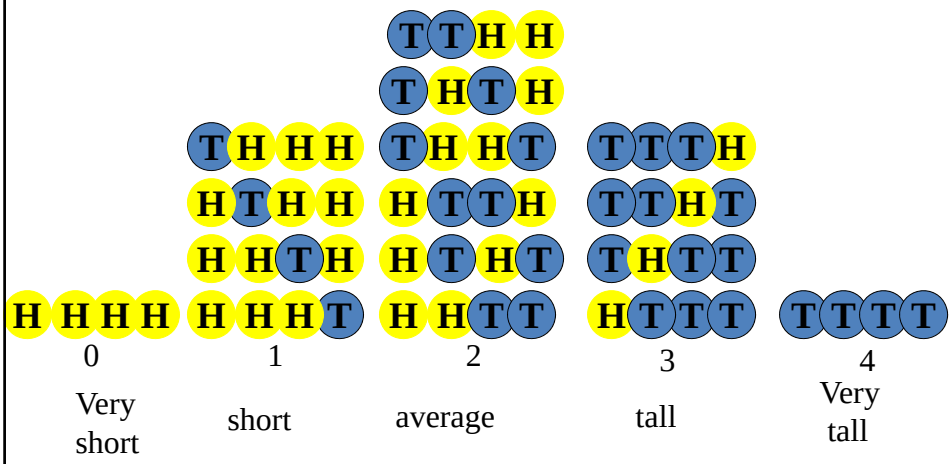
Socioeconomic status and cell aging in children.

70 white and black US children aged 7-13 from community-based AMERICO (Admixture Mapping for Ethnic and Racial Insulin Complex Outcomes) study.

Compared to children with at least one college-ed. parent, **children whose parents never attended college** had telomeres shorter by 1,178 base pairs, which is roughly equivalent to **6 years of additional aging.**



How useful is a genetic test?



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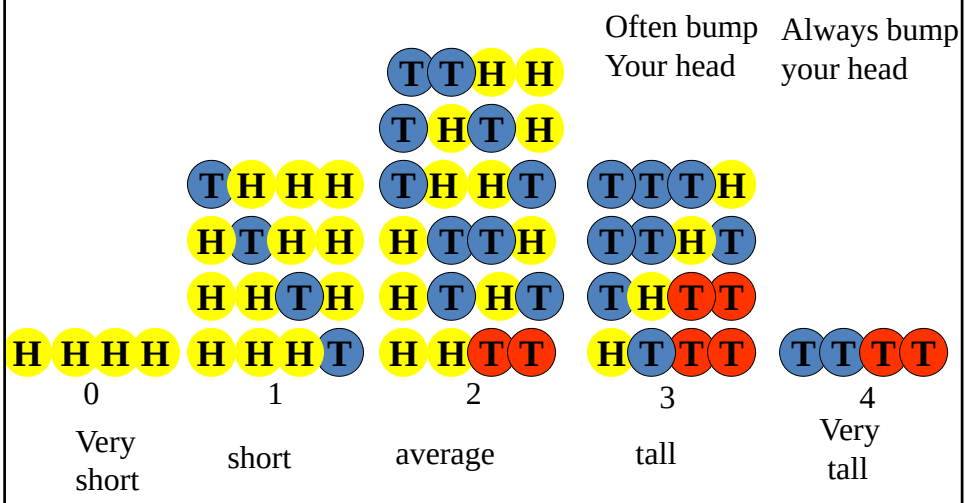
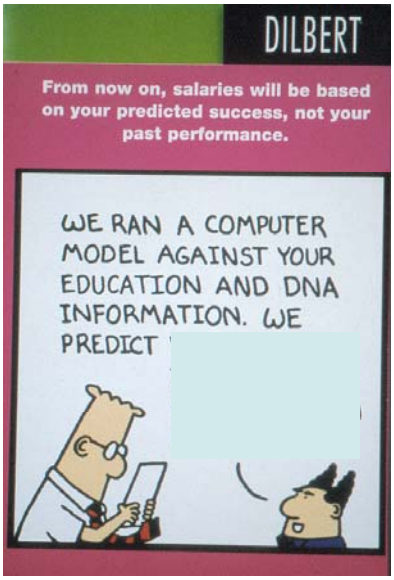
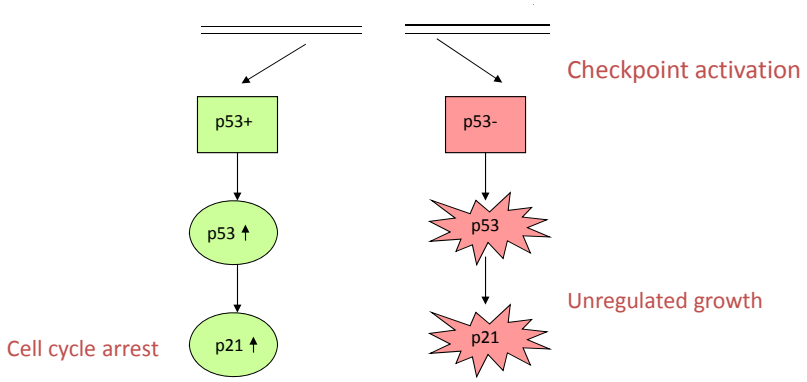
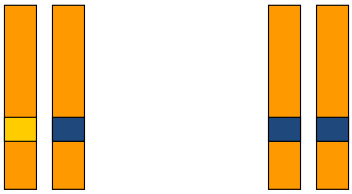




DNA pathway repair



‘hereditary’ tumour



Dr. Alfred G. Knudson

predisposed tumour

Knudsen’s hypothesis: tumour develops when both copies of a tumour suppressor gene are lost. If one faulty copy is inherited, any susceptible cell can become malignant with a single allele loss

BRCA1:		BRCA2:	
Breast cancer:	**80%**	**Breast cancer:**	**70%**
Ovarian cancer:	**50%**	**Ovarian cancer:**	**25%**
		Bilateral breast cancer	
Fallopian tube cancer		**Male breast cancer**	
Bilateral breast cancer		**Prostate, pancreatic, thyroid, laryngeal, gastrointestinal ca**	

Women who carry a pathological BRCA 1 or 2 variant need to consider prophylactic oophorectomy when family is complete

551 cases of BRCA1 & 2
259 had oophorectomy versus 292 controls

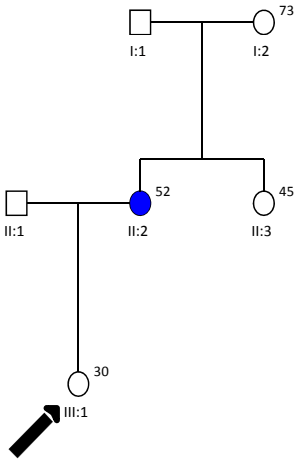
6 (2.3%) had stage 1 ovarian cancer at operation
2 (0.8%) at 3.8 and 8.6 yrs

56/292 controls (19.9%) during 8.8 years follow up

Breast cancer rate halved in oophorectomy cases

Rebbeck et al 2002 New England Journal of Medicine

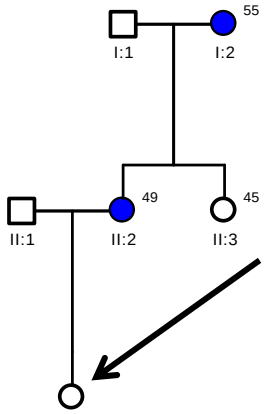
"sporadic" breast cancer



For individual: III:1

Heterozygote risk:	1.8%
10 year risk:	0.8%
20 year risk:	2.5%
30 year risk:	4.7%
Lifetime risk (85):	11.0%

familial breast cancer



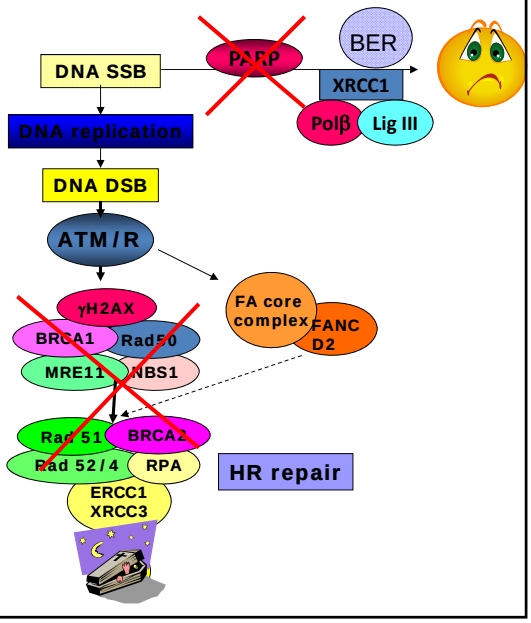
Individual III 1 at 20
Heterozygote 19%
10 year risk 0.9%
20 year risk 4.4%
30 year risk 9.7%
Lifetime risk 24%

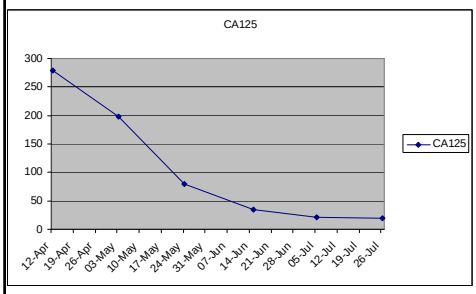
PARP inhibitors (Invented in Newcastle!)

You need PARP to fix DNA breaks

If you block it, the cell Uses a more complicated Method called Homologous Recombination

Cells that have lost both copies Of BRCA1 or BRCA2 can't do this

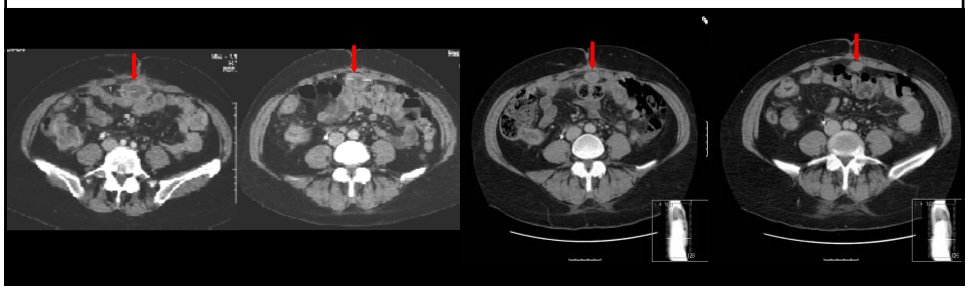




Young patient, strong family Hx breast and ovarian cancer

Data Courtesy of Johann de Bono and Stan Kaye, Royal Marsden Hospital

Baseline | Post Cycle 2 | Post Cycle 4 | Post Cycle 6

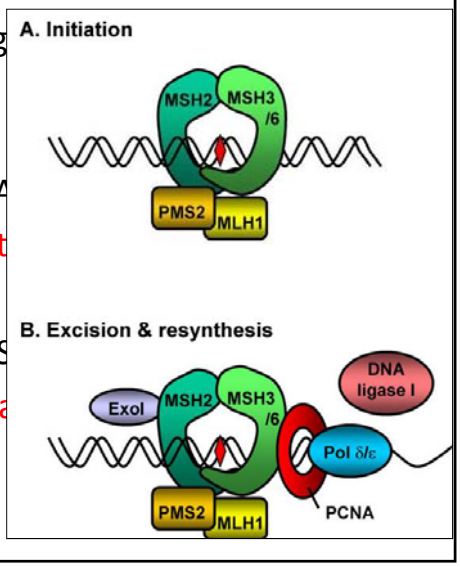


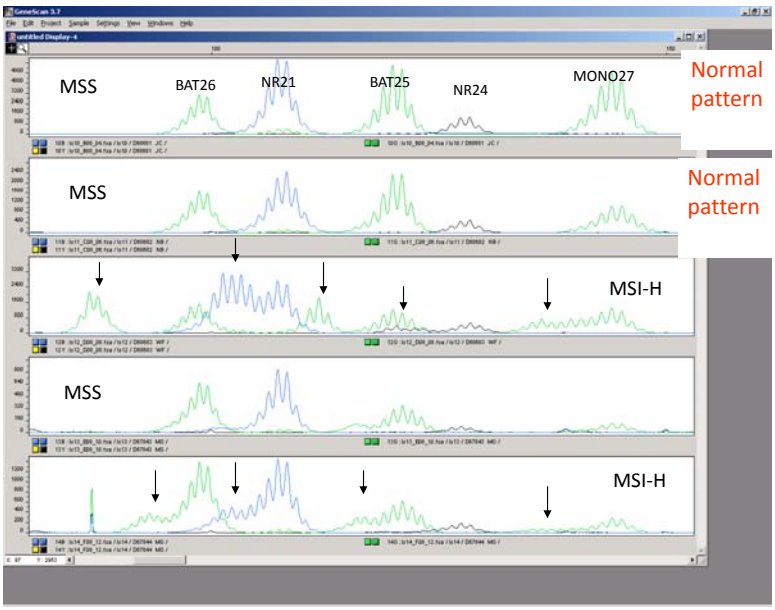
Microsatellites

– Microsatellites are leng
sequences usually

– mononucleotides eg BA
tgttttgttttttgatttttttttttttt

– or dinucleotides eg D5S
aatttacacacacacacacacacaca





Genetically Targeted Trials

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

Concerted Action Polyp Prevention

Colorectal Adenoma/carcinoma Prevention Programme

43 CAPP2 recruiting centres

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

December 11th
2008;359:2567-2578
CAPP2: 1009 Lynch syndrome recruits

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*

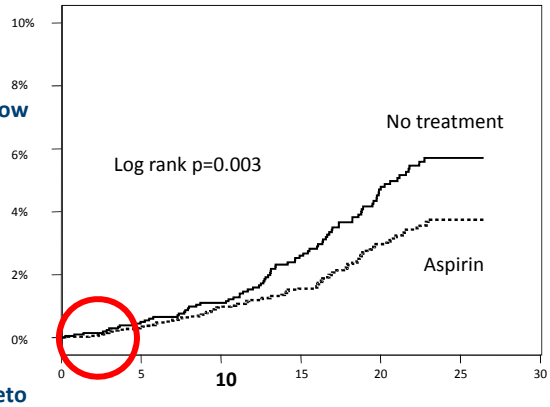
Tim Bishop John Mathers

600mg aspirin for up to 4 yrs had no effect

People who took part in the early cardiovascular aspirin trials had fewer colorectal cancers 10 years later

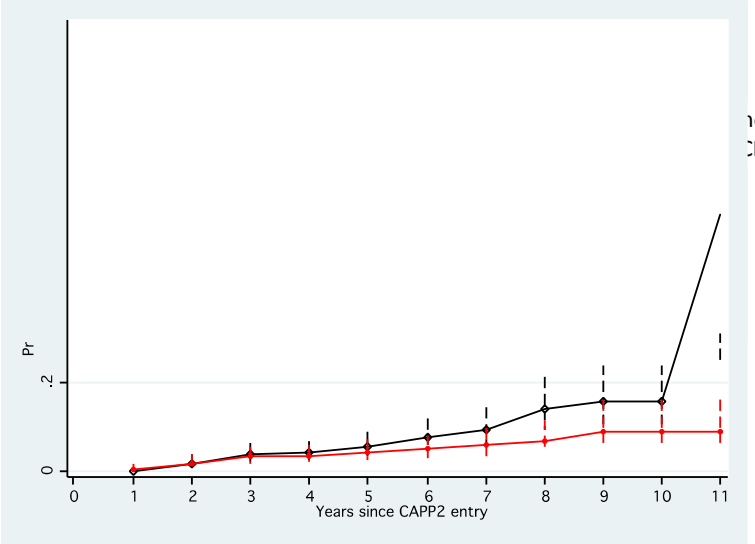
UK-TIA Aspirin Trial
1979 - 1985
Charles Warlow

British Doctors Aspirin Trial
1978 – 1984
Richard Doll & Richard Peto



Flossman and Rothwell Lancet 2007

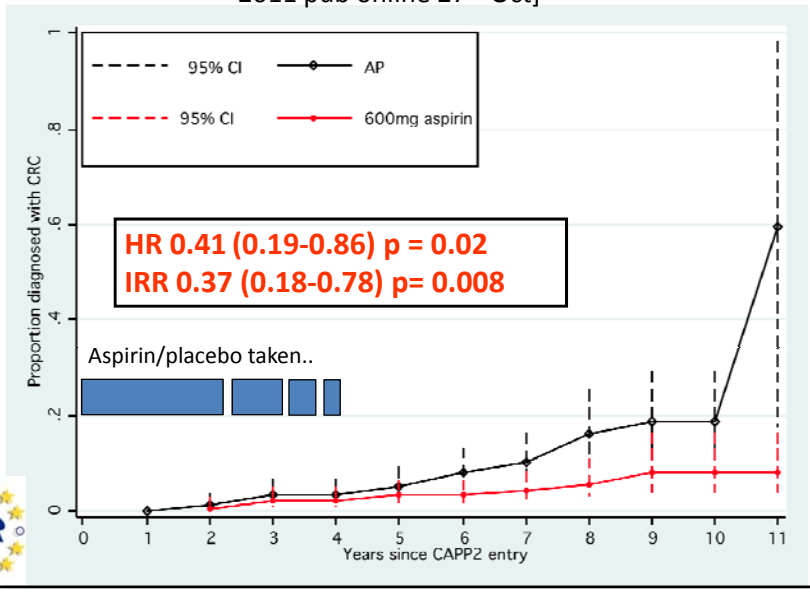
Intention to treat analysis of colorectal cancers in CAPP2 follow-up



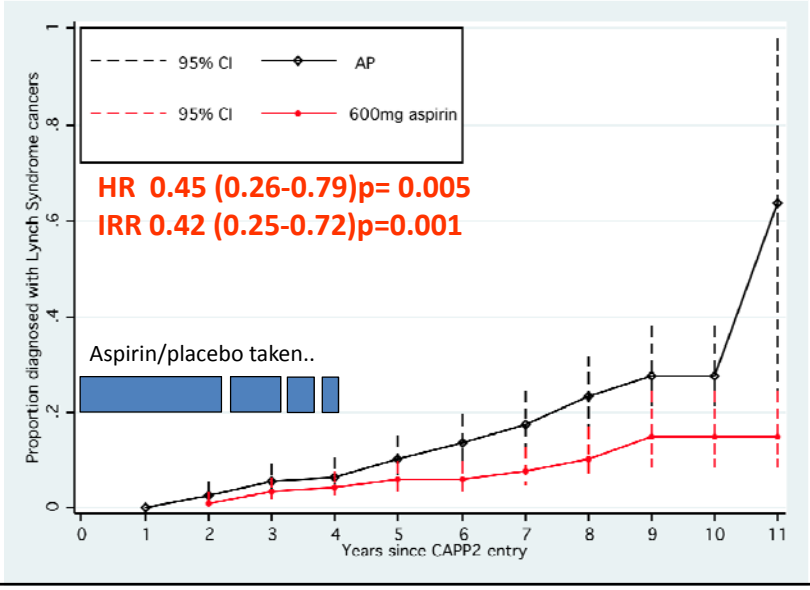
CAPP2 primary endpoint

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

CAPP2: Per protocol analysis (primary endpoint CRC after 2 years treatment) significantly fewer colorectal cancers [Burn et al Lancet 2011 pub online 27th Oct]



CAPP2 per protocol analysis
All Lynch syndrome cancers



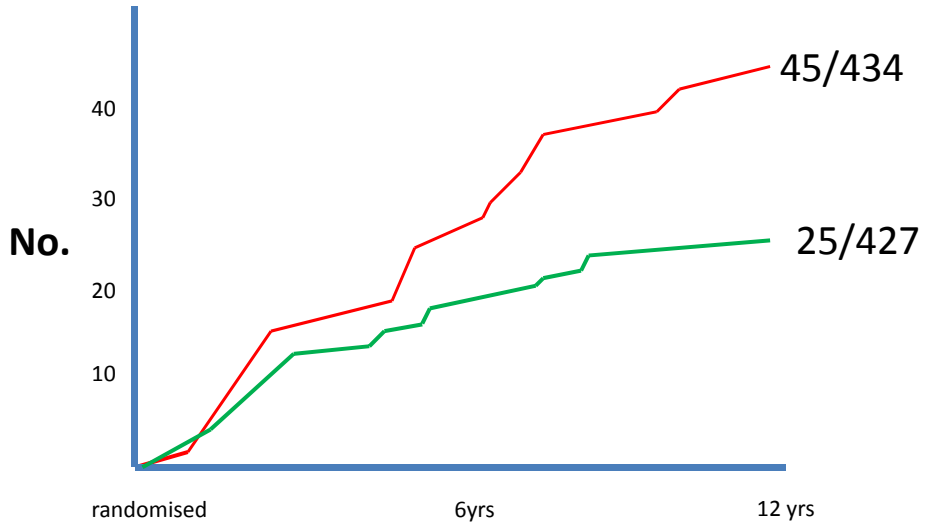
600mg aspirin/day for 2 yrs reduced Lynch syndrome cancers at 5 yrs by over 60%

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

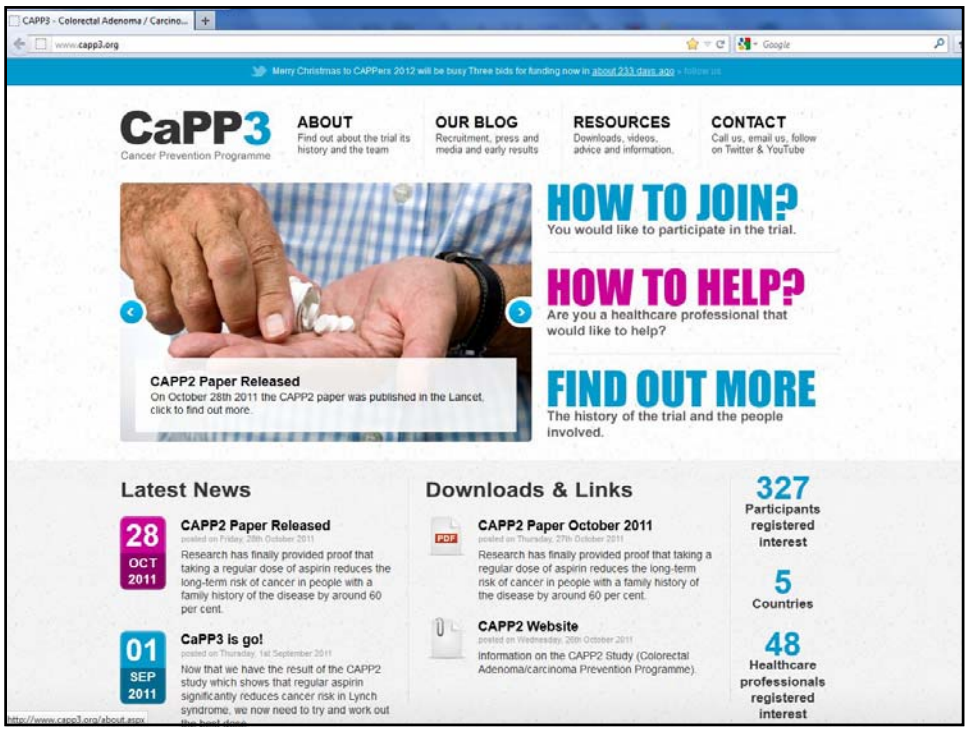
John Burn, Anne-Marie Gerdes, Finlay Macrae, Jukka-Pekka Mecklin, Gabriela Moeslein, Sylviane Olschwang, Diane Eccles, D Gareth Evans, Eamonn R Maher, Lucio Bertario, Marie-Luise Bisgaard, Malcolm Dunlop, Judy W C Ho, Shirley V Hodgson, Annika Lindblom, Jan Lubinski, Patrick J Morrison, Victoria Murday, 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

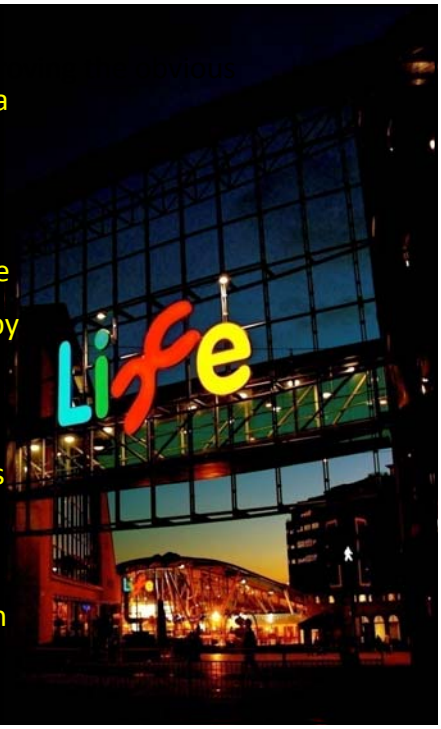
Lancet volume 378 December 11th 2011

CAPP2 follow up data May 2013



Primary colorectal cancers


CaPP3 - Colorectal Adenoma / Carcino...
www.capp3.org
Merry Christmas to CAPPers 2012 will be busy Three bids for funding now in about 233 days ago
CaPP3
Cancer Prevention Programme
ABOUT
Find out about the trial its history and the team
OUR BLOG
Recruitment, press and media and early results
RESOURCES
Downloads, videos, advice and information.
CONTACT
Call us, email us, follow on Twitter & YouTube
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.
CAPP2 Paper Released
On October 28th 2011 the CAPP2 paper was published in the Lancet, click to find out more.
Latest News
28 OCT 2011
CAPP2 Paper Released
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!
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
Downloads & Links
CAPP2 Paper 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
Information on the CAPP2 Study (Colorectal Adenoma/carcinoma Prevention Programme).
327
Participants registered interest
5
Countries
48
Healthcare professionals registered interest

THE BEST THING YOU CAN DO IS GIVE UP SMOKING, DRINKING AND FRIED FOOD

- The cost of DNA sequencing has fallen 100,000 fold in a decade
- Achieving clinical utility remains a challenge
  - Telomeres and repeats
  - Variants of uncertain significance
  - Gene gene and gene environment interaction
- BRCA1 and 2 and tp53 predispose to very early breast cancer. PARP inhibitors promise specific therapy
- Mismatch repair gene defects predispose to colorectal and endometrial cancers.
- 600mg aspirin/day for 2 yrs reduced hereditary colon cancers at 5 yrs by 63%
- All people with familial cancer should be advised to consider aspirin. CAPP3 will compare different doses of aspirin in Lynch syndrome
- AND THE TREE HOUSE?