Newcastle Hospitals

Precision Medicine
From genome to bedside
The future of personalised cancer care

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Newcastle University, UK
Hon. Consultant Geneticist, Newcastle Hospitals
Chair Research & Innovation NEY GMS

Northern Cancer Alliance Annual Conference
Metrocentre, Gateshead
9th October 2026

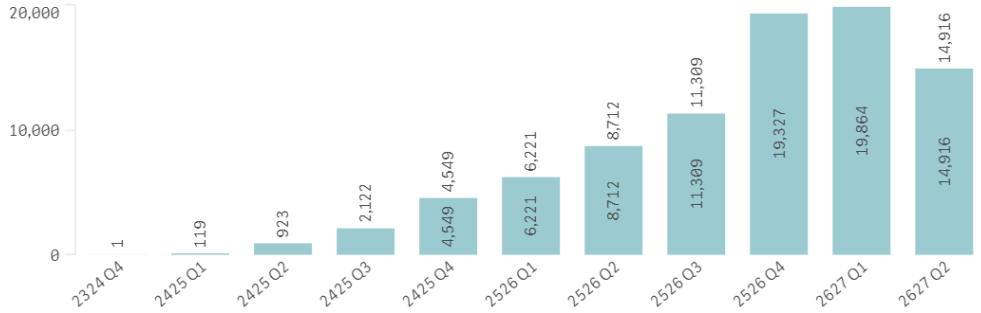
Generation Study

North East and Yorkshire Genomic Medicine Service

Recruit 100,000 newborn babies and screen them for over 200 genetic conditions. Recruitment 2024 - March 2027

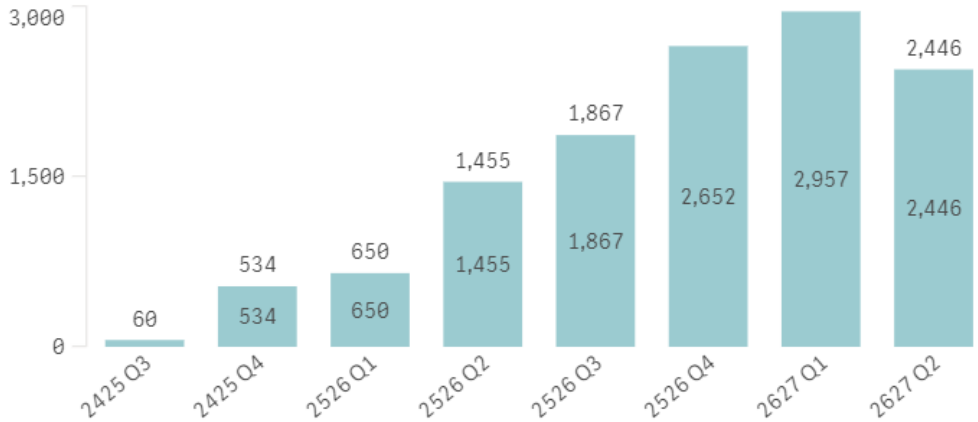
National

- 90,000+ participants enrolled
- 69,000+ results returned
- 225 suspect results returned



NEY GMS

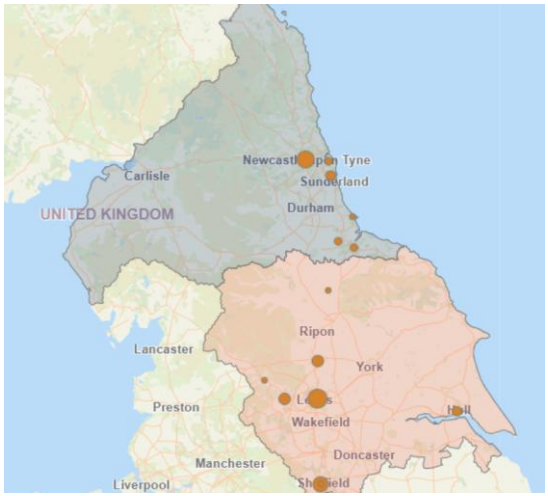
- 12,600 participants recruited, 9 Trusts (11 sites)
- 32 suspect results returned, rate of ~ 4/month



INDEPENDENT

Baby Freddie's 'completely out of the blue' cancer detected by genetic screening

The family were taking part in a study which is screening newborn babies in England for dozens of genetic conditions.



Retinoblastoma

All Cancer is “genomic” and some is “genetic”

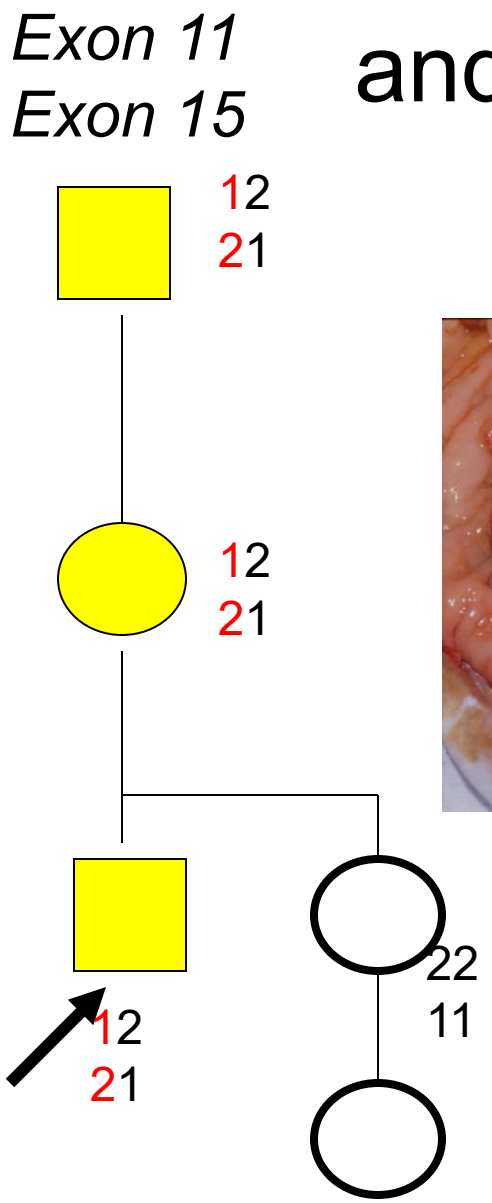
NCA
20,000 carry a “cancer gene”

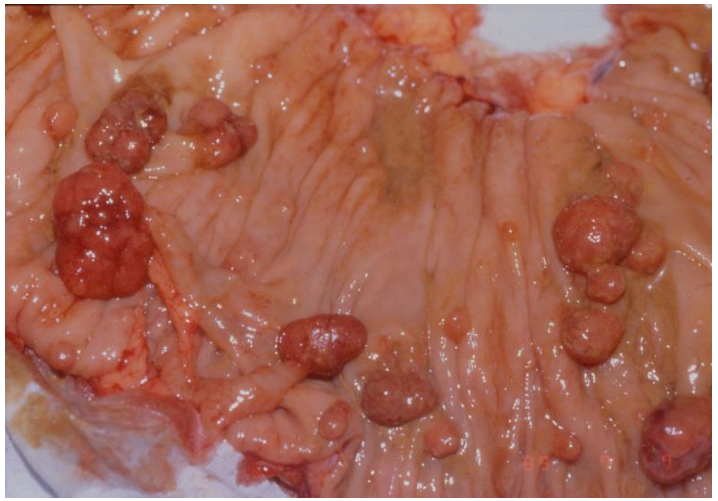
Tom Roderick
”big picture”

Prof William Bateson
Family traits

NCA
20,000 cancers per annum

Familial Adenomatous Polyposis (FAP) and the APC gene on chromosome 5

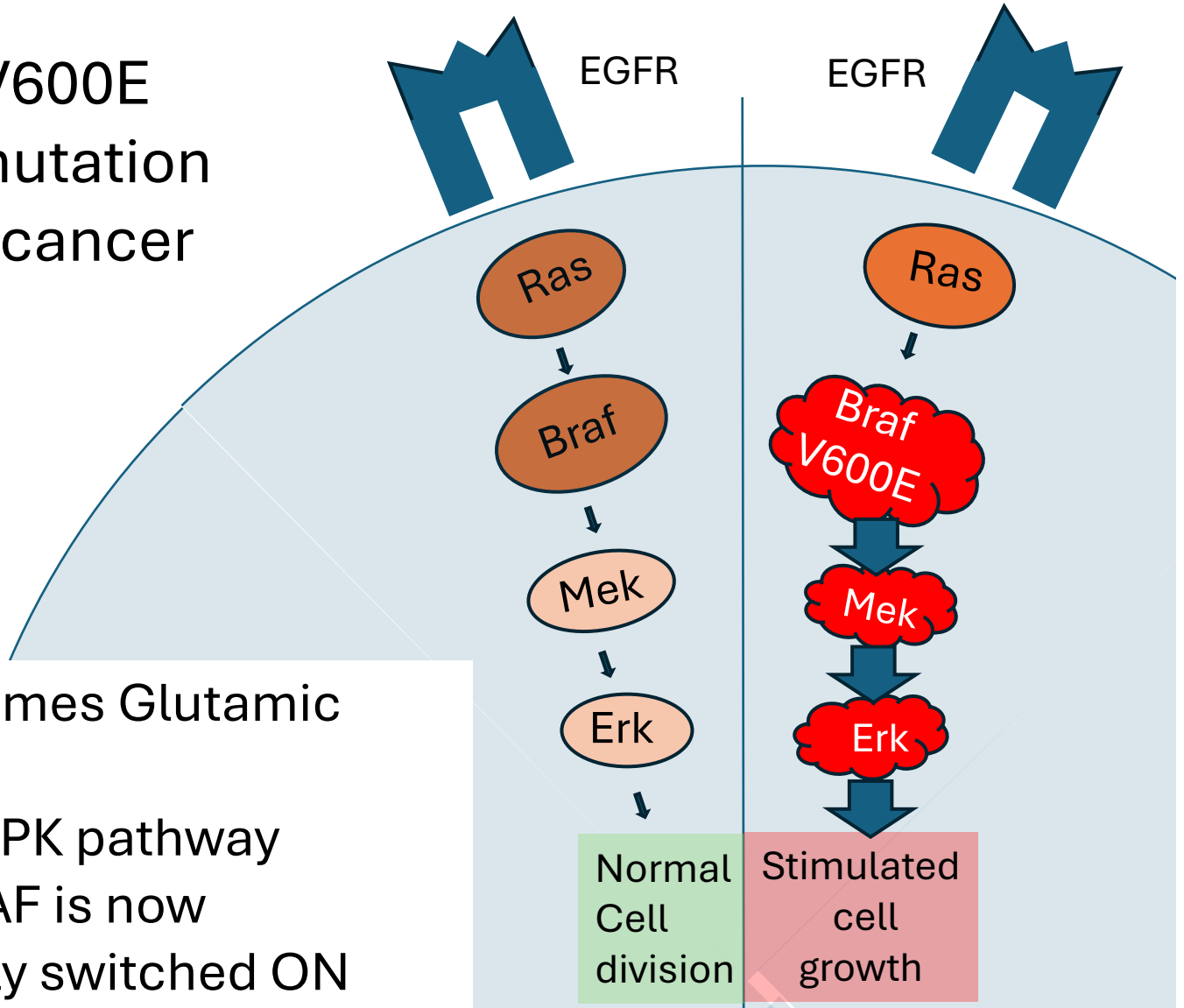




Simon

Burn et al J Med Genet1990

BRAF V600E
A point mutation “drives” cancer



BRAF Amino acid 600

G---C
A----T
G---C

Valine becomes Glutamic acid
The Ras MAPK pathway beyond BRAF is now permanently switched ON
The cell continues to divide.
This is a Driver Mutation

Vemurafenib – BRAF inhibitor
Metastatic Melanoma
Flaherty NEJM 2011

Synthetic Lethality: PARP inhibitors (Invented in Newcastle!)

Sir Bobby Robson Cancer Institute

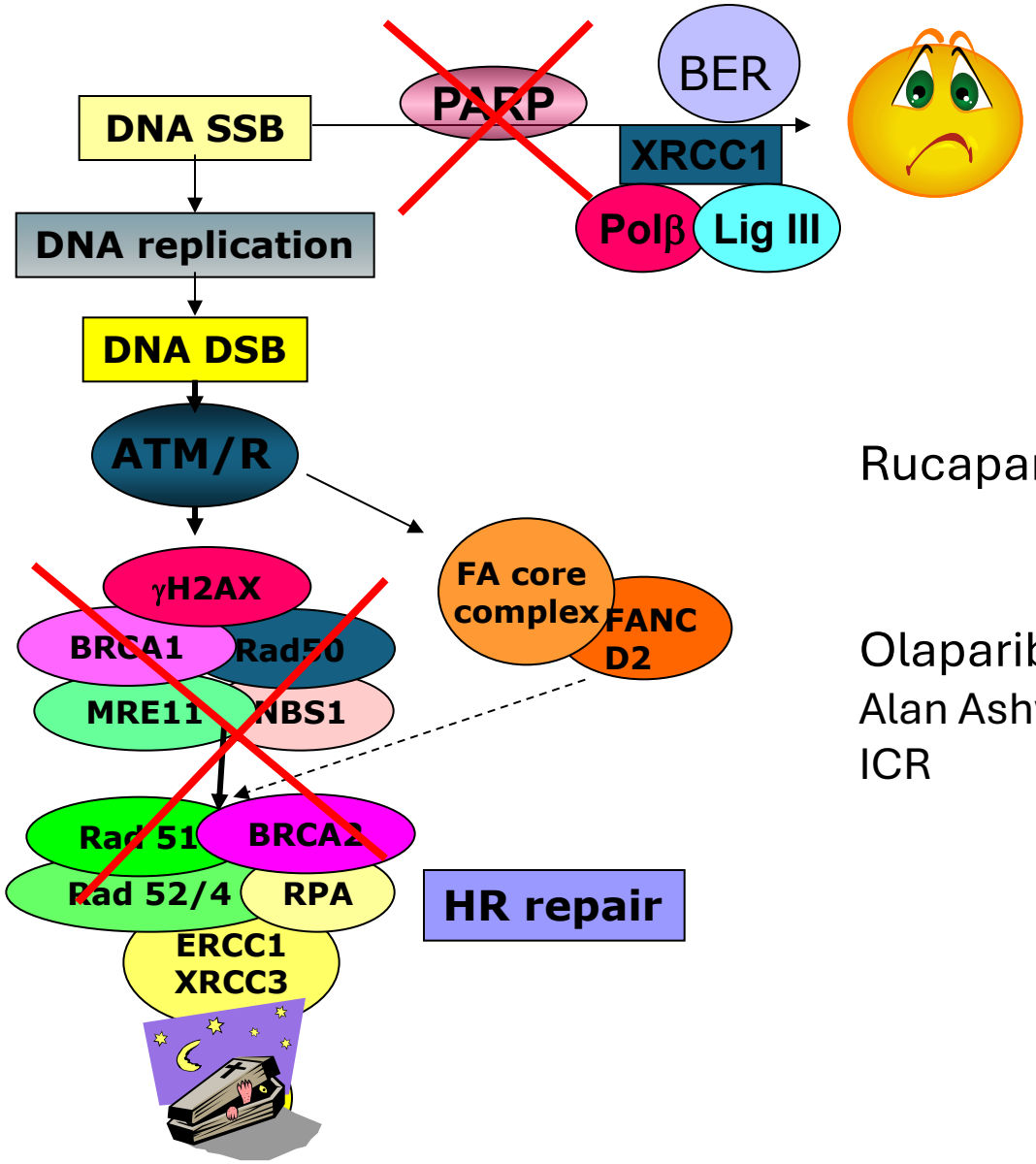
You need PARP to fix DNA breaks

Ruth Plummer

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

Thomas Helleday



Rucaparib

Olaparib (AZ)
Alan Ashworth
ICR

Melissa Cline
et al PLOS Genetics
2019

Cancers are most common in tissues with high cell turnover eg breast and colon

Benedict Paten

Gunnar Rätsch

Zack Fischmann

Joe Thomas

Rob Currie

Amy Coffin

Chloe Dlott

Faisal Alquaddoomi

Marc Zimmerman

Charlie Markello

Molly Zhang

Rachel Liao

Amanda Spurdle

Stephen Chanock

Sir John Burn

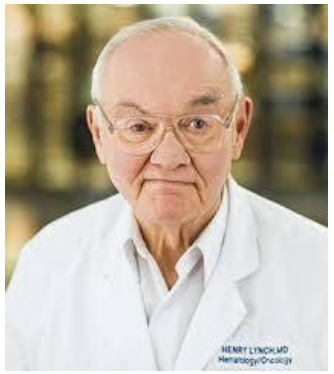
>72000 deduplicated variants
www.brcaexchange.org

Global Alliance for Genomics & Health

BRCA CHALLENGE

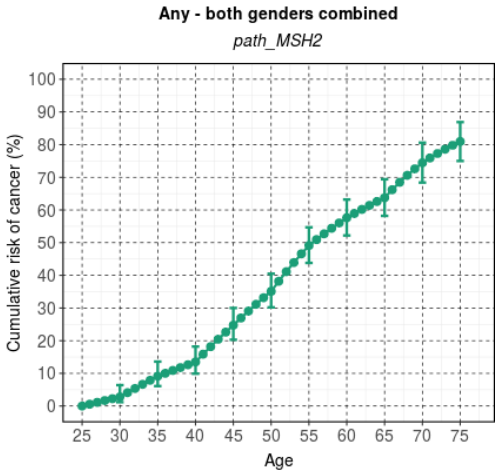
THE HUMAN VARIOME PROJECT

ENIGMA



Henry Lynch

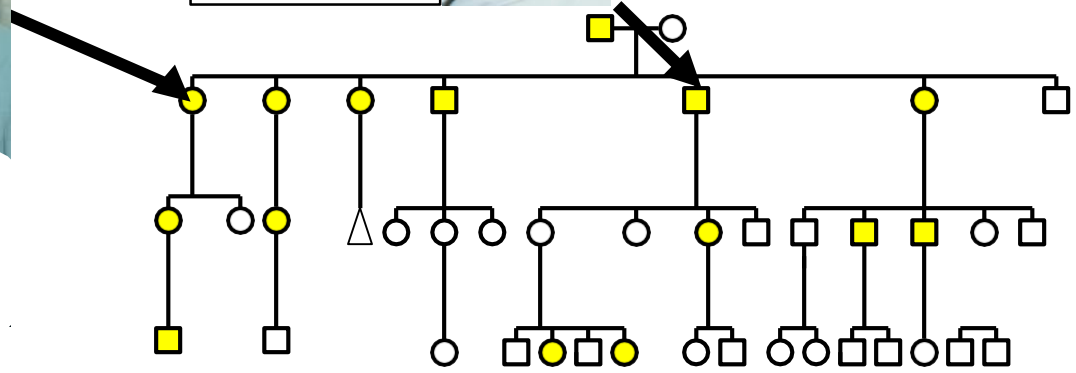
www.plsd.eu



Endometrial Carcinoma Bertha

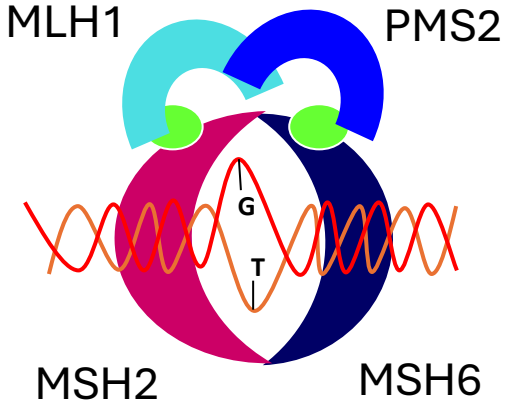
Ted
3 CRC
9 skin cancers

3/1000



PLSD
Prospective Lynch Syndrome Database

By age 75, 80% of MSH2 carriers will get cancer



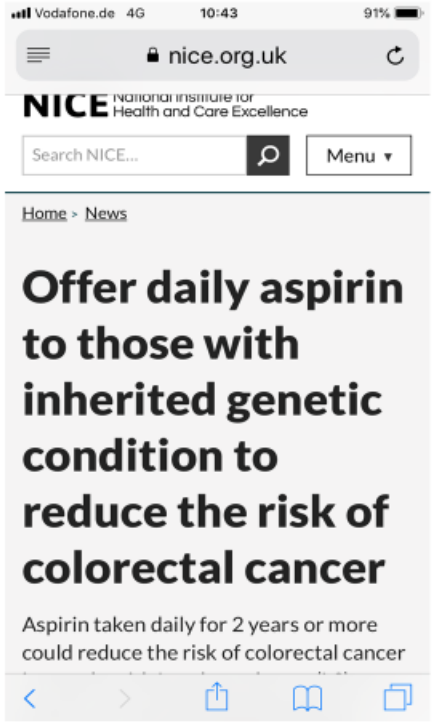
Family from which DNA used to demonstrate hMSH2 mutation by Kolodner's group Dec 1993: 1st of the MISMATCH REPAIR GENE DEFECTS

CAPP1:1993-1997
206 FAP carriers
Burn et al Ca Prev Res 2011
CAPP2: 1999-2005
937 Lynch S. carriers
43 centres, 16 countries
Burn et al Lancet 2011

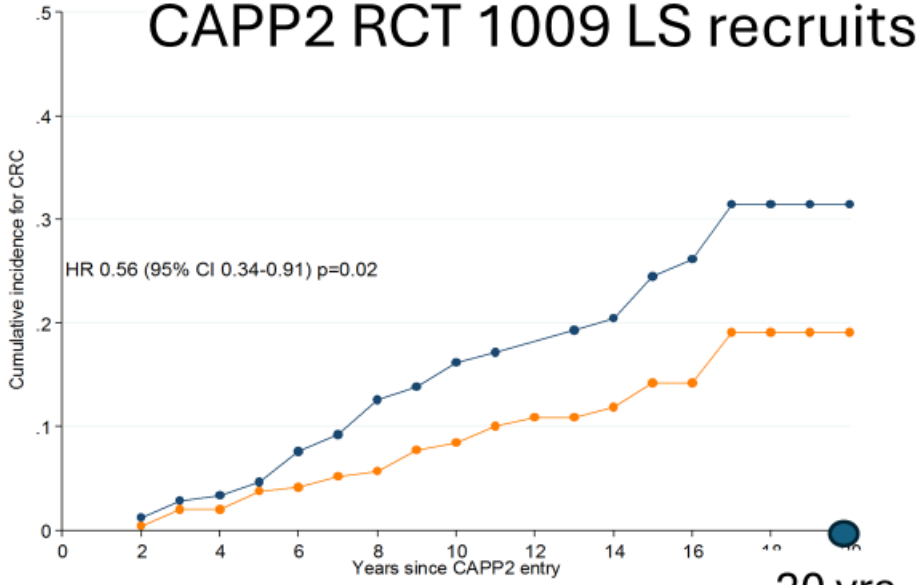
The canary down the mine

Starch + Aspirin	**Placebo + Aspirin**
Starch + Placebo	**Placebo only**

Enteric coated 2x300mg aspirin per day (Bayer)
Novelose high amylose starch 2x 15g/day
(National Starch and Chemical Co, NJ)



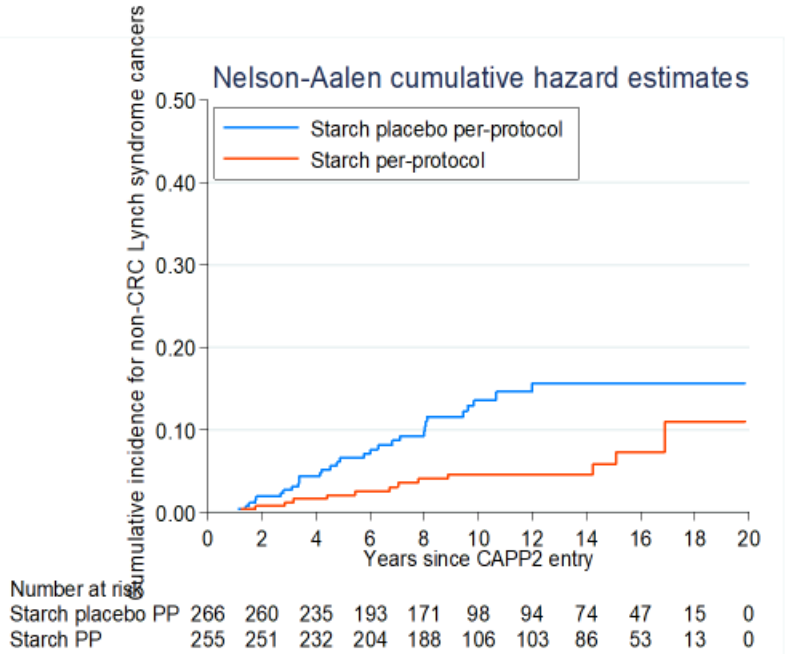
CAPP2 RCT 1009 LS recruits 16 countries 1997-2022



20 yrs

Burn J et al Lancet 2020;390:185

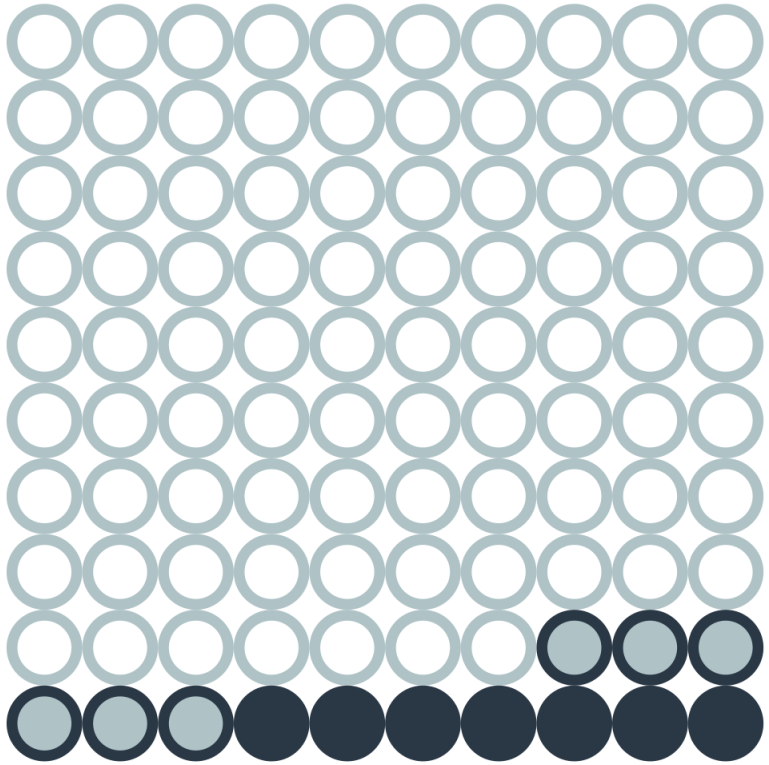
2 aspirins a day for 2 years reduces CRC in Lynch syndrome by 50%
per protocol over >15 years
(primary endpoint. Significant on ITT)
ASCO Prevention Advance of the Year



Mathers J et al Cancer Prevention Research 2022
30 g Novelose (resistant starch) for 2 yrs
Reduces Non-CRC cancers in LS by >60%
(planned secondary endpoint)
Upper GI >75% reduced ? 2ndary bile acid
AACR Paper of the Year 2023

NG151 https://www.nice.org.uk/guidance/ng151/resources/patient-decision-aid-pdf-8834927869

Bowel cancer among people who took aspirin for at least 2 years



On average, for every 100 people who took aspirin for at least 2 years, over 10 years **93 people did not get bowel cancer**, but **7 people did**:

- 6 people **did not get** bowel cancer **because they took aspirin**
- 87 people **did not get** bowel cancer, but would not have done whether they took aspirin or not.
- 7 people **got** bowel cancer, even though they took aspirin.

It is not possible to know in advance what will happen to any one person

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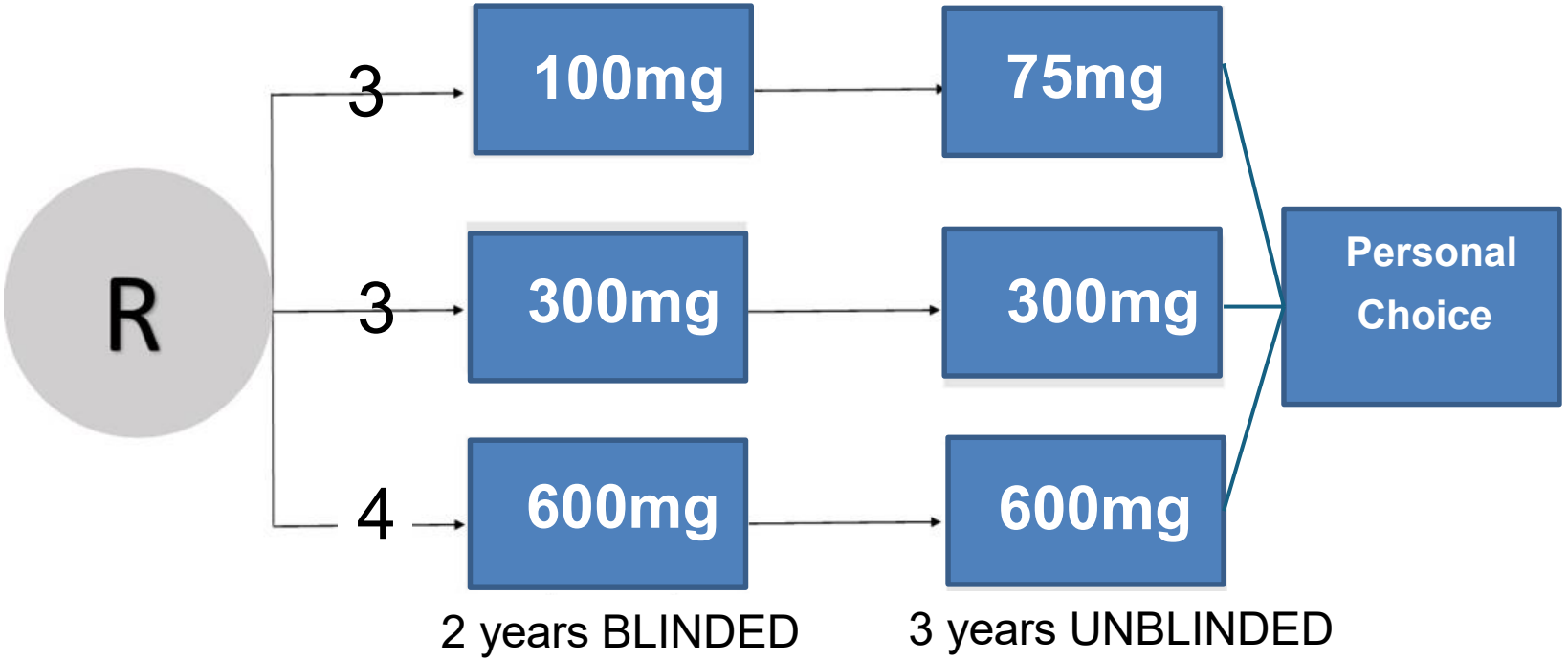
1866 Lynch syndrome gene carriers

UK, Australia, Finland, Israel and Spain

CANCER RESEARCH UK

CaPP3

Cancer Prevention Programme



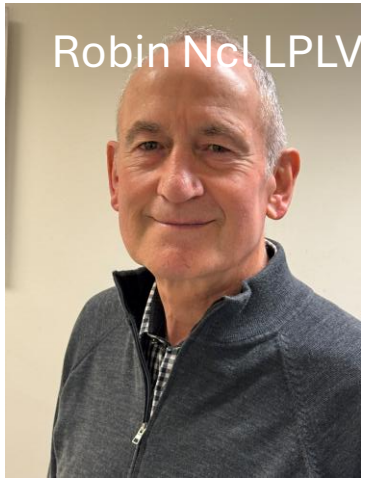
FPFV 2014 LPLV2024

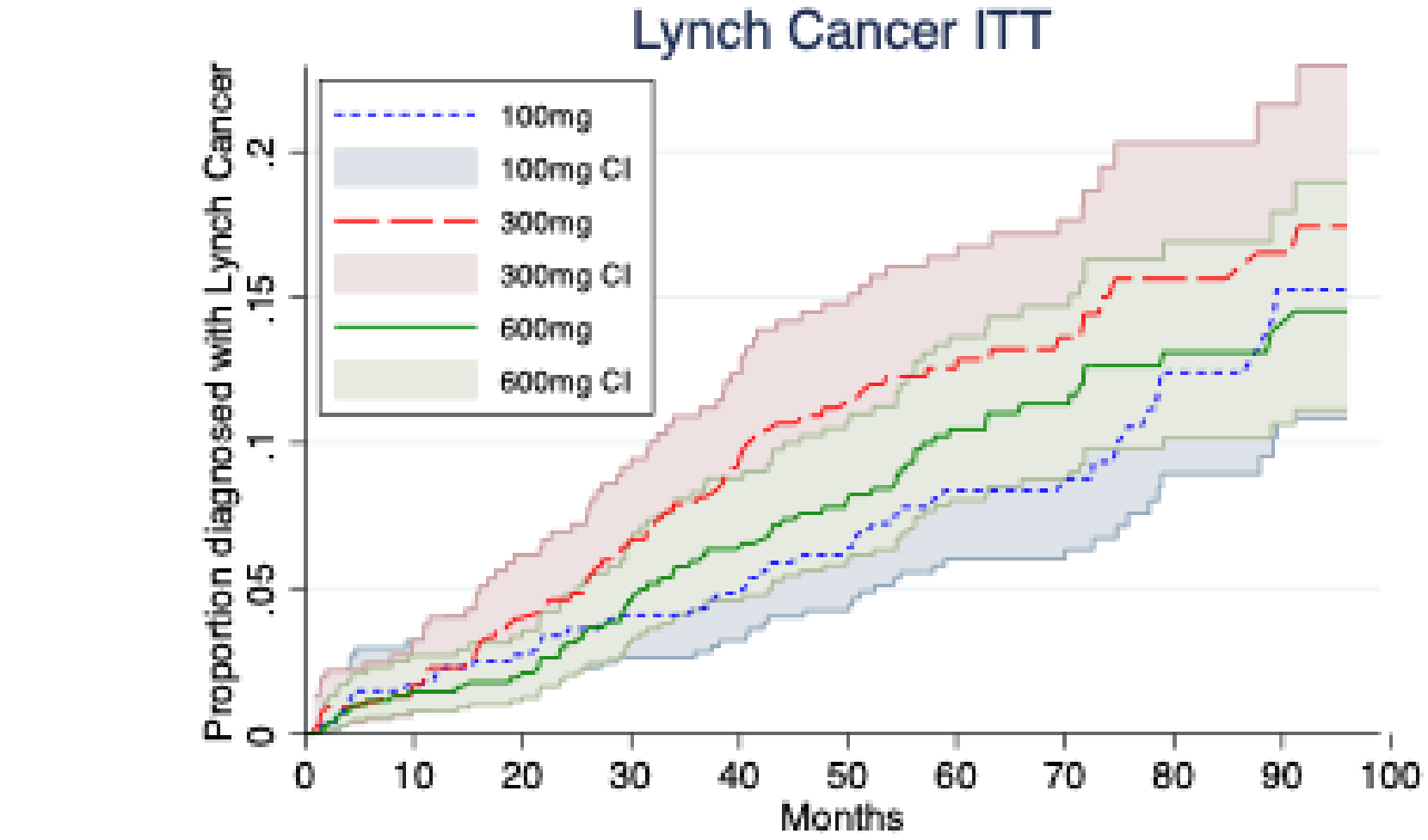
The 100mg group had the fewest cancers after 8 years

Burn et al Lancet Gastroenterology and Hepatology 2026

ADVANZ PHARMA

BAYER





Number at risk

100mg	559	502	455	413	387	371	330	247	157	103
300mg	561	510	463	420	395	374	326	252	161	110
600mg	741	646	595	529	491	469	399	312	214	141

100mg 57
300mg 75
600mg 84
Includes Bladder Ca
And Prostate Ca

CRCs
100mg 22
300mg 33
600mg 36

Burn J et al Lancet Gastroenterology & Hepatology 2026

SUMMARY: new UK guidance

- After 8 years, 30% CaPP3 recruits on lowest dose had fewest LS cancers – participants took their tablets and the dose is “non-inferior” to 600mg on ITT

- Anti-platelet doses of aspirin reduce the cancer burden in Lynch syndrome.

UK Guideline 2026

- **People with Lynch syndrome (all forms) should be advised to take aspirin**
- **Start (75mg-100mg) 5 years before colonoscopy.**
- **Double the dose if “big”** (E.S.Cardio consensus PMID: 39237457)

- Minimise side effects
  - H Pylori eradication (HEAT Trial PMID: 36335970)
  - blood pressure control (HOT Trial PMID: 9635947)
  - Don’t start after 70 yrs of age (ASPREE trial PMID: 32778876)

Burn et al Lancet Gastro & Hep 2026, Burn and Bishop. Int J Cancer 2026.
Patrono C, Burn J, Patrignani P, Langley R Pharma Reviews 2026 PMID: 41592353

Slippage in coding microsatellites generates predictable novel peptides

Magnus von Knebel Doeberitz

repeat length

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

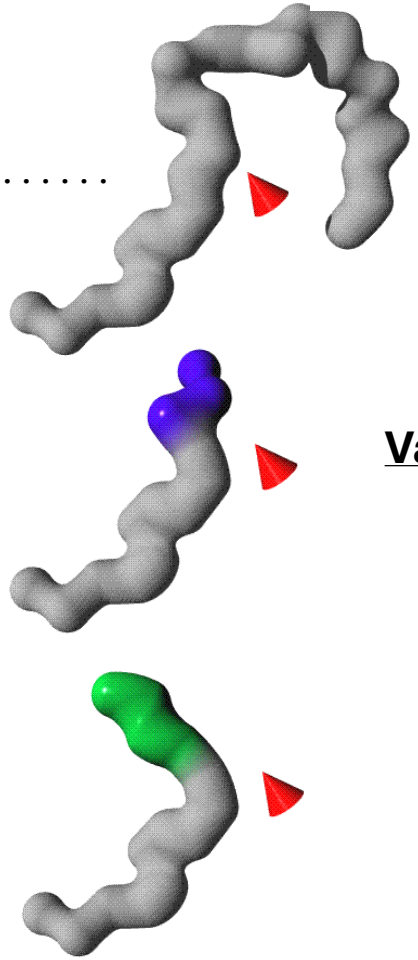
C K K K T C W L A

$(A)_9$ 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



Vaccines?

Micoryx
Nouscom
LynchVax

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

Quick Update

- **Microsatellite Instability (spelling mistakes in repetitive DNA)**
- **Is evidence of a breakdown of MisMatch Repair.**

- **1 in 6 CRCs MSI HIGH**:
- 5FU should be avoided and Immune Checkpoint Inhibitors considered
- **1 in 30 CRCs are the result of an inherited MMR defect: Lynch syndrome**
- **CRC age of onset in LS from 25 (MSH2 & MLH1) and from 35 (MSH6 and PMS2)**

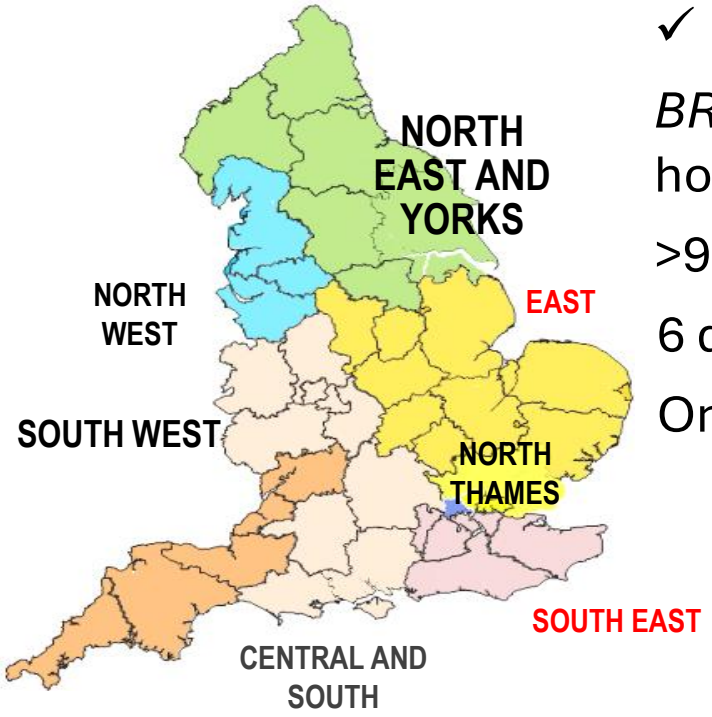
- **2017 NICE: Test all CRCs for evidence of MMR defect and refer for LS test**

- Driver mutations in the Ras pathway mean cetuximab wont work
- BRAF V600E tumours may respond to BRAF inhibitors
- **BRAF V600E is rare in Lynch syndrome: do R210 panel on MSI high BRAF neg cases**

The Newcastle MSI-plus Assay

One CRC test for Lynch syndrome screening and therapy:

UKAS Validation data : North East and Yorkshire Genome Laboratory Hub



microsatellite instability (MSI):

- ✓ accurate assessment of MMR status
- ✓ novel patented marker panel

BRAF and *KRAS/NRAS* mutation hotspots

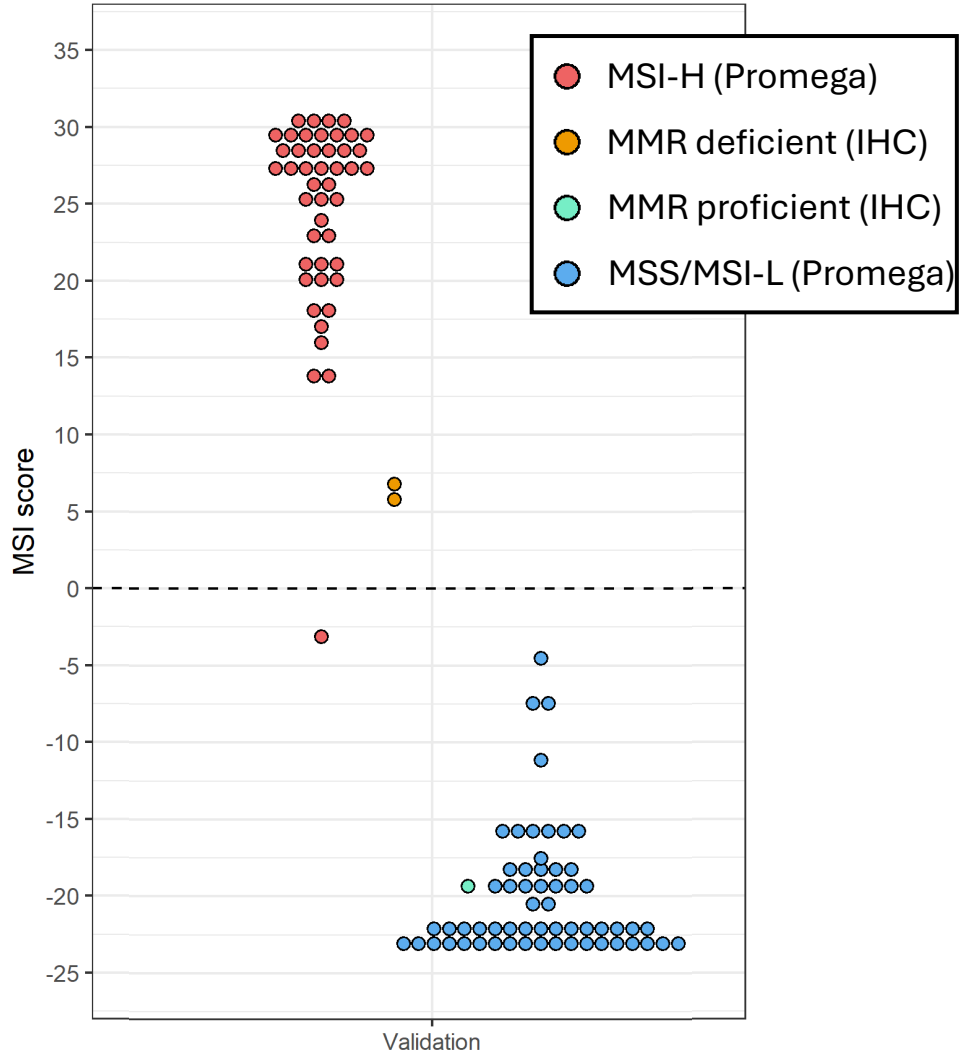
>99% sensitivity and >99% specificity

6 day TAT

One tech per region

Richard Gallon et al
BMJ reports 2024

https://doi.org/10.1038/s44276-024-00072-8



NENC Audit **2025**

109 MSI BRAF negative diagnoses

5 Known Lynch Syndrome

16 Died – no DNA sample

88: 73 (83%) referred

53 germline tested 23 diagnoses (44%)

4 pending

16 failed to complete

Only 2 declined DNA testing

Donna Job
Charlotte Burn

CaPP3

Cancer Prevention Programme

UK PIs

ABERDEEN	Zosia Miedzybrodzka
BELFAST	Patrick Morrison
BIRMINGHAM	Kai Ren Ong
BRISTOL	Alan Donaldson
CAMBRIDGE	Ruth Armstrong
CARDIFF/SWANSEA	Alex Murray
DUNDEE	Jonathan Berg
EDINBURGH	Jennie Murray
EXETER	Ruth Cleaver
GLASGOW	Rosemarie Davidson
GOSH	Ajith Kumar
LEEDS	Alison Kraus
LEICESTER	Julian Barwell
LIVERPOOL	Rachel Hart
LONDON GUYS	Adam Shaw
MANCHESTER	Emma Woodward
NOTTINGHAM	Rachel Harrison
OXFORD	Dorothy Halliday
ROYAL MARSDEN	Zoe Kemp
RHYL	Carrie Pottinger
ST GEORGES	Katie Snape
SHEFFIELD	Jackie Cook
ST MARKS	Huw Thomas
SOUTHAMPTON	Lucy Side
NEWCASTLE	John Burn

& all the research teams at each centre

Official Sponsor

NHS
The Newcastle upon Tyne Hospitals
NHS Foundation Trust

CaPP3 Australia

The Royal Melbourne Hospital

Finlay Macrae
Zafirah Khan
Mary Franich
Ingrid Winship
Alex Boussioutas
Kathy Wu
James Toh
Helen Mar Fan
Louise Lynagh
Isabelle Danos
Cassandra Mcdonald

CaPP3 Finland

ksshp

Jukka-Pekka Mecklin
Kirsi Pylvänäinen
Toni Seppälä
Laura Renkonen-Sinisalo

CaPP3 Spain

NAVARRABIOMED
CENTRO DE INVESTIGACIÓN BIOMÉDICA

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Tel-Aviv Sourasky Medical Center

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Tim Bishop
Faye Elliott

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John Mathers
Richard Gallon
Rachel Phelps
Rebecca Hall

NDRS
NATIONAL DISEASE REGISTRATION SERVICE

AsCaP
Aspirin for Cancer Prevention

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Paola Patrignani Sam Smith

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THE Barbour FOUNDATION

STAND UP TO CANCER™

BAYER

Lynch Syndrome UK

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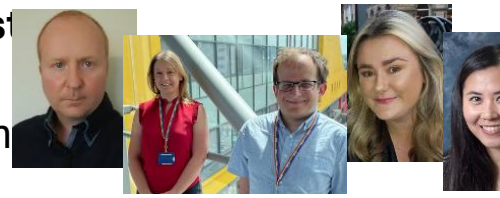

Summary

- GENOMICS: Tumour sequencing targets treatment
- GENETICS: ~20,000 people in our region are at high cancer risk
- VUS's are a big problem for the genomic scientists
- Aspirin PREVENTS cancer and should be offered if risk increased
- MSI – hallmark of MMR deficiency. MSI-Plus="1 stop shop"
  - Targets use of Immune Checkpoint Inhibitors
  - will 5FU or cetuximab work?
  - If BRAF neg, targets 5-6% of CRC and other cancers at high risk of Lynch S.
  - **We missed 20 families last year which will result in avoidable deaths**