Colorectal Cancer - Working in Partnership

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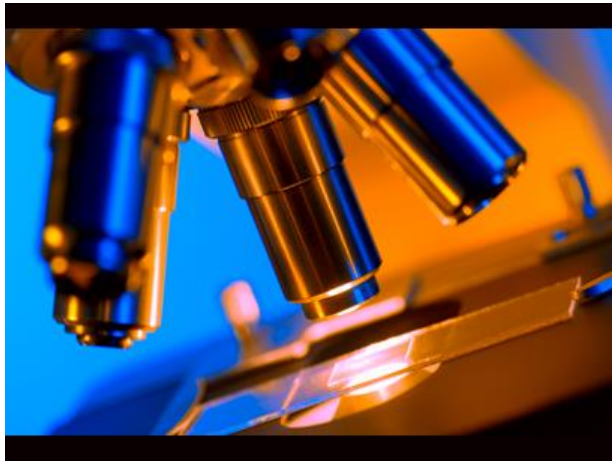
Genetics and Pathology

- National initiatives
- Colorectal cancer
- Inherited CRC
- “Sporadic” CRC
- The “Liquid Biopsy”
- The future?



The Royal College of Pathologists
Pathology: the science behind the cure

The Royal College of Pathologists
Pathology: the science behind the cure

Molecular

2015–2016

CEff 090117 1

Molecular Pathology Evaluation Panel and
Molecular Pathology Consortium
Advice Note

NHS
National
Services
Scotland

MPEP/MPC Advice
January 2016
Test evaluated: On

Molecular Patholog
The Molecular Path
tests for the NHS in
Pathology Consortiu

Status of Advice
The status of MPEP/

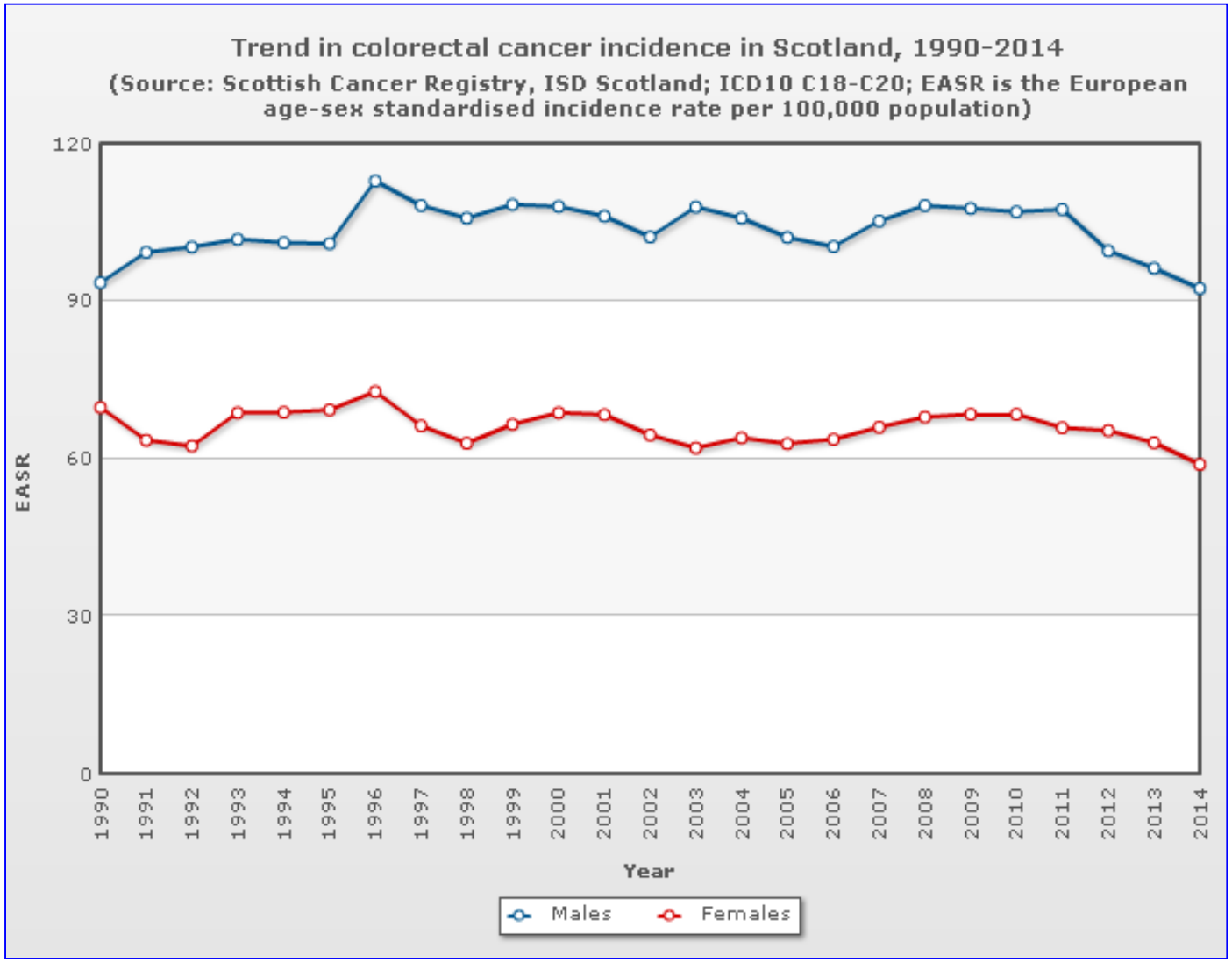
This advice represe
and evaluation of th

Collaboration

Colorectal Cancer

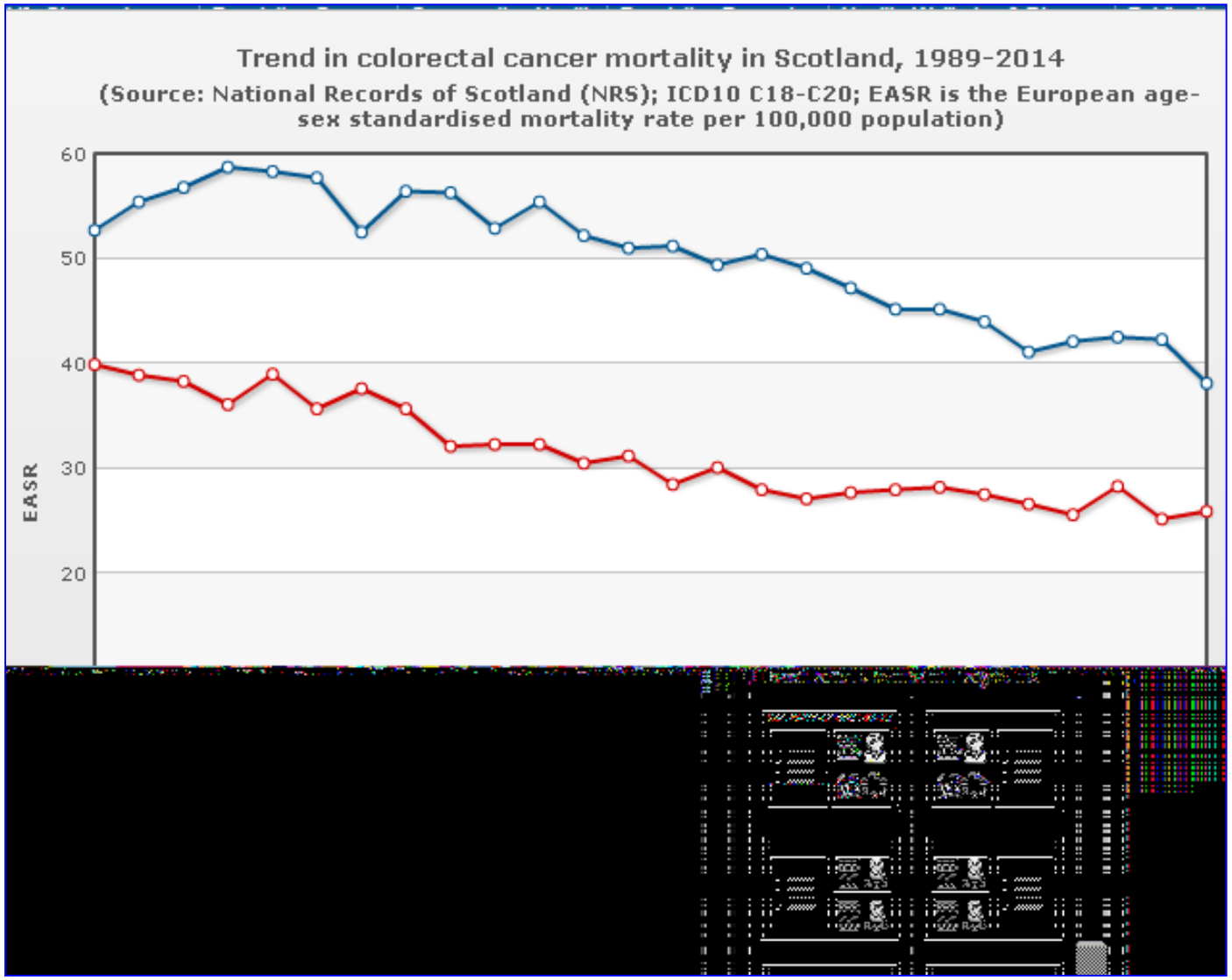
- 4th most common cancer in Scotland
- 3rd most common in terms of mortality
- Life-time risk of developing CRC is between 1 in 15 and 1 in 20.
- Incidence rates in Scotland are falling but still above rest of UK.
- Risk factors include:
  - Obesity
  - Sedentary lifestyle
  - Low fibre diet
  - Smoking and excessive alcohol
  - Inflammatory bowel disease
  - FH of CRC
  - Inherited condition
- 5yr survival has increased over last 20 years
  - 44% (1994); 65% (2014)

Incidence



From the Scottish Public Health Observatory

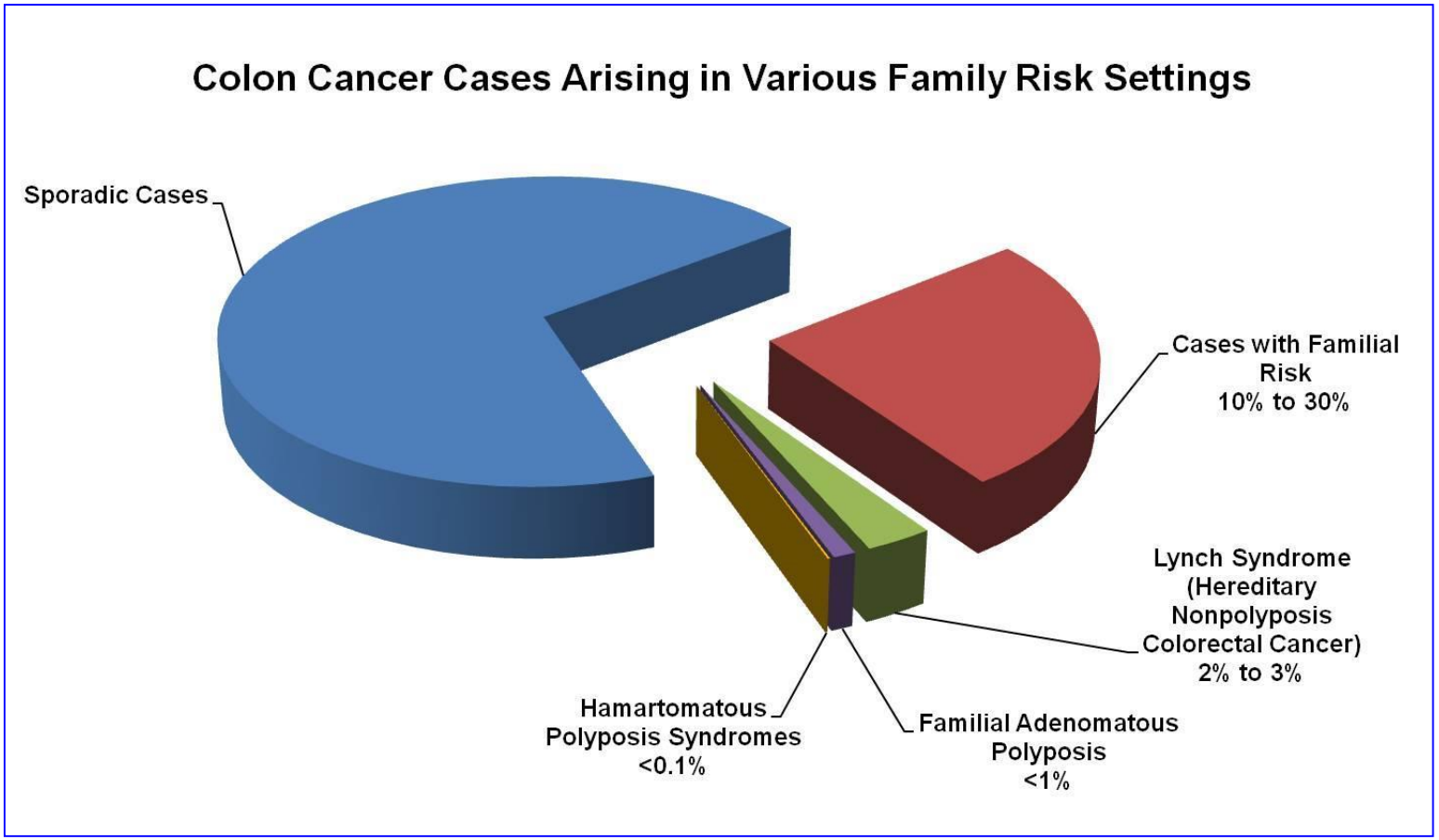
Mortality



From the Scottish Public Health Observatory

All cancer is genetic

But not all cancer is inherited!



From NIH National Cancer Institute

Major colorectal cancer syndromes

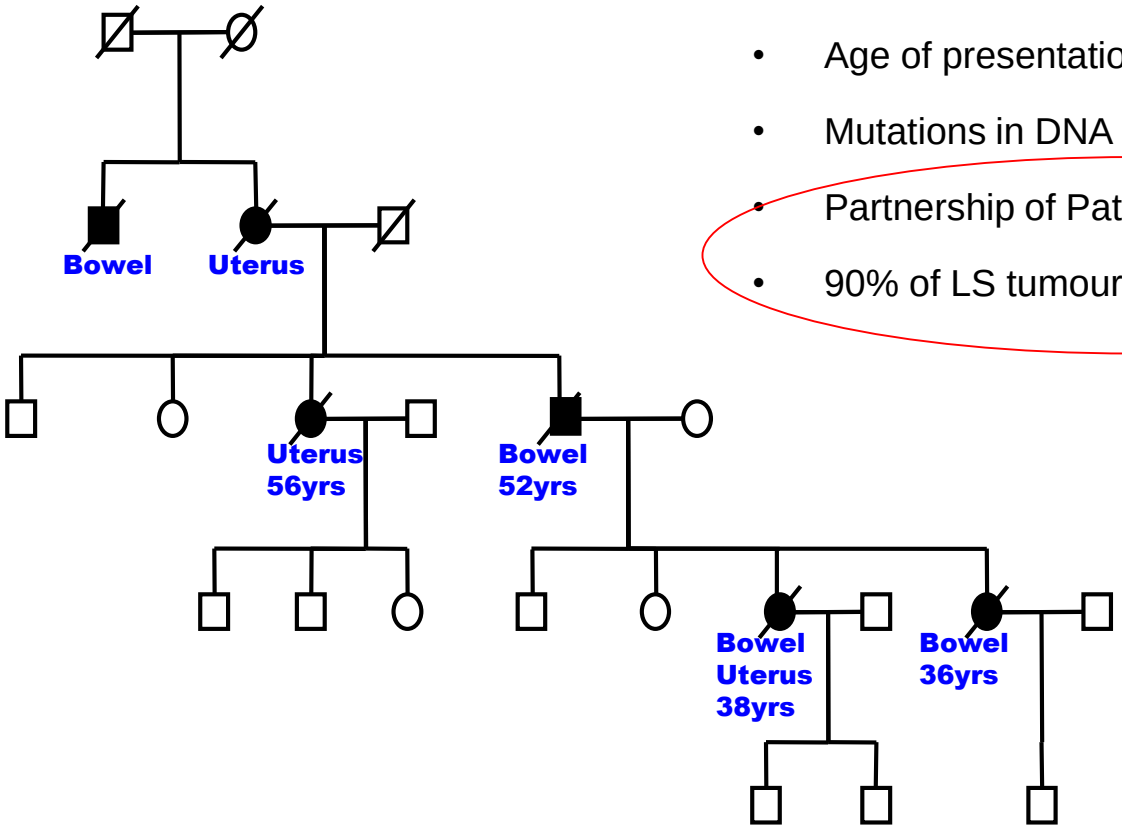
Gene	Syndrome	Inheritance	Major Cancer
APC	Familial adenomatous polyposis	Dominant	Colon, intestine
TP53	Li-Fraumeni	Dominant	Multiple, colon
STK11	Peutz-Jegher	Dominant	Multiple, intestine
PTEN	Cowden	Dominant	Multiple, intestine
BMPR1A	Juvenile polyposis	Dominant	GI
SMAD4	Juvenile polyposis	Dominant	GI
MMR Genes	Lynch	Dominant	Multiple, colon, uterus
MYH	MYH-associated polyposis	Recessive	Colon
POLD1/POLE	Oligopolyposis	Dominant	Colon, endometrial

Table 3. Absolute Risks of Colorectal Cancer for Carriers of Pathogenic Variants in Hereditary Colorectal Cancer Syndromes

Syndrome	Absolute Risk of CRC in Carriers of a Pathogenic Variant
FAP[a]	90% by age 45 y [1]
Attenuated FAP	69% by age 80 y [2]
LS	40% to 80% by age 75 y[b] [3,4]
MYH-associated polyposis	35% to 53% [5]
PJS	39% by age 70 y [6]
JPS	17% to 68% by age 60 y [7,8]

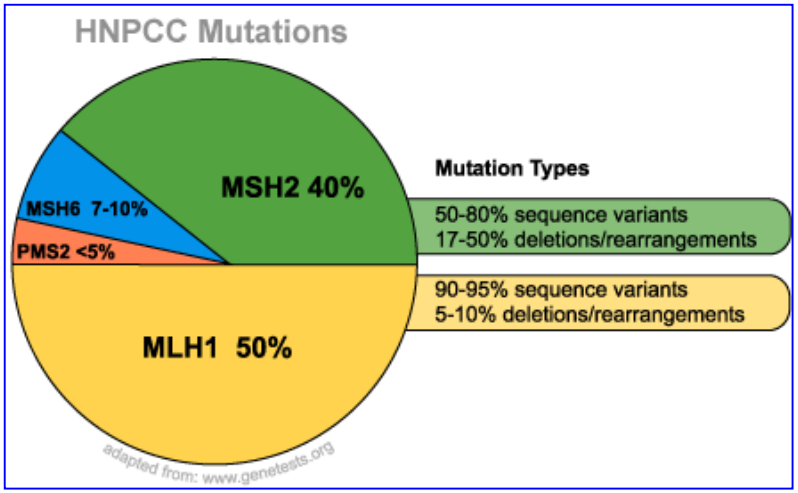
From NIH National Cancer Institute

Lynch syndrome

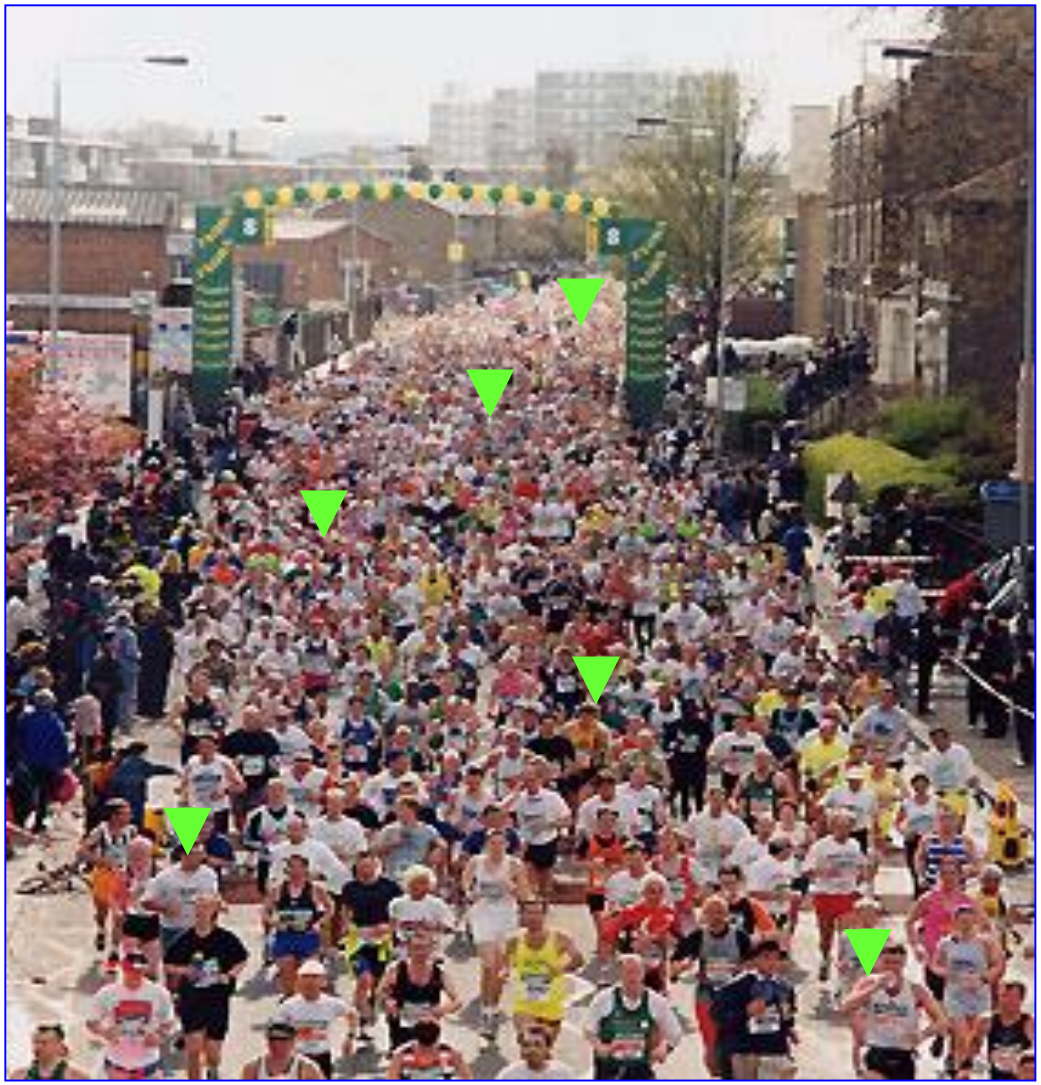


- 10-100s of polyps
- Colonic and extra-colonic tumours
- Predominance of right-sided tumours
- Age of presentation 44-52yrs
- Mutations in DNA MMR genes
- Partnership of Pathology and Genetics
- 90% of LS tumours display instability

Lynch syndrome genes



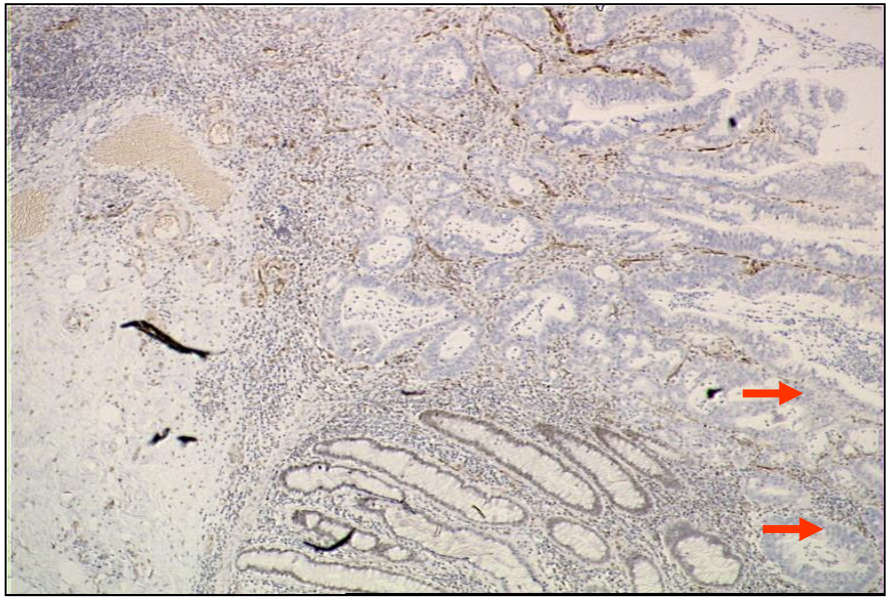
- Protein complex corrects errors in cellular DNA
- Gene mutation results in defective repair and accumulation of genetic alterations
- Manifested by instability at regions of repetitive DNA (microsatellite instability, MSI)
- Testing for MSI effective first line test for MSI

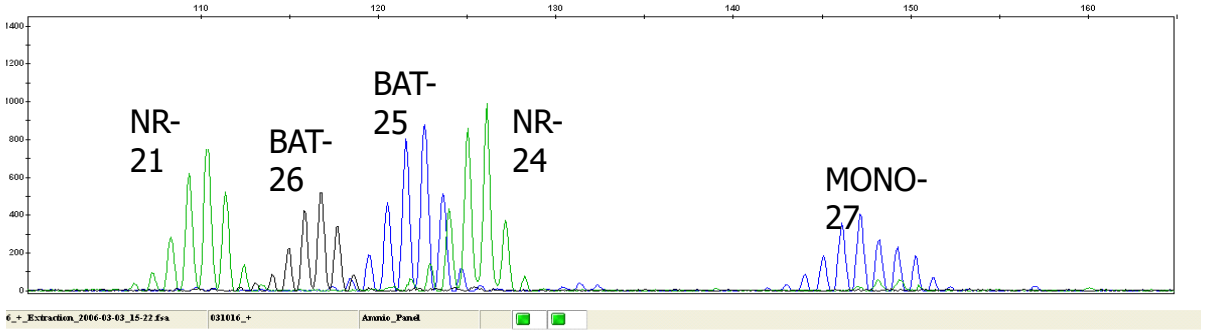


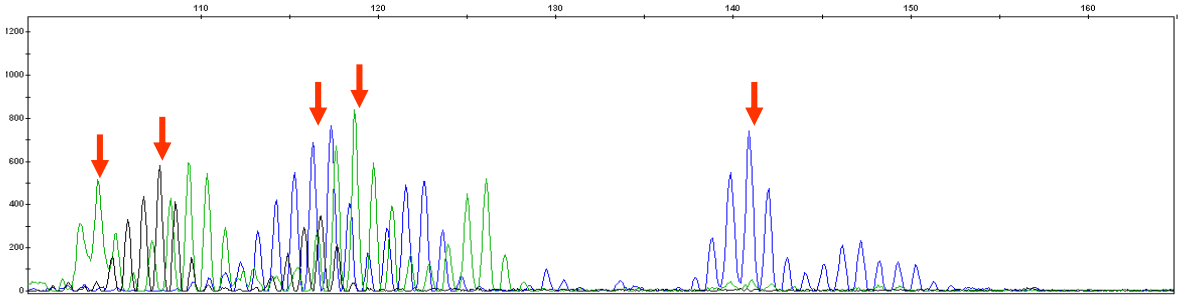
The importance of testing tumours

Pathology and Genetics

Loss of MLH1 staining

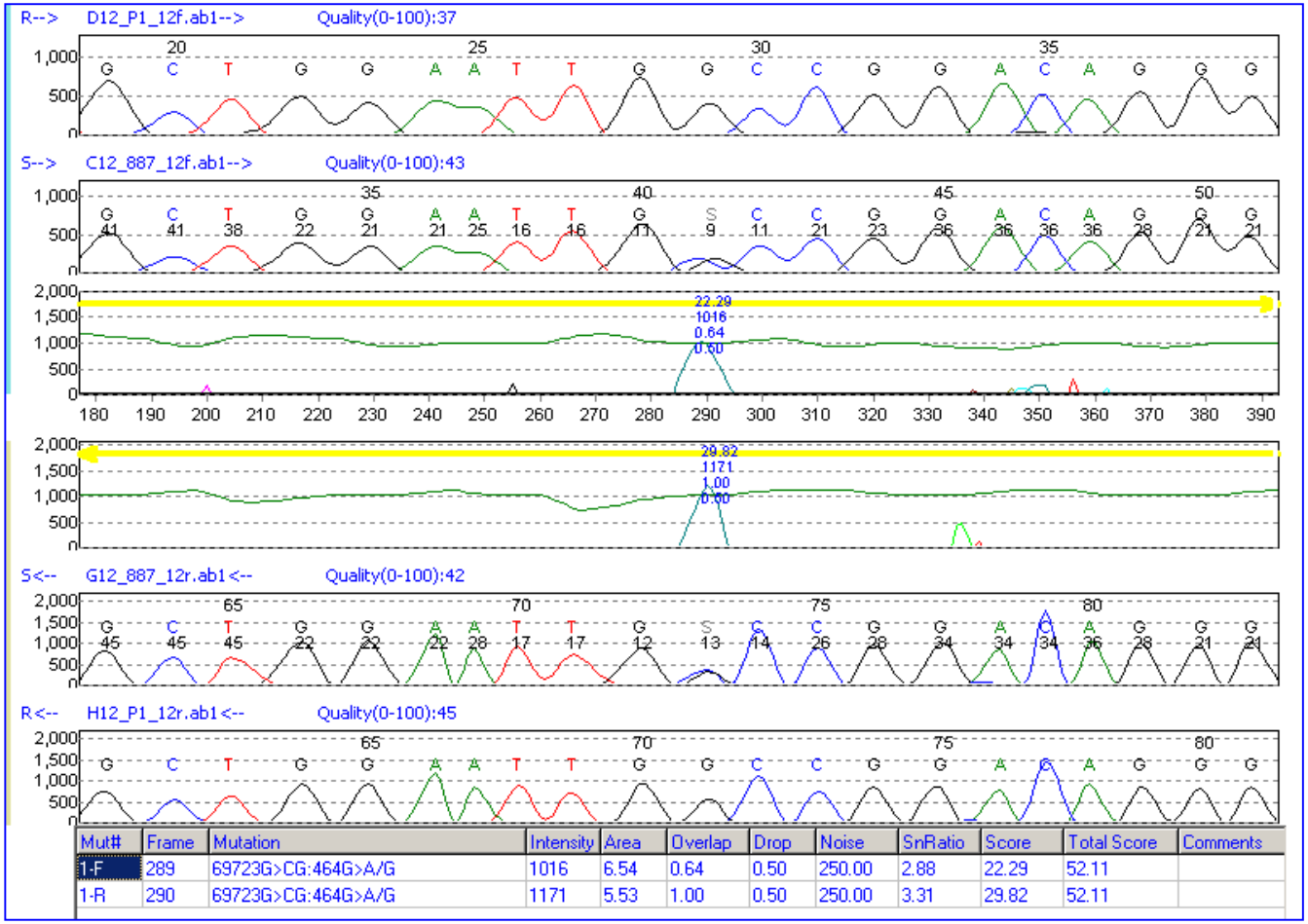






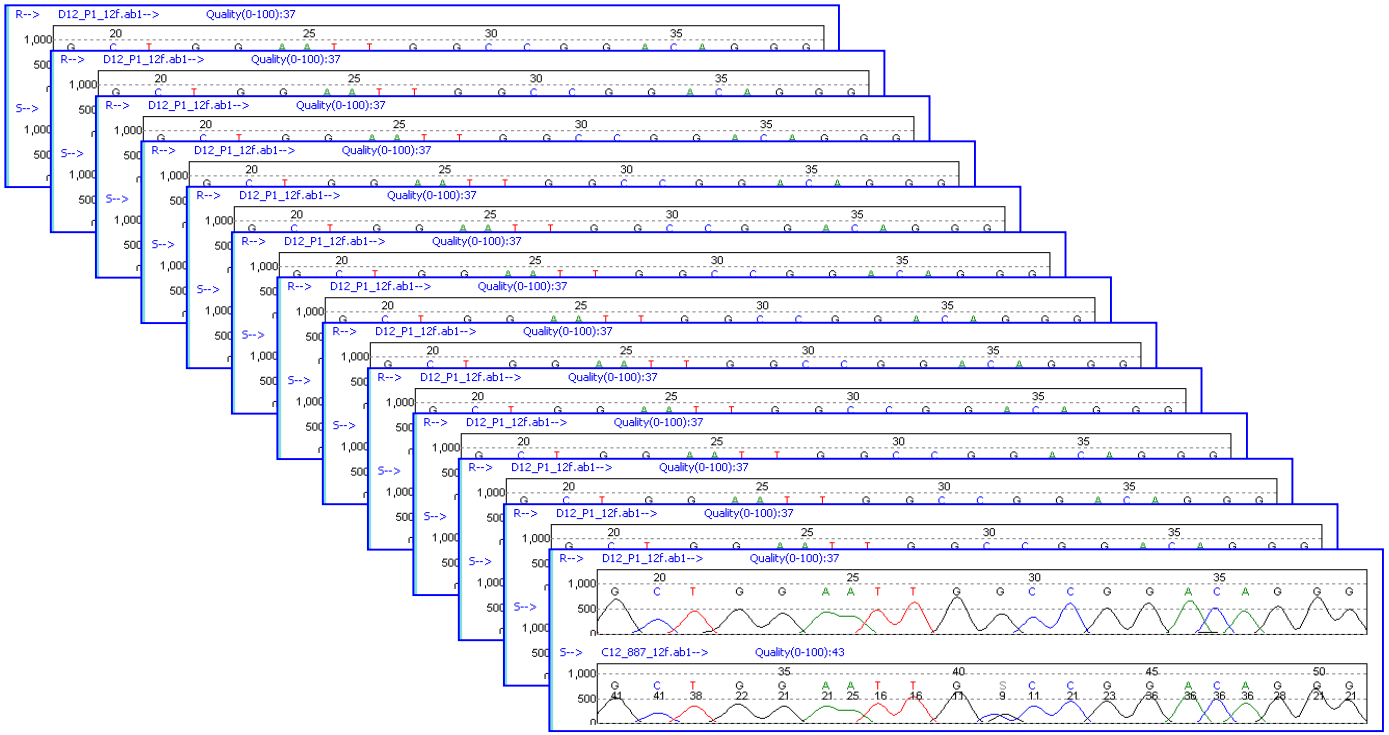
MSI +ve

Targeted sequencing of MLH1



Mut#	Frame	Mutation	Intensity	Area	Overlap	Drop	Noise	SnRatio	Score	Total Score	Comments
1-F	289	69723G>CG:464G>A/G	1016	6.54	0.64	0.50	250.00	2.88	22.29	52.11	
1-R	290	69723G>CG:464G>A/G	1171	5.53	1.00	0.50	250.00	3.31	29.82	52.11	

New sequencing technologies



TruSight Cancer 94-Gene pre-disposition Panel for detecting Germline mutations

AIP	BUB1B	DDB2	EXT2	FANCL	MEN1	PALB2	RB1	SLX4	WRN
ALK	CDC73	DICER1	EZH2	FANCM	MET	PHOX2B	RECQL4	SMAD4	WT1
APC	CDH1	DIS3L2	FANCA	FH	MLH1	PMS1	RET	SMARCB1	XPA
ATM	CDK4	EGFR	FANCB	FLCN	MSH2	PMS2	RHBDF2	STK11	XPC
BAP1	CDKN1C	EPCAM	FANCC	GATA2	MSH6	PRF1	RUNX1	SUFU	
BLM	CDKN2A	ERCC2	FANCD2	GPC3	MUTYH	PRKAR1A	SBDS	TMEM127	
BMPR1A	CEBPA	ERCC3	FANCE	HNF1A	NBN	PTCH1	SDHAF2	TP53	
BRCA1	CEP57	ERCC4	FANCF	HRAS	NF1	PTEN	SDHB	TSC1	
BRCA2	CHEK2	ERCC5	FANCG	KIT	NF2	RAD51C	SDHC	TSC2	
BRIP1	CYLD	EXT1	FANCI	MAX	NSD1	RAD51D	SDHD	VHL	

Sporadic CRC

Molecular testing in CRC aimed at:

- Identifying individuals at high risk of Lynch syndrome

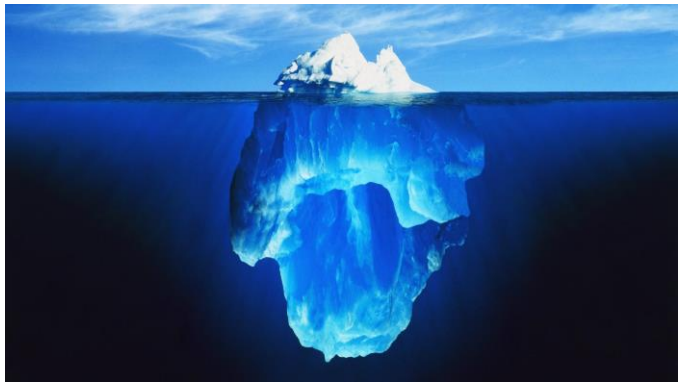
- Biomarkers and targeted treatments for metastatic cancer
  - RAS status and anti-EGFR antibodies

- Identifying tumours that will not respond to chemotherapy

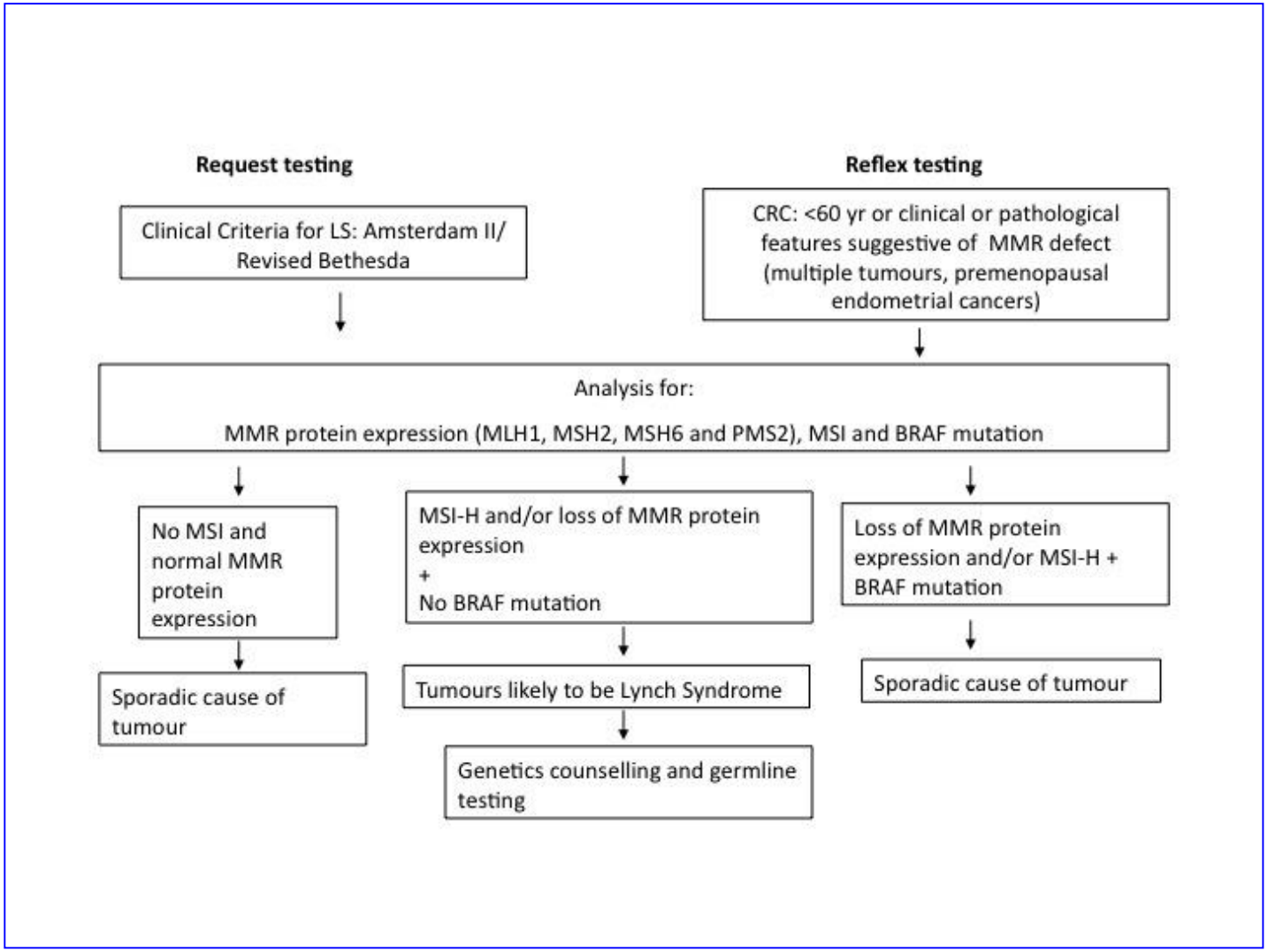
- Providing prognostic indication
  - MSI and BRAF status.

- Targeting NHS resources – drugs can cost up to £100K/patient/year

- Increasing biomarkers across range of cancers



Scottish CRC Pathway



Proposed national testing pathway

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

DIAGNOSTICS ASSESSMENT PROGRAMME

Diagnostics consultation document

Molecular testing strategies for Lynch syndrome in people with colorectal cancer

The National Institute for Health and Care Excellence (NICE) is producing guidance on using molecular testing strategies for Lynch syndrome in people with colorectal cancer in the NHS in England. The diagnostics advisory committee has considered the evidence base and the views of clinical and patient experts.

This document has been prepared for public consultation. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the committee. NICE invites comments from registered stakeholders, healthcare professionals and the public. This document should be read along with the evidence base (the diagnostics assessment report).

The advisory committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound, and a suitable basis for guidance to the NHS?

Equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:

- could have a different effect on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology
- could have any adverse effect on people with a particular disability or

National Institute for Health and Care Excellence Page 1 of 40

Diagnostics consultation document: Molecular testing strategies for Lynch syndrome in people with colorectal cancer

Issue date: October 2016

- *"All people, regardless of age, with colorectal cancer should have tumour-based testing to assess the risk of Lynch syndrome".*
- "*Testing all tumours with IHC/MSI plus BRAF and MLH1 promoter methylation could be a cost effective use of NHS resources".*
- *"IHC and MSI are broadly comparable in clinical accuracy".*

Common biomarkers in CRC

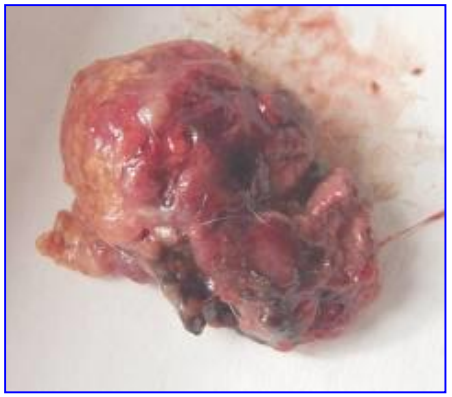
MSI	– prognostic / predictive
RAS	- prognostic / predictive
BRAF	- prognostic / predictive
UGT1A1	- predictive

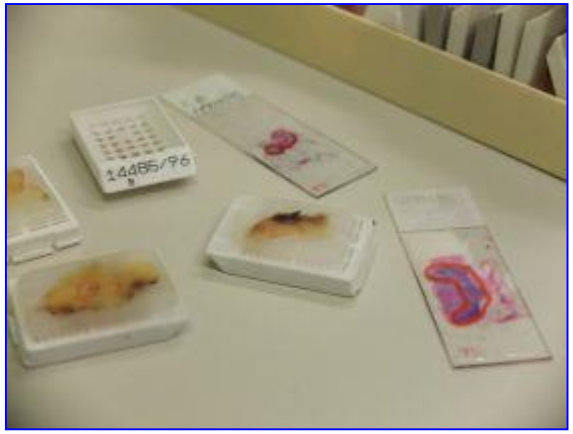
The issue of heterogeneity

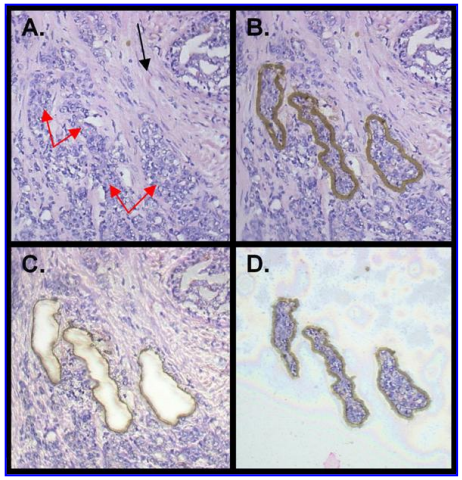
Types of heterogeneity to consider:

- Tissue heterogeneity within the sample
- Genetic heterogeneity within tumour
- Heterogeneity between primary tumour and metastases

Tissue Heterogeneity







Extract DNA and test

BRAF neg

Extract DNA and test

BRAF pos

Genetic heterogeneity revealed by deep sequencing

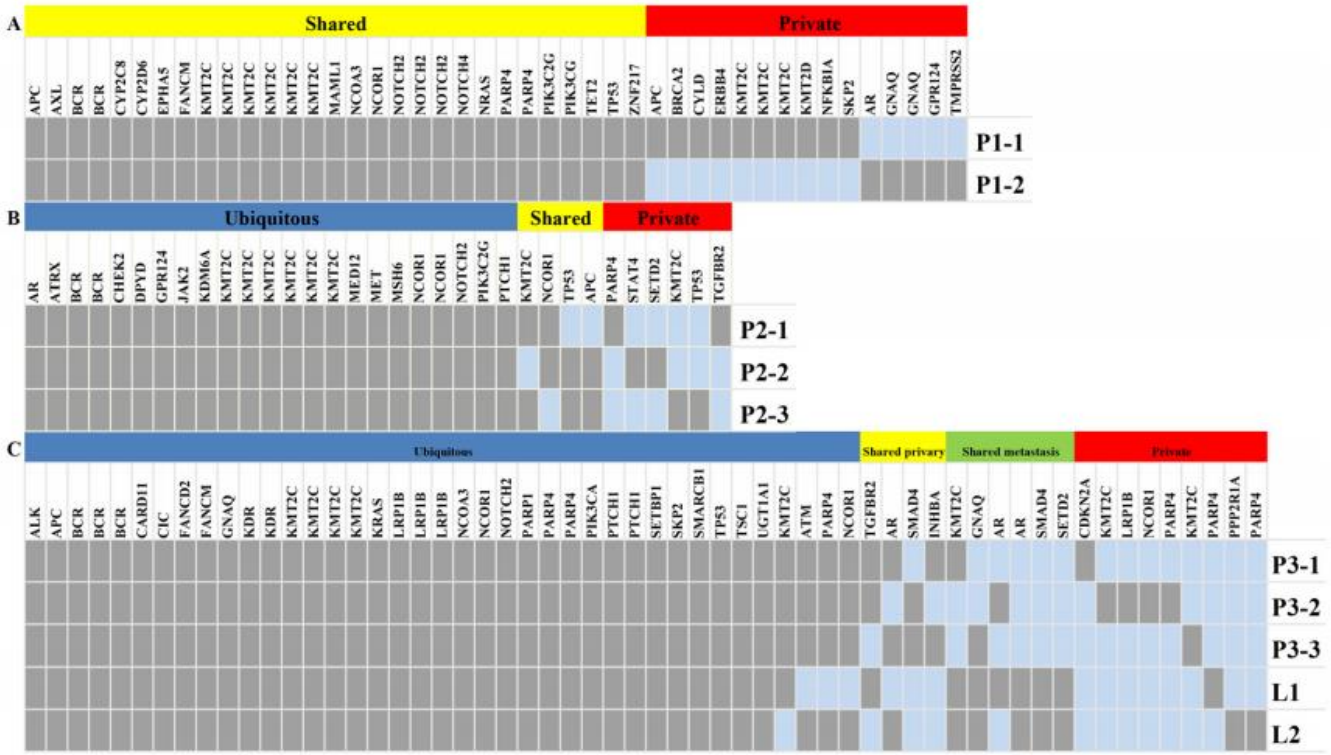
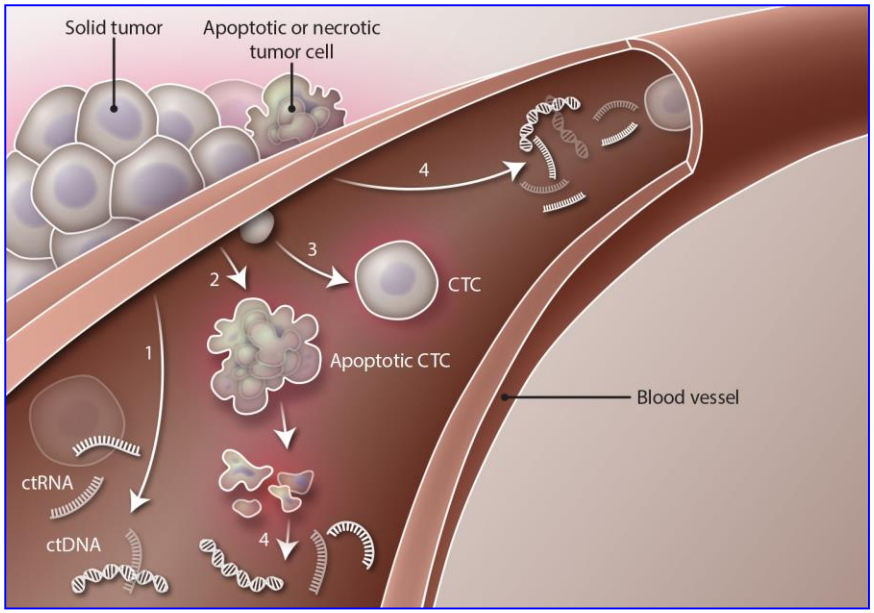


Fig 1. Genetic ITH in three Patient. A Genetic ITH in Patient 1. The regional distribution of 45 somatic variants in 3 primary tumor regions (P1-1 and P1-2); **B Genetic ITH in Patient 2.** The regional distribution of 33 somatic variants in 3 primary tumor regions (P2-1, P2-2, and P2-3); **C Genetic ITH in Patient 3.** The regional distribution of 58 somatic variants in 3 primary and 2 metastatic regions. The heat map indicates the presence (gray) or absence (dark blue) of a mutation in each region. The color bars above the heat map specify the categories of mutations.

doi:10.1371/journal.pone.0152673.g001

Lu *et al*, 2016

The Liquid Biopsy – circulating tumour DNA

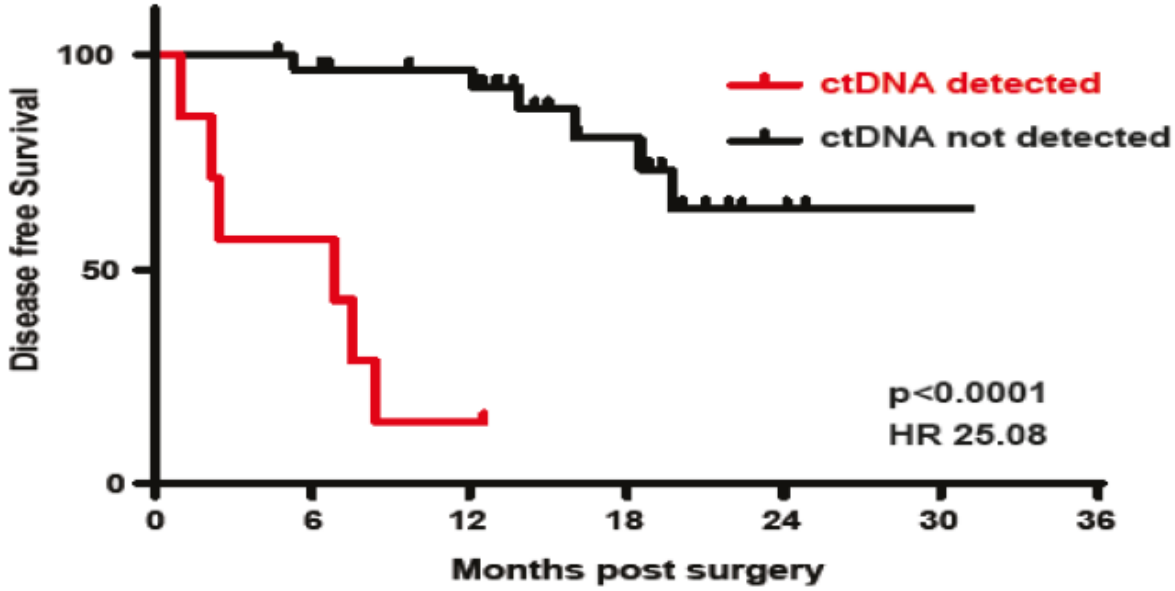


- Relatively non-invasive
- Ideal for difficult cases
- ctDNA relatively easy to extract
- Heterogeneity not such an issue
- Requires sensitive detection methodology

ctDNA - Applications

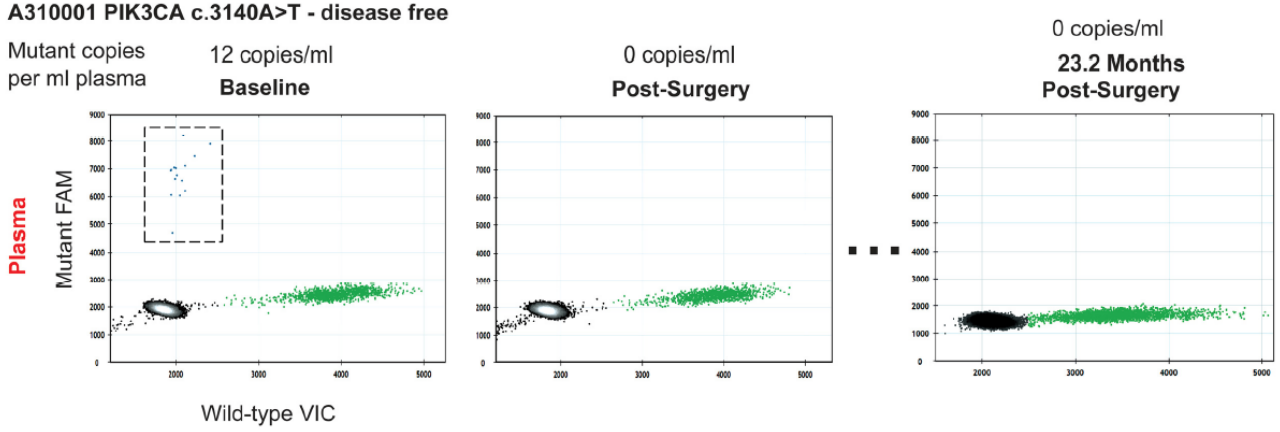
- Screening tool – early diagnosis
- Monitoring residual disease
- Monitor response to therapy
- Monitor emergence of resistance
- Prognostic marker
- Genetic and epigenetic biomarkers

Predicting early relapse – single post surgery



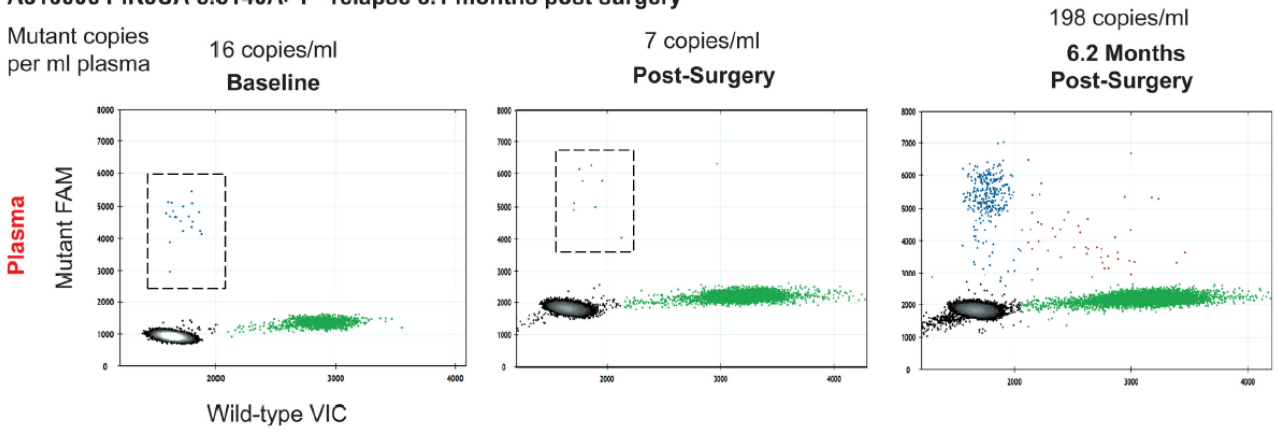
Tracking mutations in plasma DNA

A310001 PIK3CA c.3140A>T - disease free



Tracking mutations in plasma DNA

A310006 PIK3CA c.3140A>T - relapse 8.1 months post surgery



Thank you