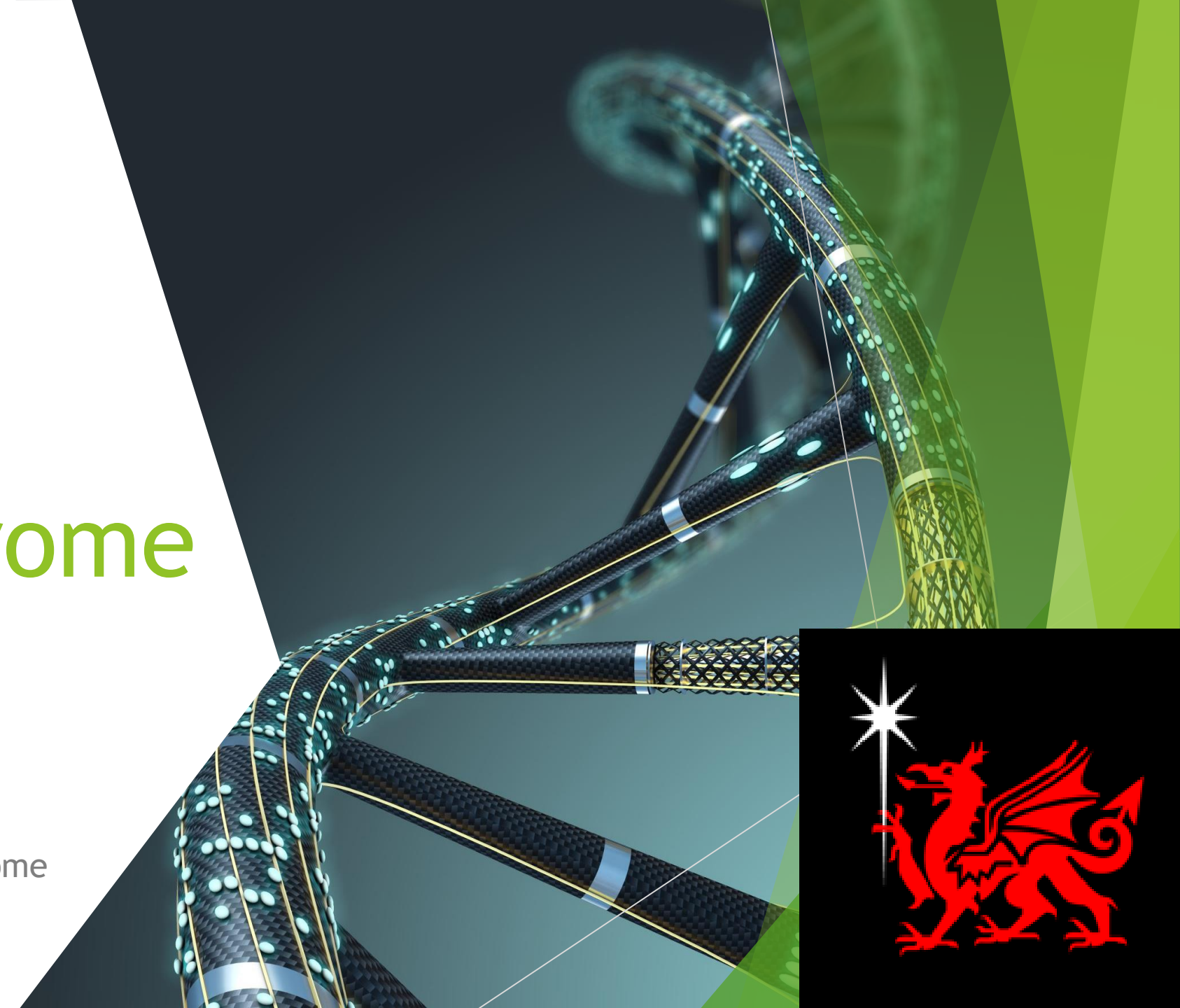
Lynch syndrome

Neil Ryan

University of Bristol

St Michael's Hospital Bristol

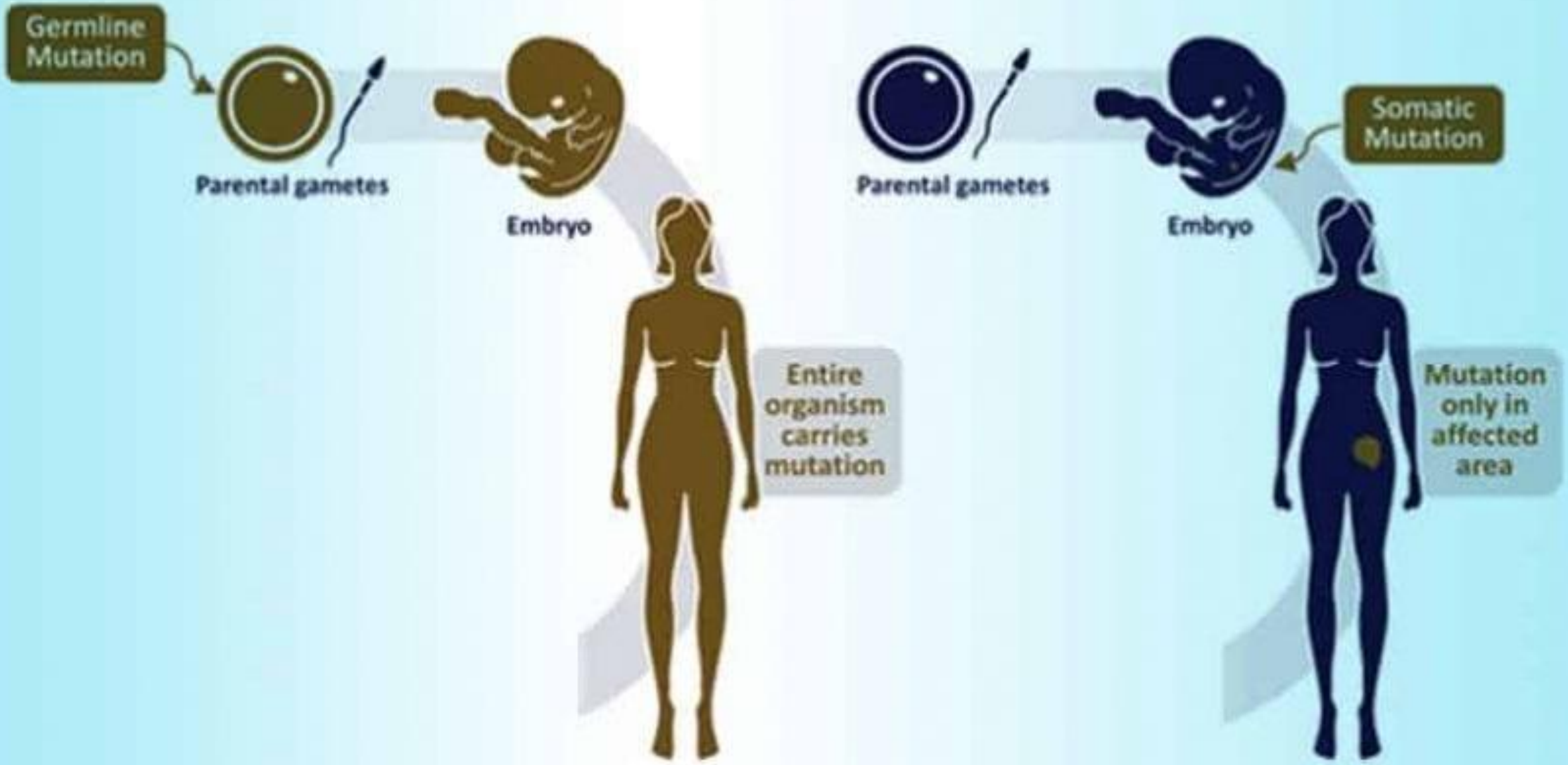
Southwest GMSA Lead for Lynch syndrome



Genomics vs Genetics

- The study of an organism's complete set of genetic information.
- The genome includes both genes (coding) and non-coding DNA.
- 'Genome': the complete genetic information of an organism.

- The study of heredity
- The study of the function and composition of single genes.
- 'Gene': specific sequence of DNA that codes for a functional molecule.


Germline Mutation
Parental gametes
Embryo
Entire organism carries mutation
Parental gametes
Somatic Mutation
Embryo
Mutation only in affected area

What is Lynch syndrome

What is Lynch syndrome?

Lynch syndrome is an autosomal dominant cancer predisposition syndrome arising from a dysfunctional DNA mismatch repair (MMR) system

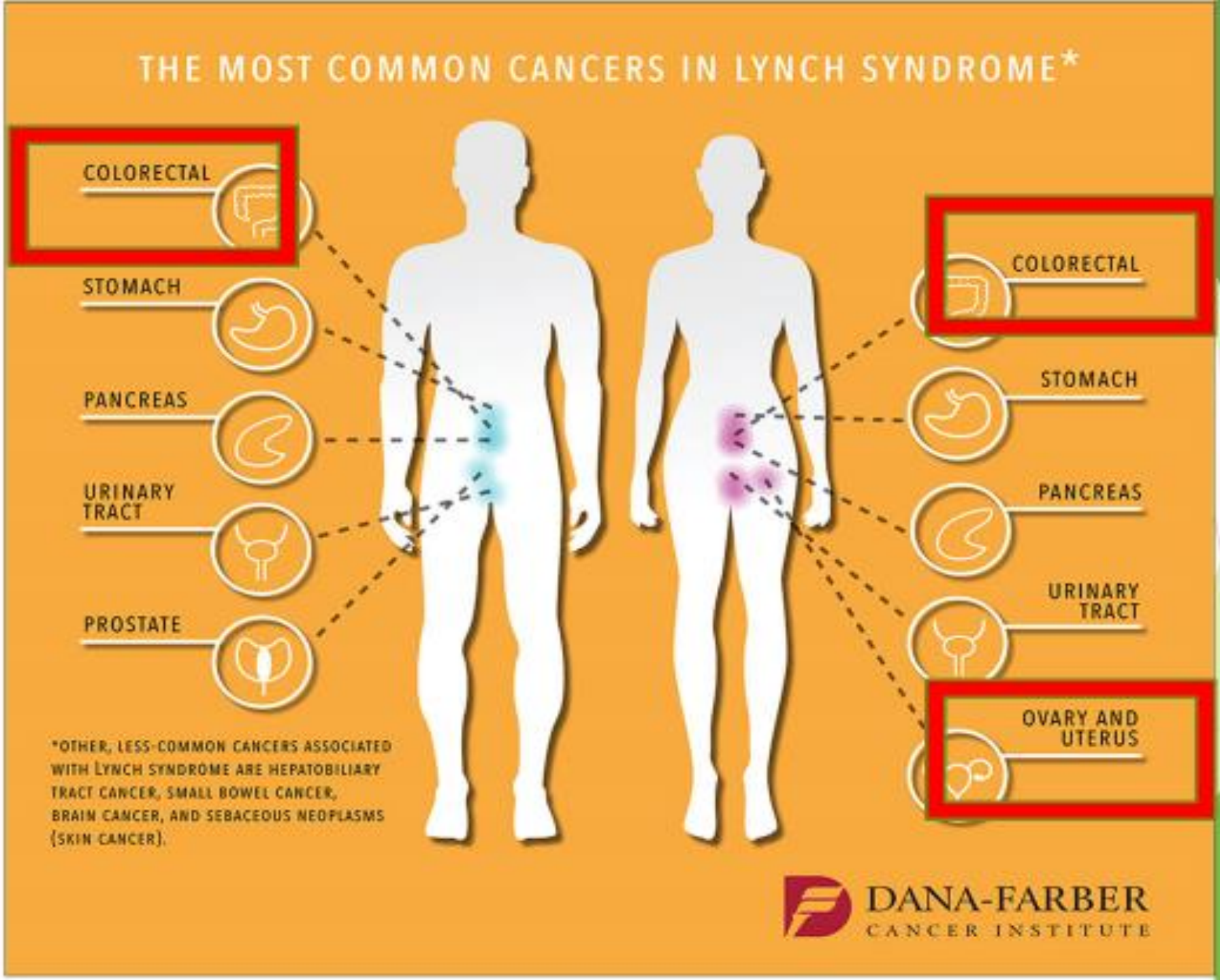
Up to 95% of Lynch syndrome carriers are unaware

Lynch syndrome may occur in up to

1 in 278

people

making it the most common inherited cause of cancer


THE MOST COMMON CANCERS IN LYNCH SYNDROME*
COLORECTAL
STOMACH
PANCREAS
URINARY TRACT
PROSTATE
COLORECTAL
STOMACH
PANCREAS
URINARY TRACT
OVARY AND UTERUS
*OTHER, LESS-COMMON CANCERS ASSOCIATED WITH LYNCH SYNDROME ARE HEPATOBILIARY TRACT CANCER, SMALL BOWEL CANCER, BRAIN CANCER, AND SEBACEOUS NEOPLASMS (SKIN CANCER).
DANA-FARBER
CANCER INSTITUTE

1994

1993

1991

1987

1966

1913

Cell, Vol. 75, 1027–1038, December 3, 1993, Copyright © 1993 by Cell Press

The Human Mutator Gene Homolog *MSH2* and Its Association with Hereditary Nonpolyposis Colon Cancer

Mutation of a *mutL* Homolog in Hereditary Colon Cancer

Nickolas Papadopoulos,* Nicholas C. Nicolaides,* Ying-Fei Wei, Steven M. Ruben, Kenneth C. Carter, Craig A. Rosen,

Ubiquitous somatic mutations in simple repeated sequences reveal a new mechanism for colonic carcinogenesis

Yurij Ionov*, Miguel A. Peinado*†, Sergei Malkhosyan*, Darryl Shibata‡ & Manuel Perucho*§

Genetic Mapping of a Locus Predisposing to Human Colorectal Cancer

Päivi Peltomäki,* Lauri A. Aaltonen,* Pertti Sistonen, Lea Pylkkänen, Jukka-Pekka Mecklin, Heikki Järvinen, Jane S. Green, Jeremy R. Jass, James L. Weber, Fredrick S. Leach, Gloria M. Petersen, Stanley R. Hamilton, Albert de la Chapelle,† Bert Vogelstein†

Clues to the Pathogenesis of Familial Colorectal Cancer

Lauri A. Aaltonen,* Päivi Peltomäki,* Fredrick S. Leach,* Pertti Sistonen, Lea Pylkkänen, Jukka-Pekka Mecklin, Heikki Järvinen, Steven M. Powell, Jin Jen, Stanley R. Hamilton, Gloria M. Petersen, Kenneth W. Kinzler, Bert Vogelstein,† Albert de la Chapelle†

Destabilization of tracts of simple repetitive DNA in yeast by mutations affecting DNA mismatch repair

Micheline Strand*, Tomas A. Prolla†§, R. Michael Liskay‡§ & Thomas D. Petes*

* Department of Biology and Curriculum in Genetics and Molecular Biology, University of North Carolina, Chapel Hill, North Carolina 27599-3280, USA
† Department of Molecular Biophysics and Biochemistry and ‡ Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, Connecticut 06510-3219, USA

Volume 15 Number 13 1987 Nucleic Acids Research

High frequencies of short frameshifts in poly-CA/TG tandem repeats borne by bacteriophage M13 in *Escherichia coli* K-12

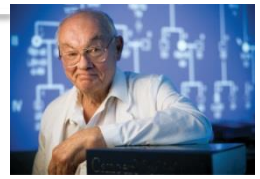
Gene Levinson* and George A.Gutman

Department of Microbiology and Molecular Genetics, University of California, Irvine, CA 92717, USA

Received March 9, 1987; Accepted June 2, 1987

Amsterdam I

- At least three family members must have histologically confirmed colorectal cancer:
- One must be a first-degree relative of the other two;
- At least two consecutive generations must be affected;
- At least one of the CRC cases must have been diagnosed before age 50;
- Familial adenomatous polyposis must be excluded.



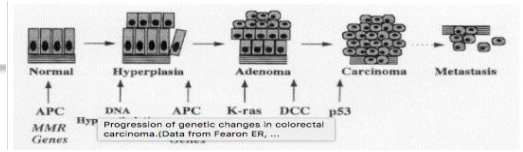
Methylation of the *hMLH1* Promoter Correlates with Lack of Expression of hMLH1 in Sporadic Colon Tumors and Mismatch Repair-defective Human Tumor Cell Lines[1]

A National Cancer Institute Workshop on Hereditary Nonpolyposis Colorectal Cancer Syndrome: meeting highlights and Bethesda guidelines.

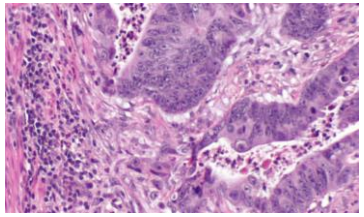
1997

Germline mutation of *MSH6* as the cause of hereditary nonpolyposis colorectal cancer

1995



Mutation in the DNA mismatch repair gene homologue *hMLH 1* is associated with hereditary non-polyposis colon cancer



1994

Surveillance in Lynch syndrome: how aggressive?

Lanspa SJ[1], Jenkins JX, Cavalieri RJ, Smyrk TC, Watson P, Lynch J, Lynch HT.

2010

ORIGINAL CONTRIBUTION

Comparison of Extended Colectomy and Limited Resection in Patients With Lynch Syndrome

Nagendra Natarajan, M.D., M.P.H.[1] • Patrice Watson, Ph.D.[2]
Edibaldo Silva-Lopez, M.D., Ph.D.[3] Henry T. Lynch, M.D.[4]

2008

Feasibility of Screening for Lynch Syndrome Among Patients With Colorectal Cancer

Heather Hampel, Wendy L. Frankel, Edward Martin, Mark Arnold, Karamjit Khanduja, Philip Kuebler, Mark Clendenning, Kaisa Sotamaa, Thomas Prior, Judith A. Westman, Jenny Panescu, Dan Fix, Janet Lockman, Jennifer LaJeunesse, Ilene Comeras, and Albert de la Chapelle

2005

DNA Mismatch Repair-dependent Response to Fluoropyrimidine-generated Damage*

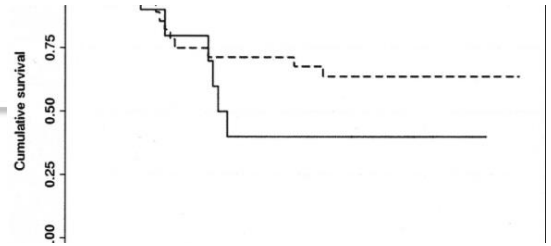
Received for publication, October 26, 2004, and in revised form, November 29, 2004
Published, JBC Papers in Press, December 14, 2004, DOI 10.1074/jbc.M412105200

2004

Mutations associated with HNPCC predisposition – Update of ICG-HNPCC/INSiGHT mutation database

Päivi Peltomäki[a,*] and Hans Vasen[b]
[a]*Department of Medical Genetics, University of Helsinki, Helsinki, Finland*
[b]*The Netherlands Foundation for the Detection of Hereditary Tumours and Department of Gastroenterology, Leiden University Medical Centre, The Netherlands*

1998



2016

BOWEL CANCER UK

Help us to STOP bowel cancer

Home | About bowel cancer | Research | Campaigns | Support us

Home / Media centre / News / NICE recommends all bowel cancer patients to be tested for Lynch Syndrome

NICE recommends all bowel cancer patients to be tested for Lynch Syndrome

Today (Friday 21 October) the National Institute for Health and Care Excellence have announced draft guidance recommending that everyone who is diagnosed with bowel cancer should be tested for Lynch syndrome. This is good news as this genetic condition increases a person's risk of a bowel cancer diagnosis by up to 80% in some cases.

2014

Lynch Syndrome UK

LYNCH SYNDROME UK

Registered Charity 1161840

2014

Application of a five-tiered scheme for standardized classification of 2,360 unique mismatch repair gene variants lodged on the InSiGHT locus-specific database

2013

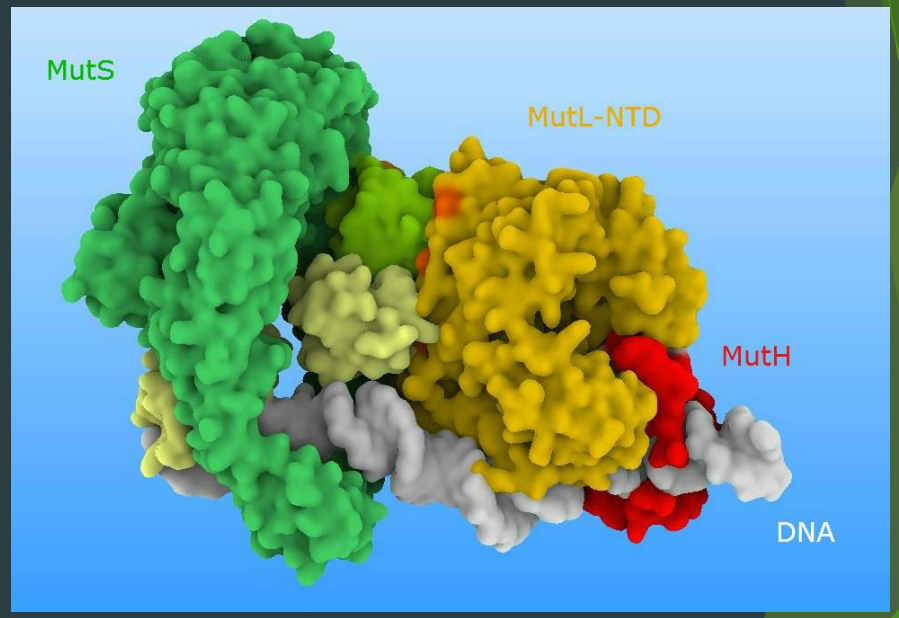
Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts

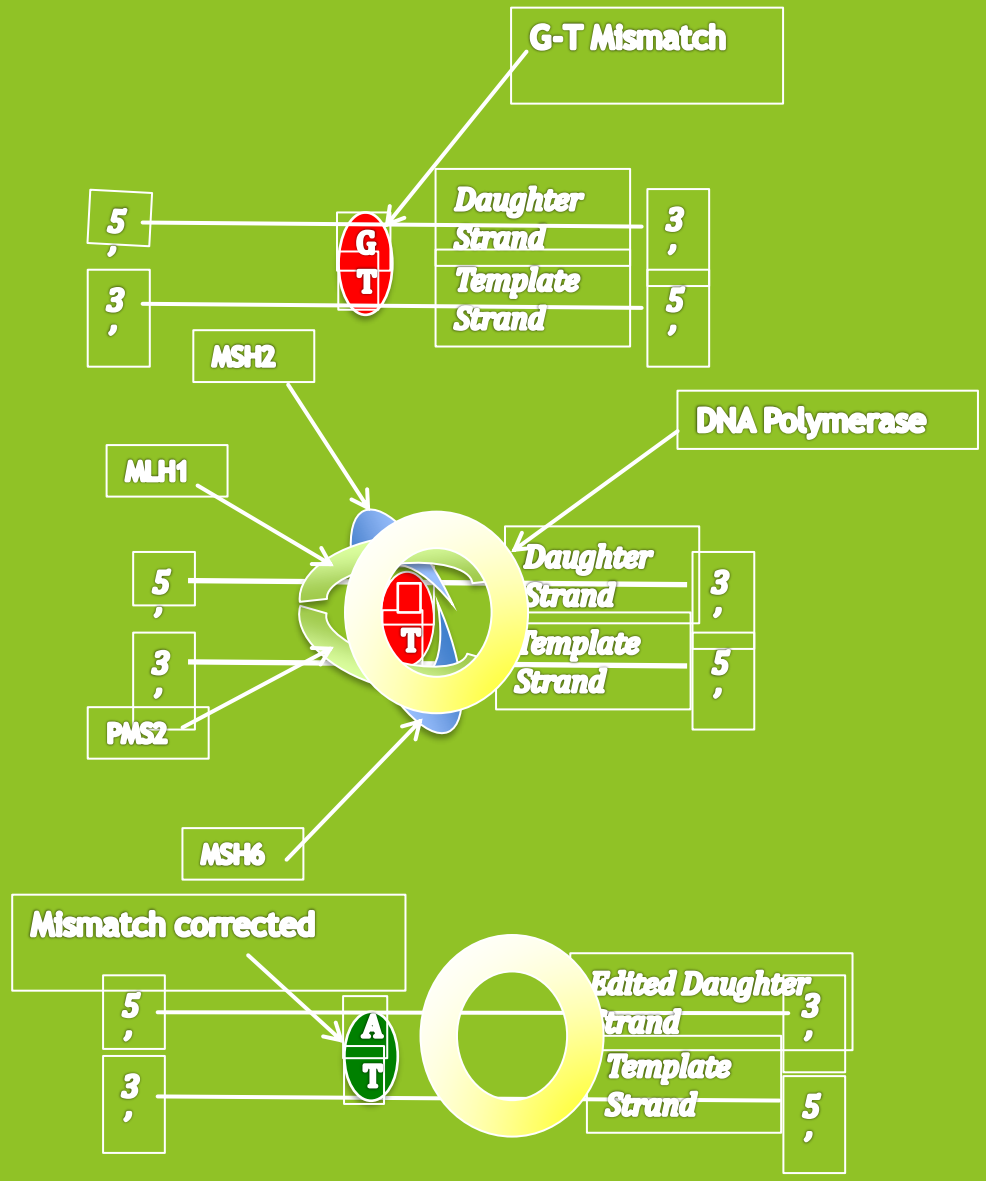
2011

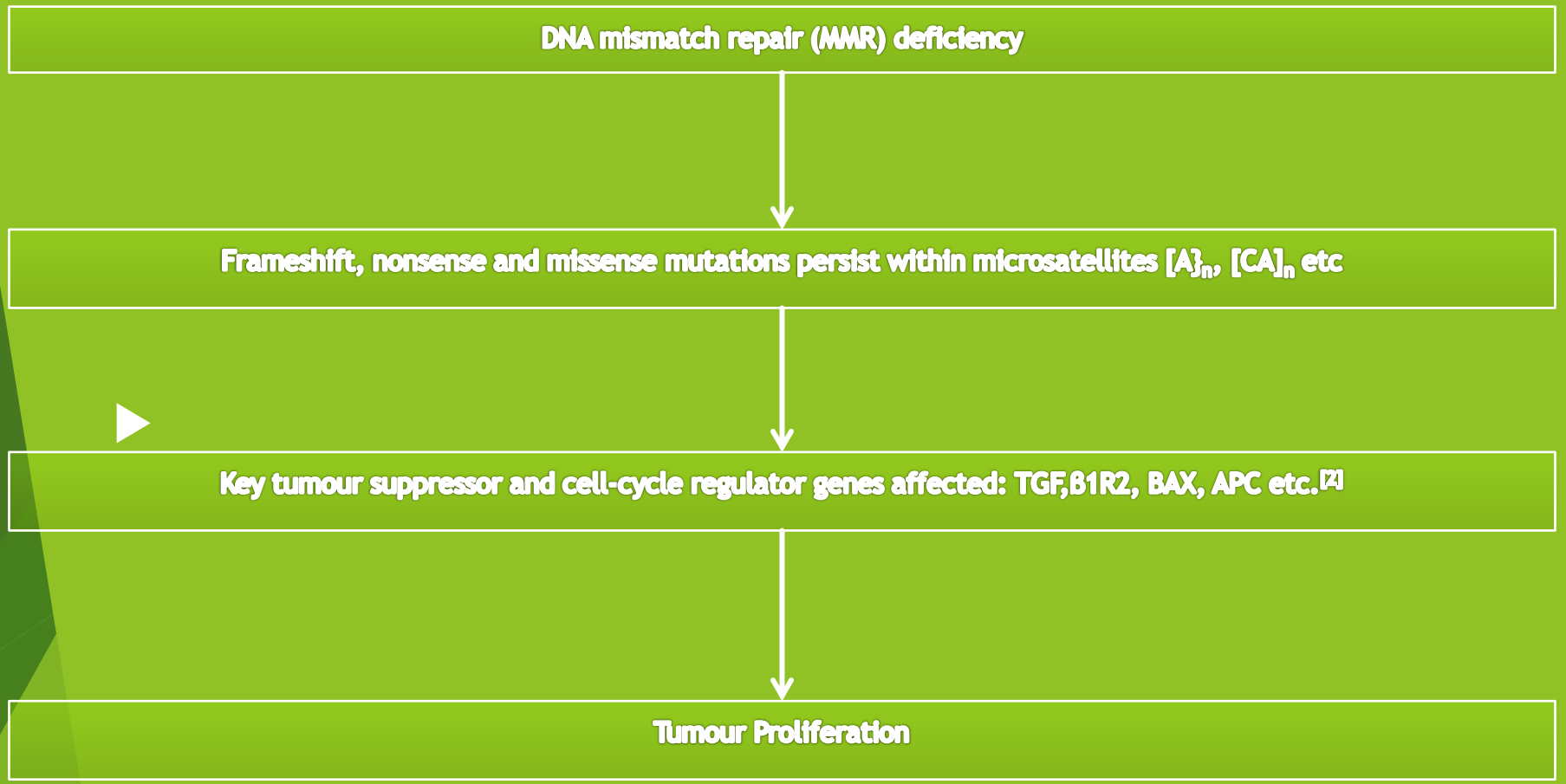
Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial

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 G 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

Mismatch repair (MMR) system

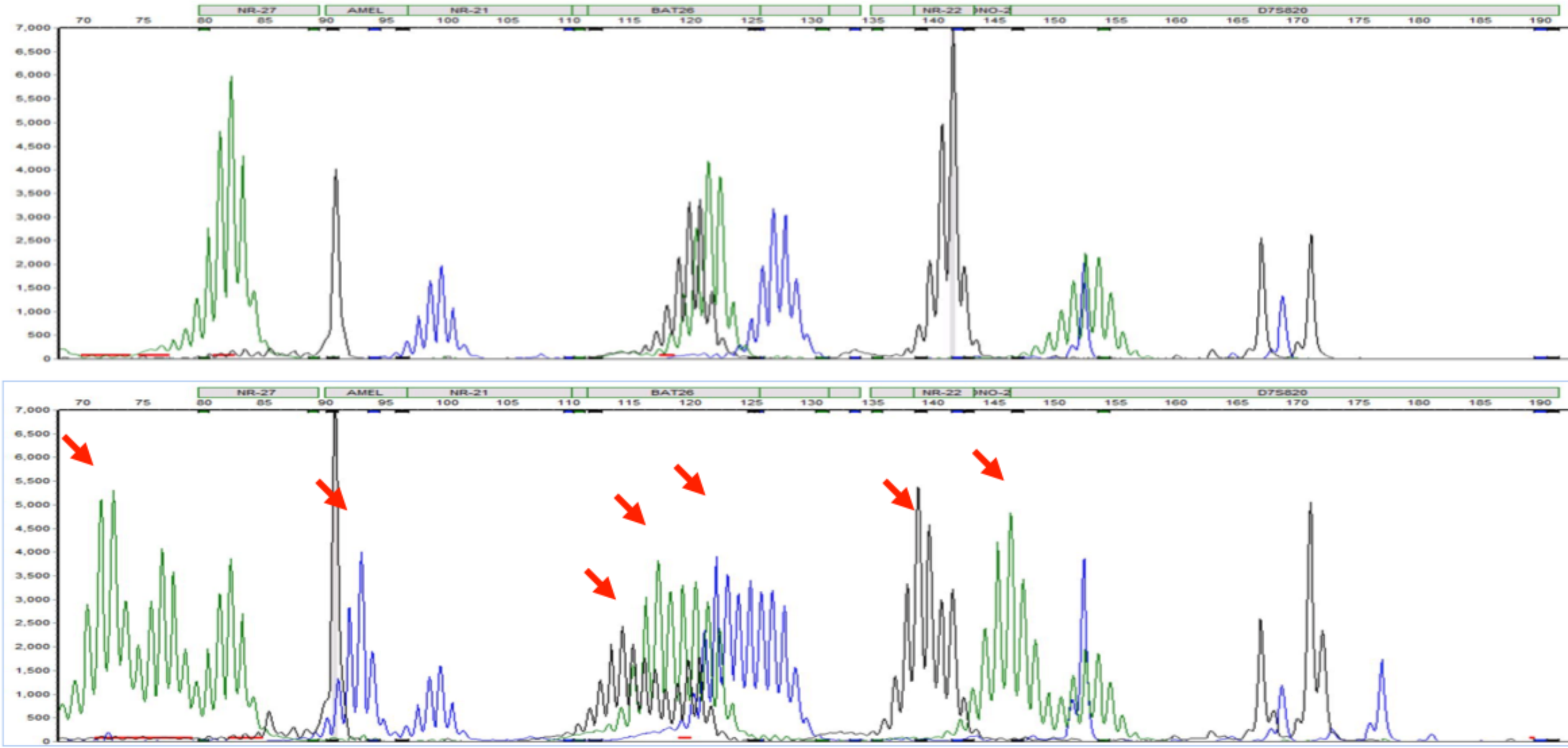


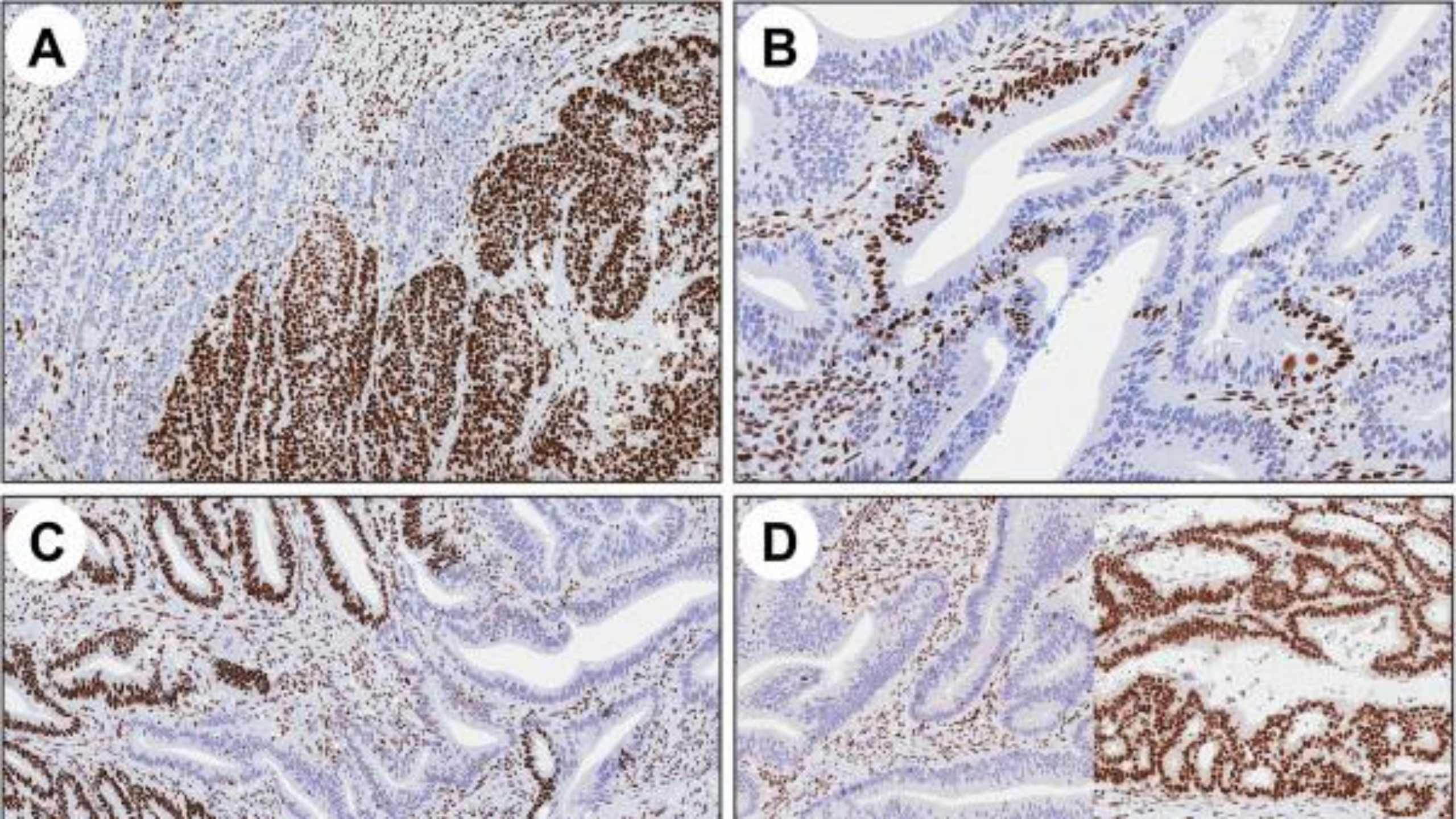


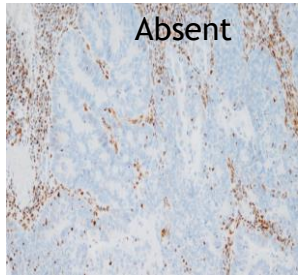

DNA mismatch repair (MMR) deficiency
Frameshift, nonsense and missense mutations persist within microsatellites $[A]_n$, $[CA]_n$ etc
Key tumour suppressor and cell-cycle regulator genes affected: TGFβ1R2, BAX, APC etc.[2]
Tumour Proliferation

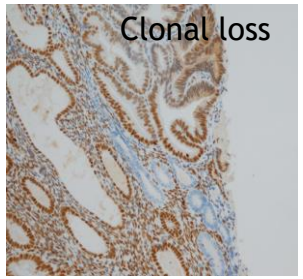
Testing for Lynch syndrome

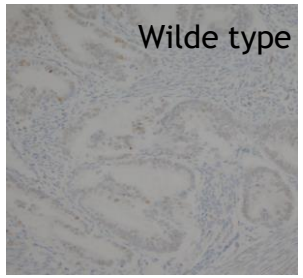
Detection of MSI in tumor tissues using the PrecisionPlex™ MSI detection system

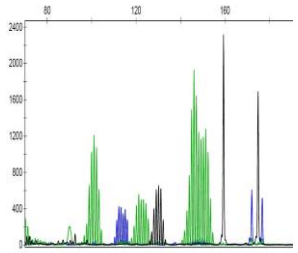


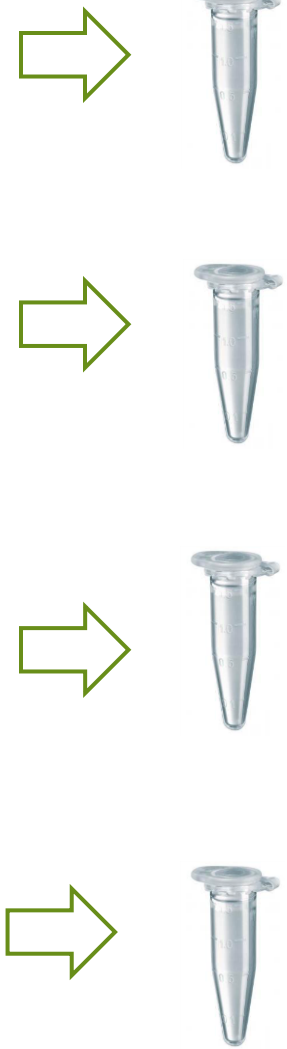

A
B
C
D

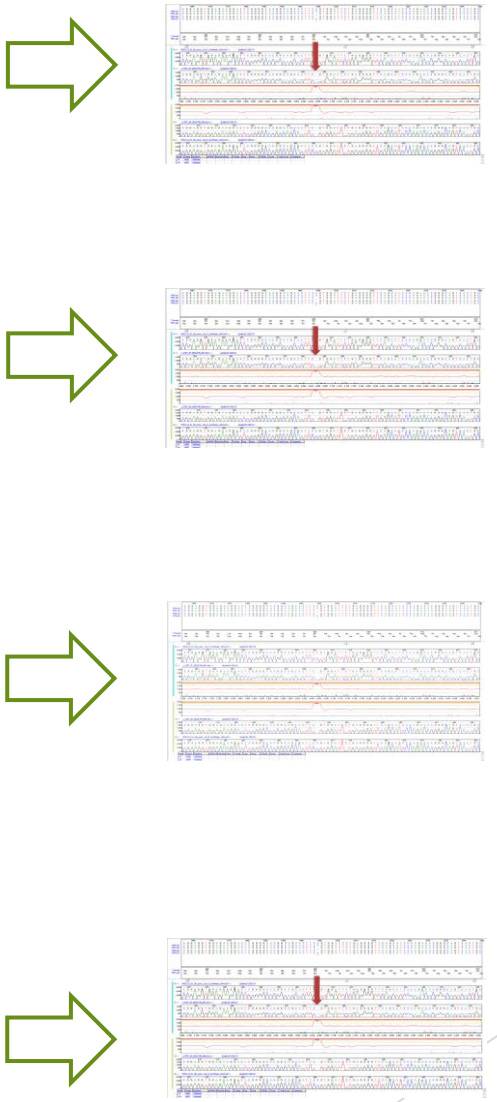

Absent


Clonal loss


Wilde type







PLOS MEDICINE

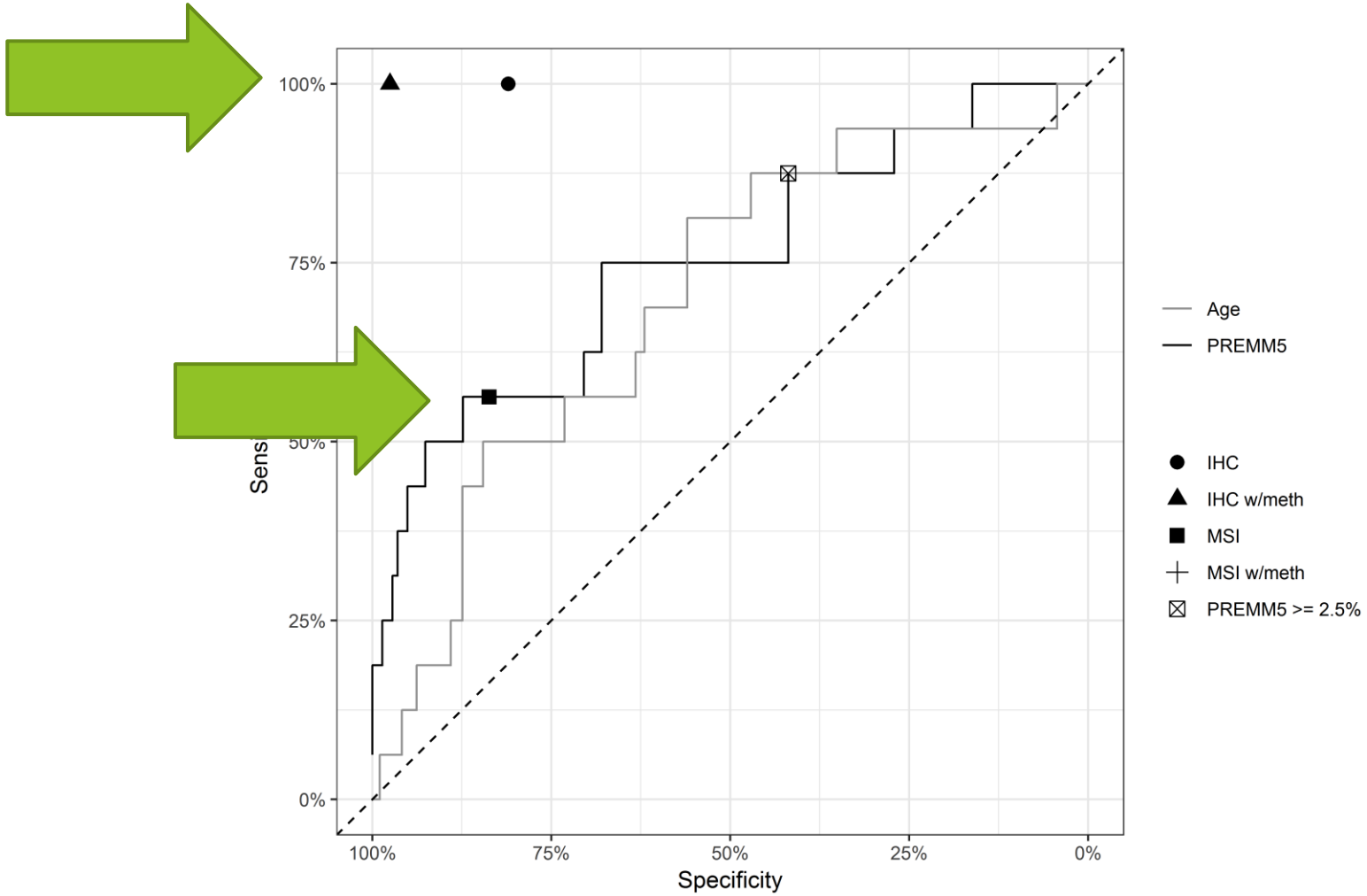
OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

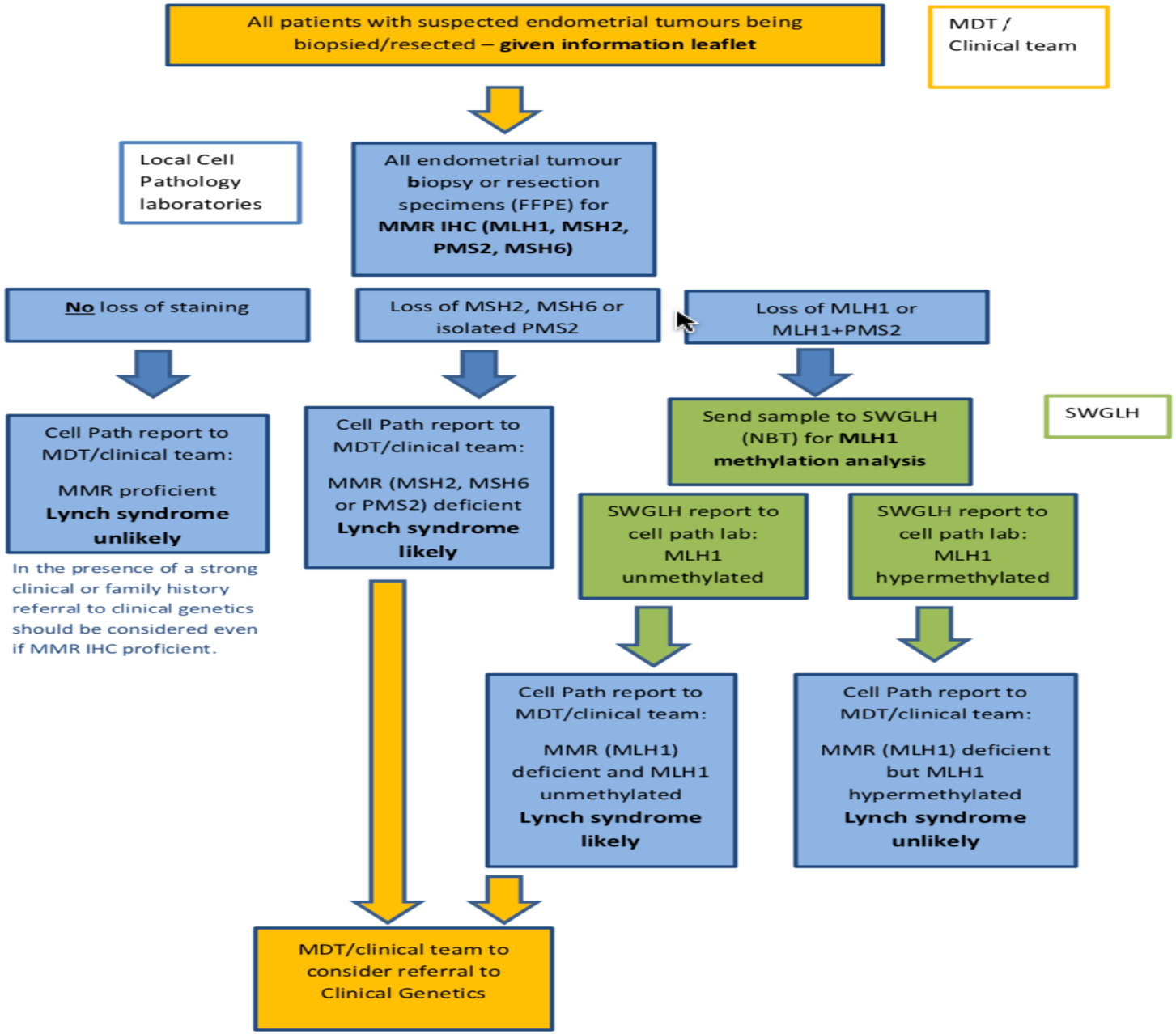
The proportion of endometrial tumours associated with Lynch syndrome (PETALS): A prospective cross-sectional study

Neil A. J. Ryan, Raymond McMahon, Simon Tobi, Tristan Snowsill, Shona Esquibel, Andrew J. Wallace, Sancha Bunstone, Naomi Bowers, Ioana E. Mosneag, Sarah J. Kitson, Helena O'Flynn, Neal C. Ramchander, Vanitha N. Sivalingam, [...], Emma J. Crosbie [view all]

Published: September 17, 2020 • https://doi.org/10.1371/journal.pmed.1003263


100%
75%
50%
25%
0%
Sens
100%
75%
50%
25%
0%
Specificity
Age
PREMM5
IHC
IHC w/meth
MSI
MSI w/meth
PREMM5 >= 2.5%

Draft SW pathway for MMR IHC for endometrial cancer (DG42)
For the identification of patients with Lynch syndrome



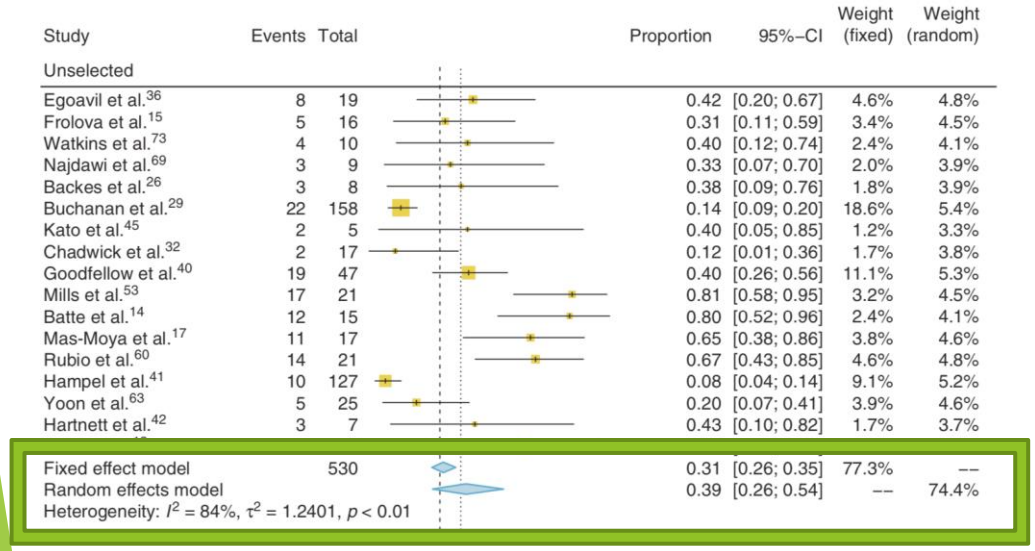
Why test

SYSTEMATIC REVIEW | Genetics inMedicine

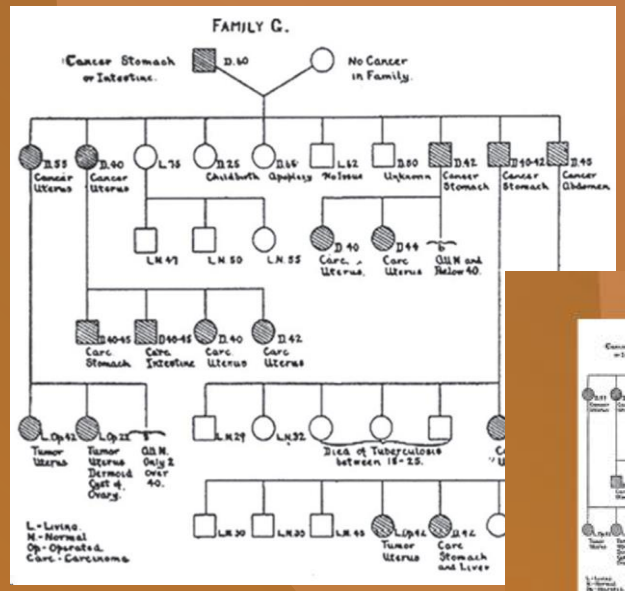
Open

The proportion of endometrial cancers associated with Lynch syndrome: a systematic review of the literature and meta-analysis

N. A. J. Ryan, MBChB [1,2], M. A. Glaire, MBChB[3], D. Blake, MBChB[4], M. Cabrera-Dandy, MBChB[5], D. G. Evans, MD[2,6] and E. J. Crosbie, PhD [1,7]



3% (2.6-3.5%)

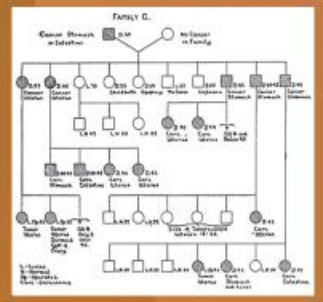


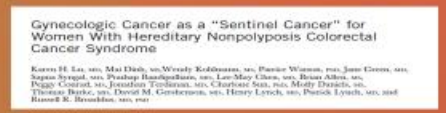
Gynecologic Cancer as a "Sentinel Cancer" for Women With Hereditary Nonpolyposis Colorectal Cancer Syndrome

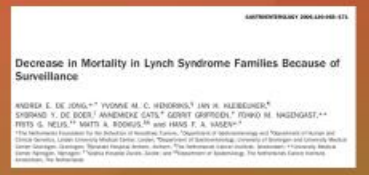
Karen H. Lu, MD, Mai Dinh, MS, Wendy Kohlmann, MS, Patrice Watson, PhD, Jane Green, MD, Sapna Syngal, MD, Prathap Bandipalliam, MD, Lee-May Chen, MD, Brian Allen, MS, Peggy Conrad, MS, Jonathan Terdiman, MD, Charlotte Sun, PhD, Molly Daniels, MS, Thomas Burke, MD, David M. Gershenson, MD, Henry Lynch, MD, Patrick Lynch, MD, and Russell R. Broaddus, MD, PhD

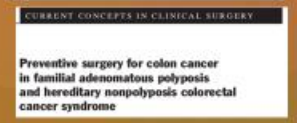
Familial Cancer (2016) 15:423–427
DOI 10.1007/s10689-016-9893-5

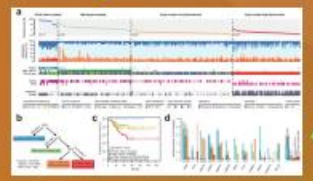
CrossMark

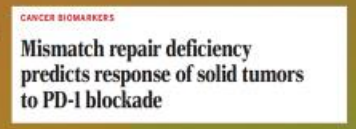


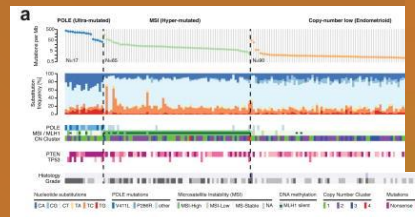


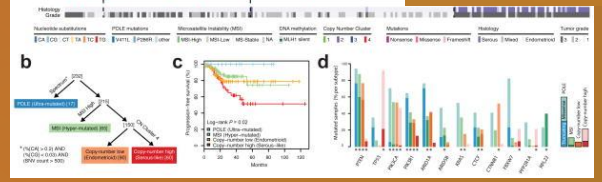








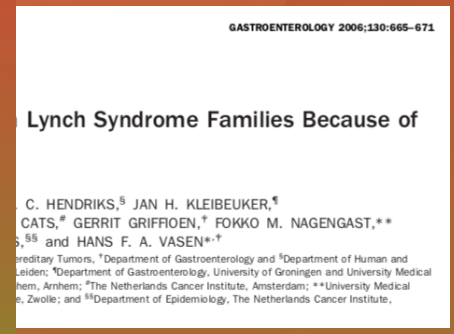


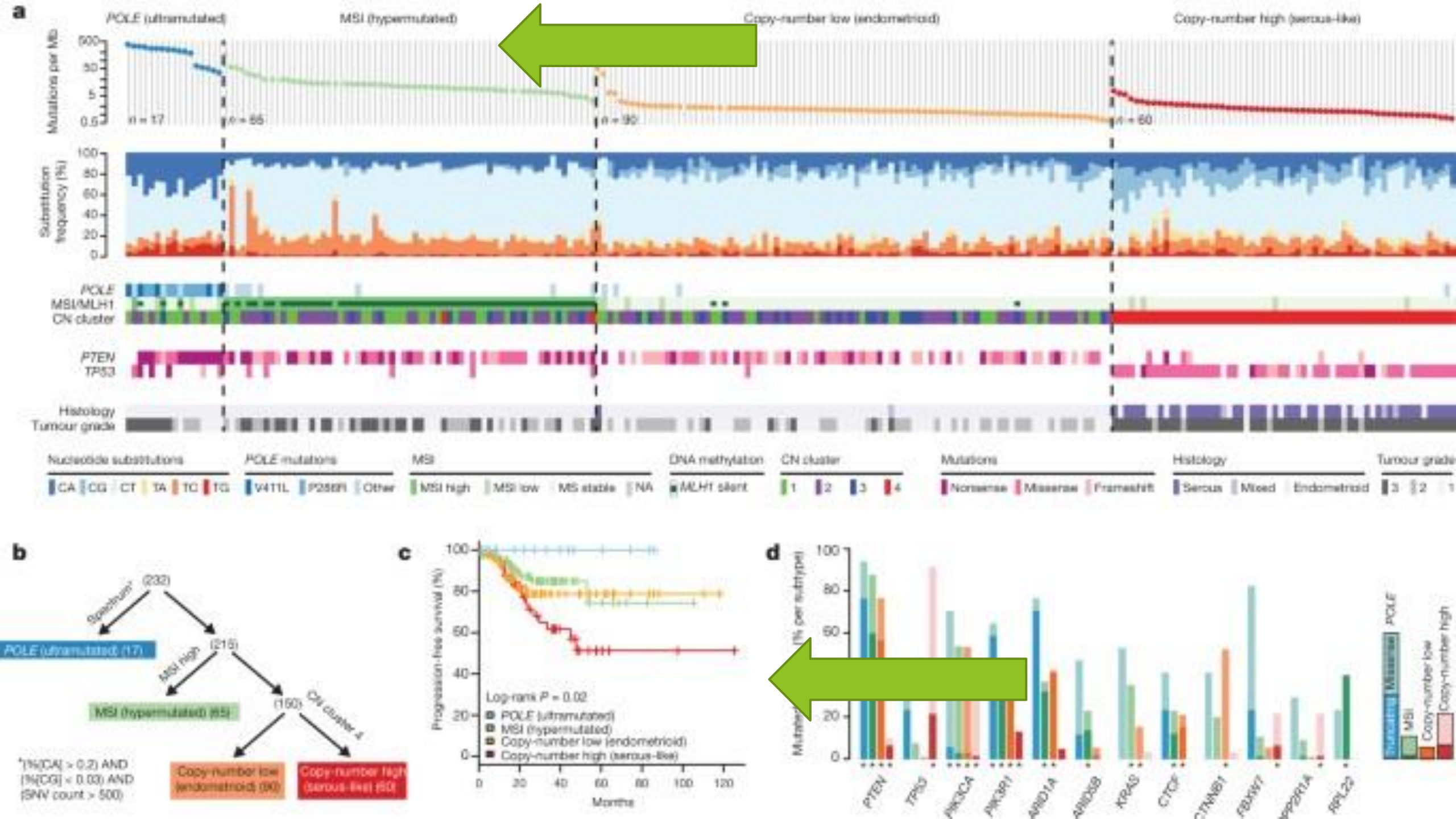


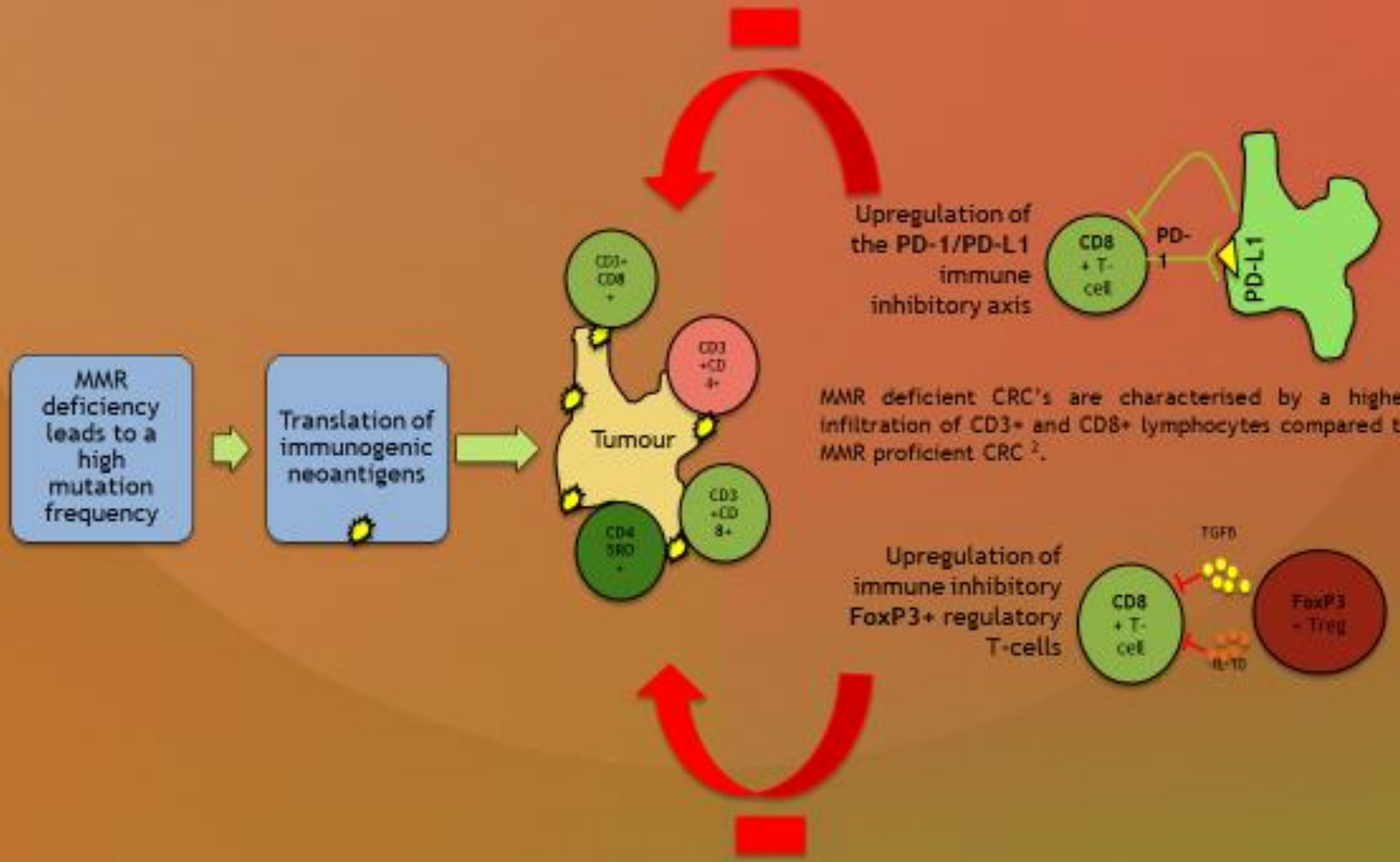
cancer syndrome

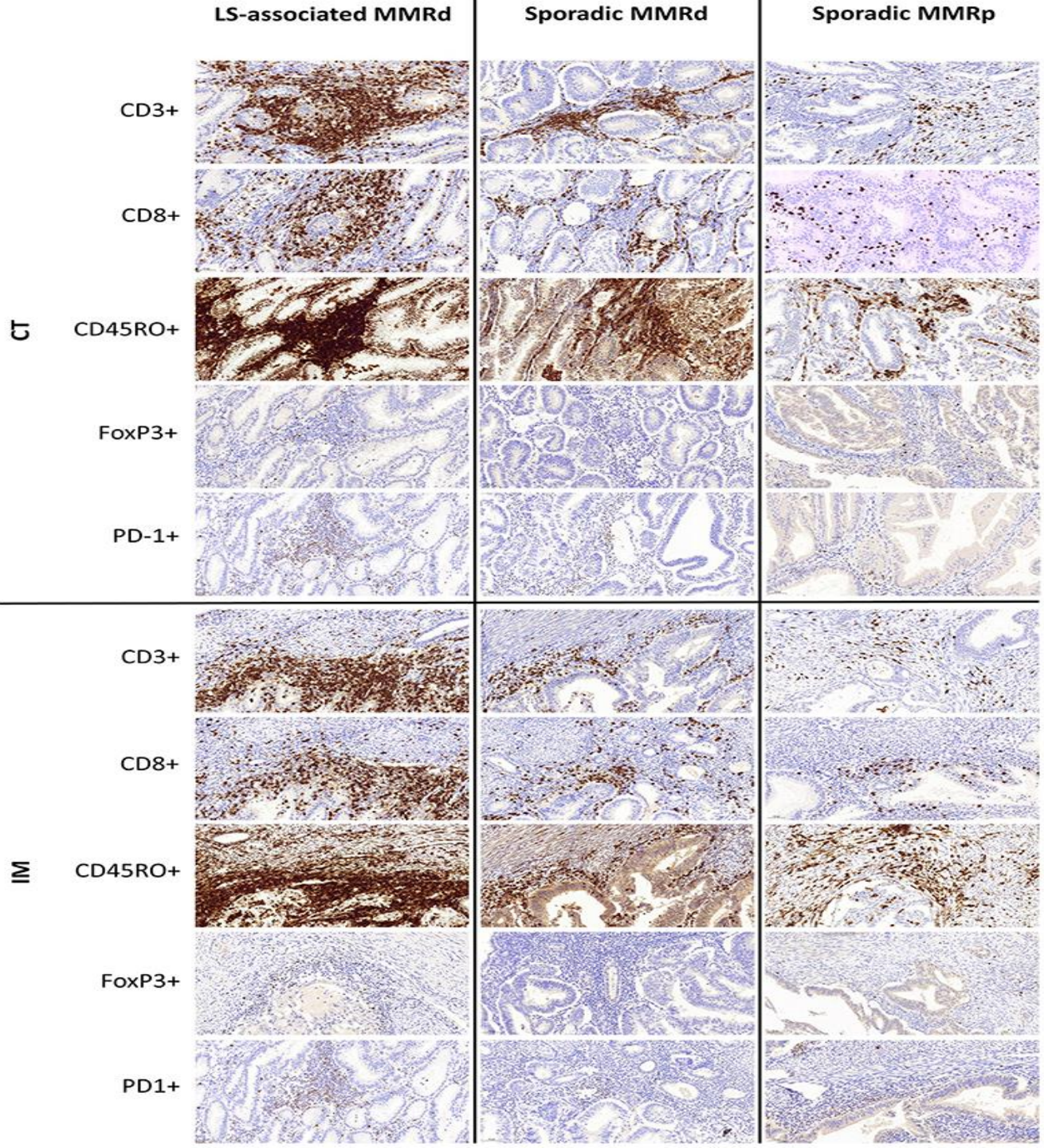
CANCER BIOMARKERS

Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade




a
POLE (ultramutated)
MSI (hypermutated)
Copy-number low (endometrioid)
Copy-number high (serous-like)
Mutations per Mb
n = 17
n = 65
n = 90
n = 60
Substitution frequency (%)
POLE
MSI/MLH1
CN cluster
PTEN
TP53
Histology
Tumour grade
Nucleotide substitutions
CA CG CT TA TC TG
POLE mutations
V411L P286R Other
MSI
MSI high MSI low MS stable NA
DNA methylation
MLH1 silent
CN cluster
1 2 3 4
Mutations
Nonsense Missense Frameshift
Histology
Serous Mixed Endometrioid
Tumour grade
3 2 1
b
(232)
Spectrum*
POLE (ultramutated) (17)
MSI high
(215)
MSI (hypermutated) (65)
(150)
CN cluster 4
Copy-number low (endometrioid) (90)
Copy-number high (serous-like) (60)
*([%CA] > 0.2) AND ([%CG] < 0.03) AND (SNV count > 500)
c
Progression-free survival (%)
Log-rank P = 0.02
POLE (ultramutated)
MSI (hypermutated)
Copy-number low (endometrioid)
Copy-number high (serous-like)
Months
d
Mutated (% per subtype)
PTEN
TP53
PIK3CA
PIK3R1
ARID1A
ARID5B
KRAS
CTCF
CTNNB1
FBXW7
PPP2R1A
RPL22
POLE
MSI
Copy-number low
Copy-number high
Missense
Truncating


MMR deficiency leads to a high mutation frequency
Translation of immunogenic neoantigens
CD3+ CD8 +
CD3 +CD 4+
Tumour
CD3 +CD 8+
CD4 5RO +
Upregulation of the PD-1/PD-L1 immune inhibitory axis
CD8 + T-cell
PD-1
PD-L1
MMR deficient CRC's are characterised by a higher infiltration of CD3+ and CD8+ lymphocytes compared to MMR proficient CRC [2].
Upregulation of immune inhibitory FoxP3+ regulatory T-cells
TGFb
CD8 + T-cell
FoxP3 - Treg
IL-10

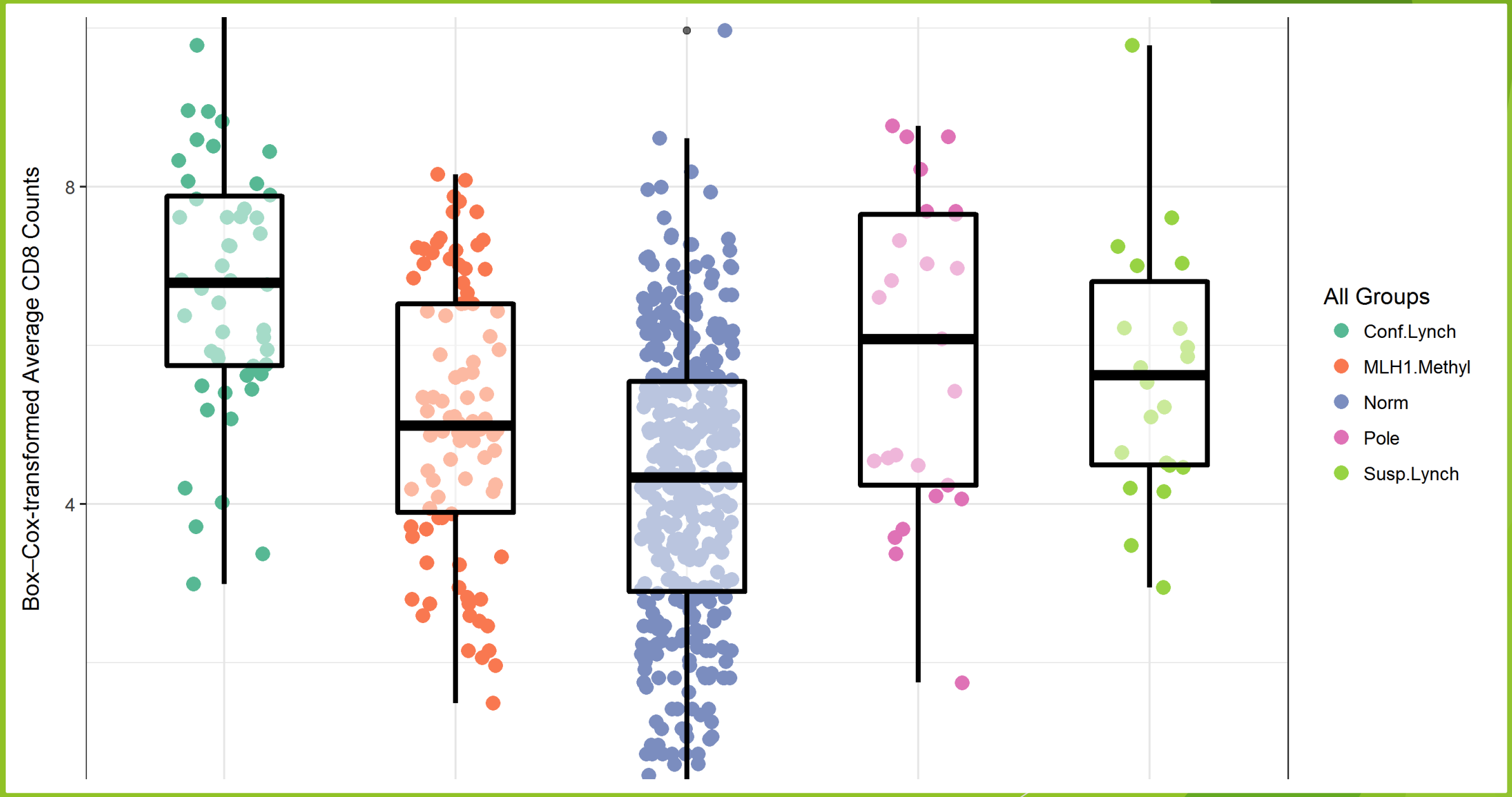


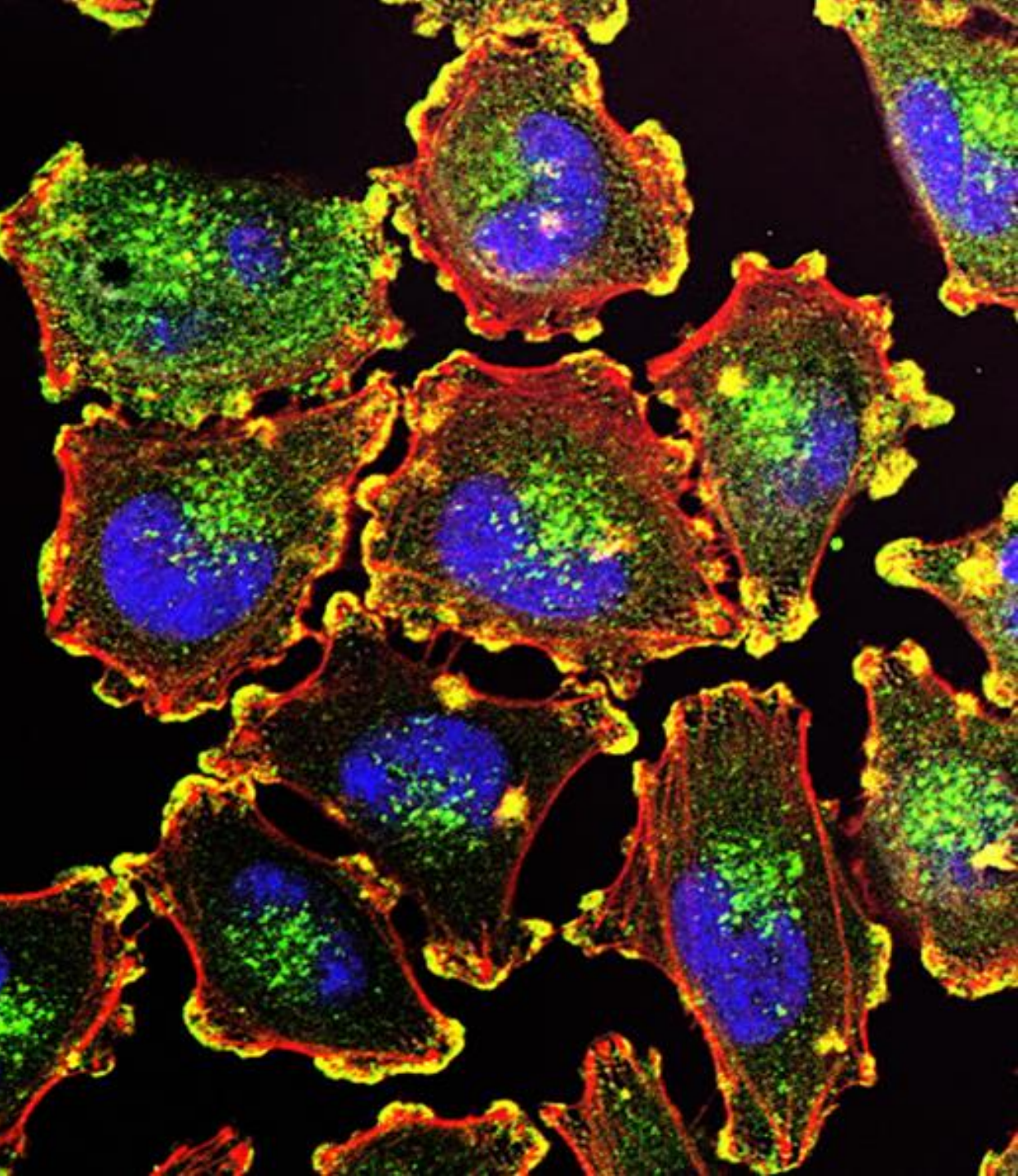
frontiers in Immunology

ORIGINAL RESEARCH
published: 09 January 2020
doi: 10.3389/fimmu.2019.03023

Distinct Immunological Landscapes Characterize Inherited and Sporadic Mismatch Repair Deficient Endometrial Cancer

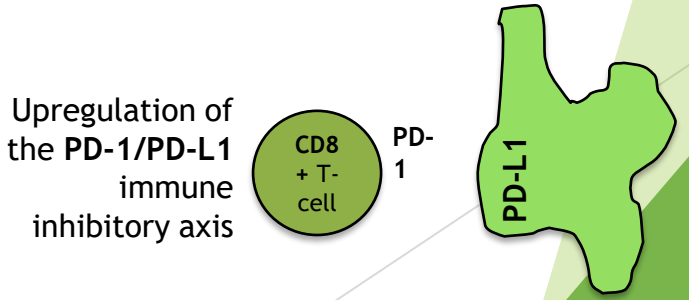
Neal C. Ramchander[1,2†], Neil A. J. Ryan[3,4†], Thomas D. J. Walker[3], Lauren Harries[5], James Bolton[5], Tjalling Bosse[6], D. G. Evans[4,7] and Emma J. Crosbie[3,8]*


Box–Cox-transformed Average CD8 Counts
8
4
All Groups
Conf.Lynch
MLH1.Methyl
Norm
Pole
Susp.Lynch



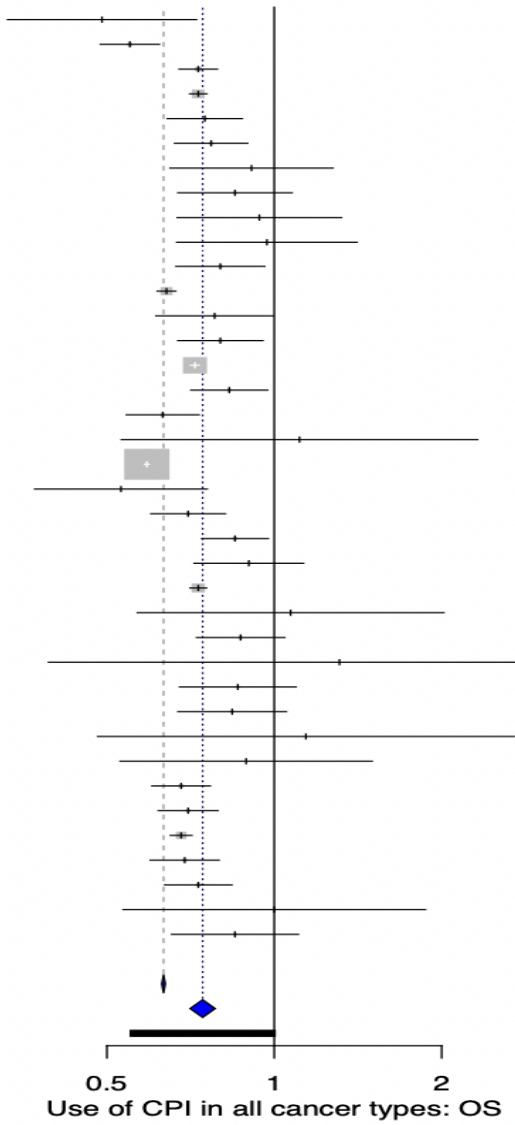
Checkpoint inhibitors

- Immune check point mechanisms can be targeted by mono-clonal antibody-based therapies
- In 2000 Medarex launched its first clinical trials with a human Mab binding to CTLA-4.
- Approval of ipilimumab for the treatment of metastatic melanoma by the FDA in 2011.



Study	TE	seTE	Int Total	Ctrl Total	HR	95%–CI	Weight (common)	Weight (random)
Gandhi et al., 2018	−0.71	0.1995	410	206	0.49	[0.33; 0.72]	0.0%	1.4%
Kim et al., 2019	−0.60	0.0622	.	.	0.55	[0.49; 0.62]	0.3%	3.5%
Fradet et al., 2019	−0.31	0.0403	270	272	0.73	[0.67; 0.79]	0.8%	3.8%
Borghaei et al., 2015	−0.31	0.0181	292	290	0.73	[0.70; 0.76]	4.1%	4.1%
Zhou et al., 2017	−0.29	0.0790	213	212	0.75	[0.64; 0.88]	0.2%	3.2%
Kojima et al., 2020	−0.26	0.0770	198	203	0.77	[0.66; 0.90]	0.2%	3.2%
Shitara et al., 2020	−0.09	0.1721	256	250	0.91	[0.65; 1.28]	0.0%	1.7%
Shitara et al., 2020	−0.16	0.1205	257	250	0.85	[0.67; 1.08]	0.1%	2.5%
Shitara et al., 2018	−0.06	0.1735	296	296	0.94	[0.67; 1.32]	0.0%	1.7%
Winer et al., 2021	−0.03	0.1904	312	310	0.97	[0.67; 1.41]	0.0%	1.5%
Rudin et al., 2020	−0.22	0.0936	228	225	0.80	[0.67; 0.96]	0.2%	2.9%
Paz–Ares et al., 2020	−0.45	0.0195	278	281	0.64	[0.62; 0.66]	3.5%	4.1%
Finn et al., 2020	−0.25	0.1237	278	135	0.78	[0.61; 1.00]	0.1%	2.4%
Cohen et al., 2019	−0.22	0.0897	247	248	0.80	[0.67; 0.95]	0.2%	3.0%
Burtness et al., 2019	−0.33	0.0089	281	278	0.72	[0.71; 0.73]	16.7%	4.1%
Burtness et al., 2019	−0.19	0.0809	300	300	0.83	[0.71; 0.97]	0.2%	3.2%
Kang et al., 2017	−0.46	0.0767	268	131	0.63	[0.54; 0.73]	0.2%	3.2%
Bang et al., 2018	0.10	0.3762	185	186	1.11	[0.53; 2.32]	0.0%	0.5%
Vokes et al., 2018	−0.53	0.0046	135	137	0.59	[0.58; 0.60]	63.7%	4.1%
Vokes et al., 2018	−0.63	0.1822	135	137	0.53	[0.37; 0.76]	0.0%	1.6%
Ferris et al., 2016	−0.36	0.0786	240	121	0.70	[0.60; 0.82]	0.2%	3.2%
Powles et al., 2018	−0.16	0.0702	467	464	0.85	[0.74; 0.98]	0.3%	3.4%
Barlesi et al., 2018	−0.11	0.1155	396	396	0.90	[0.72; 1.13]	0.1%	2.5%
Rittmeyer et al., 2017	−0.31	0.0173	425	425	0.73	[0.71; 0.76]	4.5%	4.1%
Carbone et al., 2017	0.07	0.3237	271	270	1.07	[0.57; 2.02]	0.0%	0.7%
Emens et al., 2021	−0.14	0.0932	451	451	0.87	[0.72; 1.04]	0.2%	2.9%
Miles et al., 2021	0.27	0.6146	431	220	1.31	[0.39; 4.37]	0.0%	0.2%
Spigel et al., 2021	−0.15	0.1230	284	285	0.86	[0.68; 1.09]	0.1%	2.4%
Owonikoko et al., 2021	−0.17	0.1145	280	275	0.84	[0.67; 1.05]	0.1%	2.6%
Pujade–Lauraine et al., 2021	0.13	0.4399	188	190	1.14	[0.48; 2.70]	0.0%	0.4%
Pujade–Lauraine et al., 2021	−0.12	0.2661	188	190	0.89	[0.53; 1.50]	0.0%	1.0%
Wu et al., 2019	−0.39	0.0615	338	166	0.68	[0.60; 0.77]	0.4%	3.5%
Horn et al., 2018	−0.36	0.0629	201	202	0.70	[0.62; 0.79]	0.3%	3.5%
Antonia et al., 2018	−0.39	0.0227	476	237	0.68	[0.65; 0.71]	2.6%	4.0%
Fennell et al., 2021	−0.37	0.0725	221	111	0.69	[0.60; 0.80]	0.3%	3.3%
Motzer et al., 2015	−0.31	0.0708	410	411	0.73	[0.64; 0.84]	0.3%	3.3%
Hamanishi et al., 2021	0.00	0.3193	131	125	1.00	[0.53; 1.87]	0.0%	0.7%
Jassem et al., 2021	−0.16	0.1339	277	277	0.85	[0.65; 1.11]	0.1%	2.2%
Common effect model			**10514**	**9163**	**0.63**	**[0.63; 0.64]**	**100.0%**	**––**
Random effects model					**0.74**	**[0.71; 0.78]**	**––**	**100.0%**
Prediction interval						**[0.55; 1.00]**		

Heterogeneity: $I^2 = 95\%$ [94%; 96%], $\tau^2 = 0.0211$, $p < 0.01$



frontiers in Oncology

Front Oncol. 2019; 9: 61.
Published online 2019 Feb 26. doi: 10.3389/fonc.2019.00061
PMCID: PMC6399107
PMID: 30863719

A Micro-Costing Study of Screening for Lynch Syndrome-Associated Pathogenic Variants in an Unselected Endometrial Cancer Population: Cheap as NGS Chips?

Neil A. J. Ryan,[1,2] Niall J. Davison,[3] Katherine Payne,[3] Anne Cole,[4] D. Gareth Evans,[2,4,5] and Emma J. Crosbie[1,5,6,*]

PLOS ONE

OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

Cost-effectiveness analysis of reflex testing for Lynch syndrome in women with endometrial cancer in the UK setting

Tristan M. Snowsill, Neil A. J. Ryan, Emma J. Crosbie, Ian M. Frayling, D. Gareth Evans, Chris J. Hyde

Published: August 30, 2019 • https://doi.org/10.1371/journal.pone.0221419

Journal of Clinical Medicine

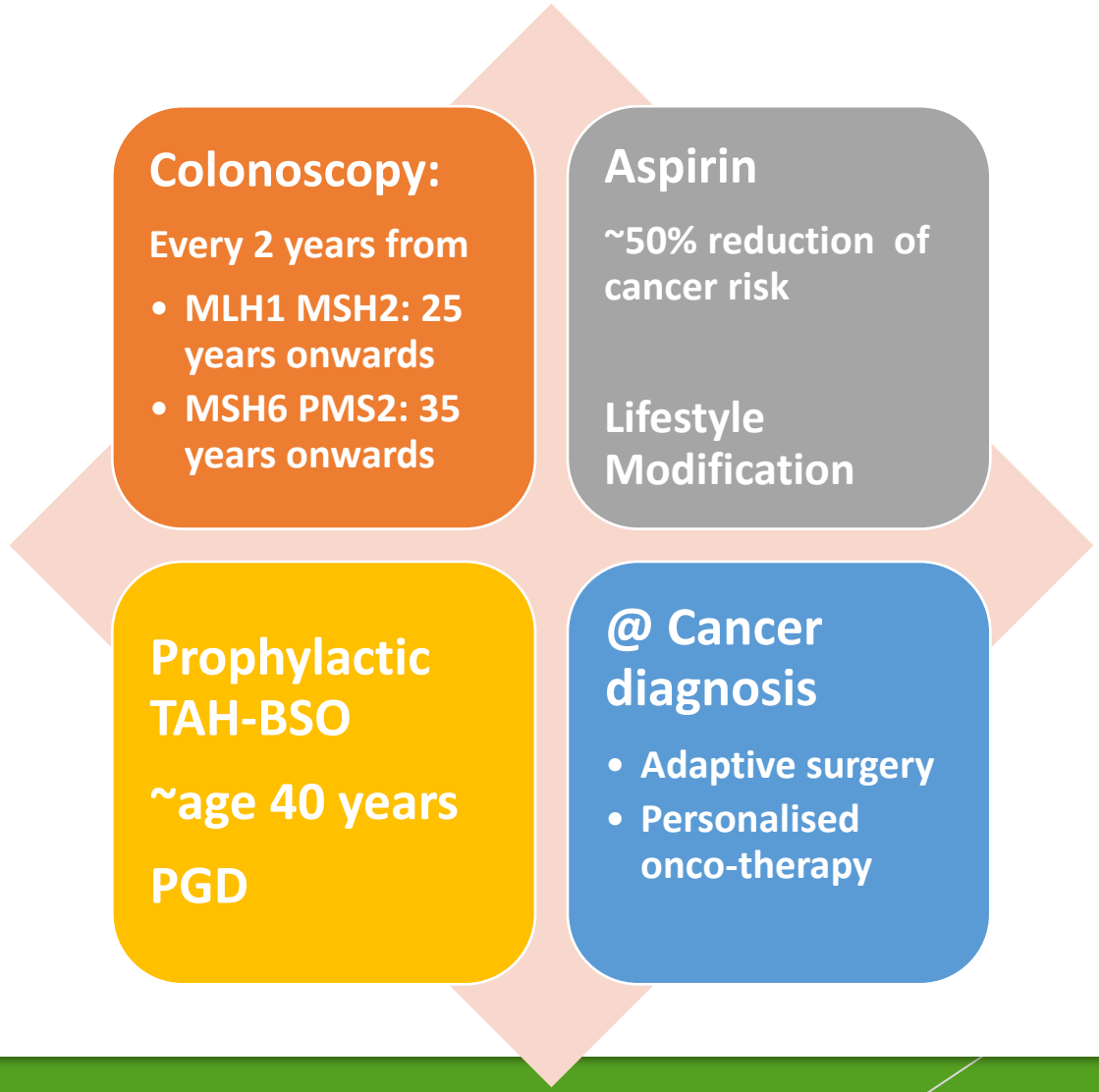
MDPI

J Clin Med. 2020 Jun; 9(6): 1664.
Published online 2020 Jun 1. doi: 10.3390/jcm9061664
PMCID: PMC7356917
PMID: 32492863

Cost-Effectiveness of the Manchester Approach to Identifying Lynch Syndrome in Women with Endometrial Cancer

Tristan M. Snowsill,[1,*] Neil A. J. Ryan,[2,3,4] and Emma J. Crosbie[3,5]

Lynch Syndrome Management



	Red (1)	Amber (2)	Green (3)
Bowel screening	Absent	Present but not up to date	Up to date
Aspirin chemoprevention	Not discussed	Discussed and declined/Not indicated	Taken or not applicable
Helicobacter pylori test and eradication	Not discussed	Testing planned	Tested and managed accordingly
Cascading of genetic risk information to relatives	Not considered or refused	Considered and pending discussion at appropriate age	In place or not applicable
Gynaecological review	Not considered and patient potentially at risk	Considered and pending review	In place or not applicable
Prostate Review	Not considered and patient potentially at risk	Considered and pending review	In place or not applicable
Symptom awareness, access to additional support if required	Not discussed	Partially in place	In place

What should we be doing

SPECIAL ARTICLE | Genetics inMedicine

Open

The Manchester International Consensus Group recommendations for the management of gynecological cancers in Lynch syndrome

Emma J. Crosbie, PhD[1,2,3], Neil A. J. Ryan, MBChB[1,4], Mark J. Arends, PhD[5], Tjalling Bosse, PhD[6], John Burn, MD[7], Joanna M. Cornes, BSc[8], Robin Crawford, MD[9], Diana Eccles, MD[10], Ian M. Frayling, PhD[11], Sadaf Ghaem-Maghami, PhD[12], Heather Hampel, MS[13], Noah D. Kauff, MD[14], Henry C. Kitchener, MD[1], Sarah J. Kitson, PhD[1], Ranjit Manchanda, PhD[15], Raymond F. T. McMahon, MD[16], Kevin J. Monahan, PhD[17], Usha Menon, MD[18], Pål Møller, PhD[19,20,21], Gabriela Möslein, MD[21], Adam Rosenthal, PhD[22], Peter Sasieni, PhD[23], Mourad W. Seif, MD[1,2], Naveena Singh, MD[24], Pauline Skarrott, MBChB[25], Tristan M. Snowsill, PhD[26,27], Robert Steele, MD[28], Marc Tischkowitz, MD[29,30] Manchester International Consensus Group, and D. Gareth Evans, MD[3,4,31]

Purpose: There are no internationally agreed upon clinical guidelines as to which women with gynecological cancer would benefit from Lynch syndrome screening or how best to manage the risk of gynecological cancer in women with Lynch syndrome. The Manchester International Consensus Group was convened in April 2017 to address this unmet need. The aim of the Group was to develop clear and comprehensive clinical guidance regarding the management of the gynecological sequelae of Lynch syndrome based on existing evidence and expert opinion from medical professionals and patients.

Methods: Stakeholders from Europe and North America worked together over a two-day workshop to achieve consensus on best practice.

Results: Guidance was developed in four key areas: (1) whether women with gynecological cancer should be screened for Lynch syndrome and (2) how this should be done, (3) whether there was a role for gynecological surveillance in women at risk of Lynch syndrome, and (4) what preventive measures should be recommended for women with Lynch syndrome to reduce their risk of gynecological cancer.

Conclusion: This document provides comprehensive clinical guidance that can be referenced by both patients and clinicians so that women with Lynch syndrome can expect and receive appropriate standards of care.

Genetics in Medicine (2019) https://doi.org/10.1038/s41436-019-0485-y

Keywords: Lynch syndrome; endometrial cancer; screening; surveillance; guidance

BJS

Review | Open Access

European guidelines from the EHTG and ESCP for Lynch syndrome: an updated third edition of the Mallorca guidelines based on gene and gender

T. T. Seppälä, A. Latchford, I. Negoi, A. Sampaio Soares, R. Jimenez-Rodriguez ... See all authors

First published: 21 September 2020 | https://doi.org/10.1002/bjs.11982

SPECIAL ARTICLE | Genetics inMedicine

Open

The Manchester International Consensus Group recommendations for the management of gynecological cancers in Lynch syndrome

Emma J. Crosbie, PhD[1,2,3], Neil A. J. Ryan, MBChB[1,4], Mark J. Arends, PhD[5], Tjalling Bosse, PhD[6], John Burn, MD[7], Joanna M. Cornes, BSc[8], Robin Crawford, MD[9], Diana Eccles, MD[10], Ian M. Frayling, PhD[11], Sadaf Ghaem-Maghami, PhD[12], Heather Hampel, MS[13], Noah D. Kauff, MD[14], Henry C. Kitchener, MD[1], Sarah J. Kitson, PhD[1], Ranjit Manchanda, PhD[15], Raymond F. T. McMahon, MD[16], Kevin J. Monahan, PhD[17], Usha Menon, MD[18], Pål Møller, PhD[19,20,21], Gabriela Möslein, MD[21], Adam Rosenthal, PhD[22], Peter Sasieni, PhD[23], Mourad W. Seif, MD[1,2], Naveena Singh, MD[24], Pauline Skarrott, MBChB[25], Tristan M. Snowsill, PhD[26,27], Robert Steele, MD[28], Marc Tischkowitz, MD[29,30] Manchester International Consensus Group, and D. Gareth Evans, MD[3,4,31]

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TEST

SURVEILLANCE

SURGERY

LIFESTYLE

ASPIRIN


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Standards and indicators
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Testing strategies for Lynch syndrome in people with endometrial cancer
Diagnostics guidance [DG42] Published date: 28 October 2020


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Molecular testing strategies for Lynch syndrome in people with colorectal cancer
Diagnostics guidance [DG27] Published date: 22 February 2017

NICE National Institute for Health and Care Excellence

NICE guidance

Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency

Technology appraisal guidance
Published: 16 March 2022
www.nice.org.uk/guidance/ta779

ESGO Guidelines
and Quality Indicators

NDOMETRIAL
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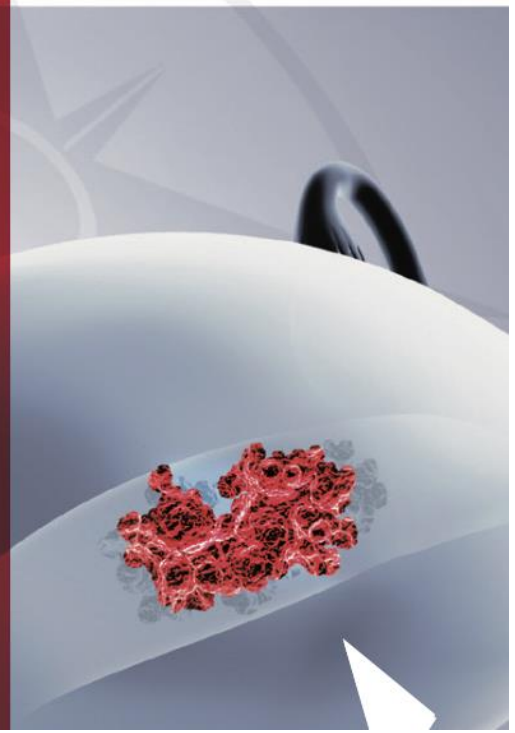
UIDELINES



lefinition of prognostic risk groups for both situations when mo classification is known or unknown is presented as follows:

	Molecular Classification Unknown	Molecular Classification Known[A,*]
	• Stage IA endometrioid + low-grade** + LVSI negative or focal	• Stage I-II ***POLE*mut** endometrial residual disease • Stage IA **MMRd/NSMP** endometrioi low-grade** + LVSI negative or focal
ate	• Stage IB endometrioid + low-grade** + LVSI negative or focal • Stage IA endometrioid + high-grade** + LVSI negative or focal • Stage IA non-endometrioid (serous, clear cell, undifferentiared carcinoma, carcinosarcoma, mixed) without myometrial invasion	• Stage IB **MMRd/NSMP** endometrioi low-grade** + LVSI negative or focal • Stage IA **MMRd/NSMP** endometrioi high-grade** + LVSI negative or focal • Stage IA **p53abn** and/or non-endome clear cell, undifferentiated carcinosarcoma, mixed) without invasion
ate	• Stage I endometrioid + substantial LVSI, regardless of grade and depth of invasion • Stage IB endometrioid high-grade**, regardless of LVSI status • Stage II	• Stage I **MMRd/NSMP** endometrioid substantial LVSI, regardless of grade invasion • Stage IB **MMRd/NSMP** endometri high-grade**, regardless of LVSI status • Stage II **MMRd/NSMP** endometrioid c
	• Stage III-IVA with no residual disease • Stage I-IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease	• Stage III-IVA **MMRd/NSMP** endometr with no residual disease • Stage I-IVA **p53abn** endometrial c myometrial invasion, with no residual • Stage I-IVA **NSMP/MMRd** serous, u carcinoma, carcinosarcoma with invasion, with no residual disease
d c	• Stage III-IVA with residual disease • Stage IVB	• Stage III-IVA with residual disease of type • Stage IVB of any molecular type

BRITISH GYNAECOLOGICAL CANCER SOCIETY

Ovarian and Endometrial Cancer Guidelines

13 March 2017

The BGCS has now released the first national comprehensive Ovarian and Endometrial cancer guidelines after completing public consultation and international and national peer reviewing.

Commissioning responsibilities

Implementation of the Lynch syndrome pathway was included in the NHS Planning and Contracting Guidance for 2020/21 and has been identified as a priority for Cancer Alliances and Genomic Medicine Service Alliances.

Stage	Funding responsibility
Initial tumour test	IHC: Clinical Commissioning Groups (CCGs) are responsible for providing funding to pathology services for IHC testing MSI: MSI is included in National Genomic Test Directory and is therefore funded nationally by specialised commissioning. There will also need to be funding for histopathological assessment, the responsibility for this lies with CCGs.
Germline testing	Germline testing for Lynch syndrome is included in the National Genomic Test Directory and is therefore funded nationally by specialised commissioning
Surveillance and management of people with Lynch syndrome	CCGs are responsible for funding surveillance pathways for people with Lynch syndrome including colonoscopy and gynaecological prevention strategies

Surveillance

Surveillance for women with Lynch syndrome

How?

What?

When?

1 The Academic Women's Health Unit, Translational Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK

2 Department of Obstetrics and Gynaecology, St Michael's Hospital, Bristol, UK

3 Health Economics Group, University of Exeter Medical School, University of Exeter, Exeter, Devon, UK

4 The Lynch Syndrome and Family Cancer Clinic, St Mark's Hospital and Academic Institute, Harrow, London, UK Imperial College London, London, UK

UNCERTAINTIES

Should women with Lynch syndrome be offered gynaecological cancer surveillance?

NAJ Ryan, [1,2] T Snowsill, [3] E McKenzie, KJ Monahan, [4] D Nebgen[5]

What you need to know

- Lynch syndrome is an inherited genetic condition associated with an increased risk of endometrial and ovarian cancer in women
- Limited low quality evidence from observational studies show that gynaecological surveillance detects cancers in women with Lynch syndrome, but it is

the Prospective Lynch Syndrome database (http://www.plsd.eu). For a woman with Lynch syndrome, the lifetime risk of endometrial or ovarian cancer is 40-60% and 10-17%, respectively, the incidence increasing with age beyond 40 years.[2]

Data sources and selection strategy

We searched CENTRAL, Medline, Embase, and the

Table 1 | UK, European, US, and National Comprehensive Cancer Network gynaecological surveillance recommendations for women with Lynch syndrome

Guidelines	UK 2019[6]	ESMO 2016[7]	ASCO 2015[8]	NCCN2021[9]
Symptom awareness Education	Yes, age 25	Yes	Yes	Yes
Gynaecological examination	Yes	Yes	Yes	-
Pelvic ultrasound	No	Yes	Yes	No†
CA125	No	Not stated	No	No†
Endometrial biopsy	No	Annually from age 30-35	Annually from age 30-35	Every 1-2 years from age 30-35
Hysterectomy and bilateral salpingo-oophorectomy	Yes‡	Yes	Yes	Yes
Research needed	Yes	-	-	-

† Can consider at the physician's preference. ‡No earlier than 35-40 years and preoperative endometrial biopsy and pelvic ultrasound. United Kingdom (UK) Manchester guidelines (NICE does not currently offer a recommendation on surveillance), European Society for Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN).

Study	Modality	Interval	Pathological variant status	Symptomatic	AEH detected	Cancers detected	Stage of cancers detected	Cancers Missed	Stage of Cancers missed
Cornou 2016 (n=177)	TVS+Bx+OPH	Annual	Proven LS	NK	NK	5 EC + 1OC	NK	0	NA
Dove-Edwin 2000 (n=222)	TVS	Annual or Biennial	Mixed	NA	0	0	NA	2 EC	2xI
Eikenboom 2021 (n=164)	TVS +/- CA125 +/- Bx	Annual	Proven LS	8	7	4 EC 1 OC	EC: 4xI OC: IV	2 EC	2xI
Gerritzen 2009 (n=100)	TVS +/- Bx	Annual	Mixed	NK	4	3 EC* 2 OC	EC: Ib, Ic, IIIc OC: Ia, IIIc	0	NA
Helder-Woolderink 2013 (n=75)	TVS + CA125 +/-Bx	Annual	Mixed	0	1	1 OC	Ia	0	NA
Jarvinen 2009 (n=103)	Bx + TVS	2-3 years	Proven LS	2	0	18 EC 3 OC	EC: 12xI, 2xII, 2xIII	6	EC: 2xI OC: 2xI III
Ketabi 2014 (n=871)	TVS +/- Bx	Various	Mixed	10	3	7 EC + 1 OC	EC: Ia, 2x Ib, 2xIc, IV, 1xNK OC: IIb	2 AEH, 6 EC, 3 OC	EC: 3xIb, II, IIc, IIIc OC: 2x1c, IIIc
Le´curu 2007 (n=57)	TVS+CA125+Bx+OPH	Annual	Mixed	2	0	2 EC	NK	0	NA
Manchanda 2012 (n=41)	TVS+Bx+OPH	Annual	Mixed	2	1	3 EC*	EC: 3xIa	0	NA
Nebgen 2014 (n=55)	TVS+Bx^	Annual or Biennial	Mixed	0	2	1 EC	Ia	0	NA
Renkonen-Sinisalo 2006 (n=175)	Various	2-3 years	Proven LS	NK	4	11 EC	EC: 5xIa, 4xIb,IIb IIIa,	4 OC	3x I & 1x III
Rijcken 2003 (n=41)	TVS + CA125 +/- Bx	Annual	Mixed	0	3	0	NA	1 EC	1B
Rosenthal 2013 (n=95)	TVS and CA125	Annual	Mixed	0	NK	3 OC (EC not reported)	OC: 1a, 2x1c	0	NA
Stuckless 2013 (n=54)	TVS or Bx or CA125	Annual or Biennial	MSH2 only	NK	0	5 EC 1 OC	EC: 4xIa, IIIa OC: IIc	4 EC 4 OC	EC: 2x Ia, Ib, 1 NK OC: Ia, IIb, IIc, 1 NK
Tzortzatos 2015 (n=45)	Various	Annual	Proven LS	0	2	3 EC + 2 OC	EC: 2xII 1xIa OC: 2xIa	4 EC#	Ia, 2x Ib, II

What to do then …

Family

Symptoms

Access

Surveillance

Surgery

Current Priorities

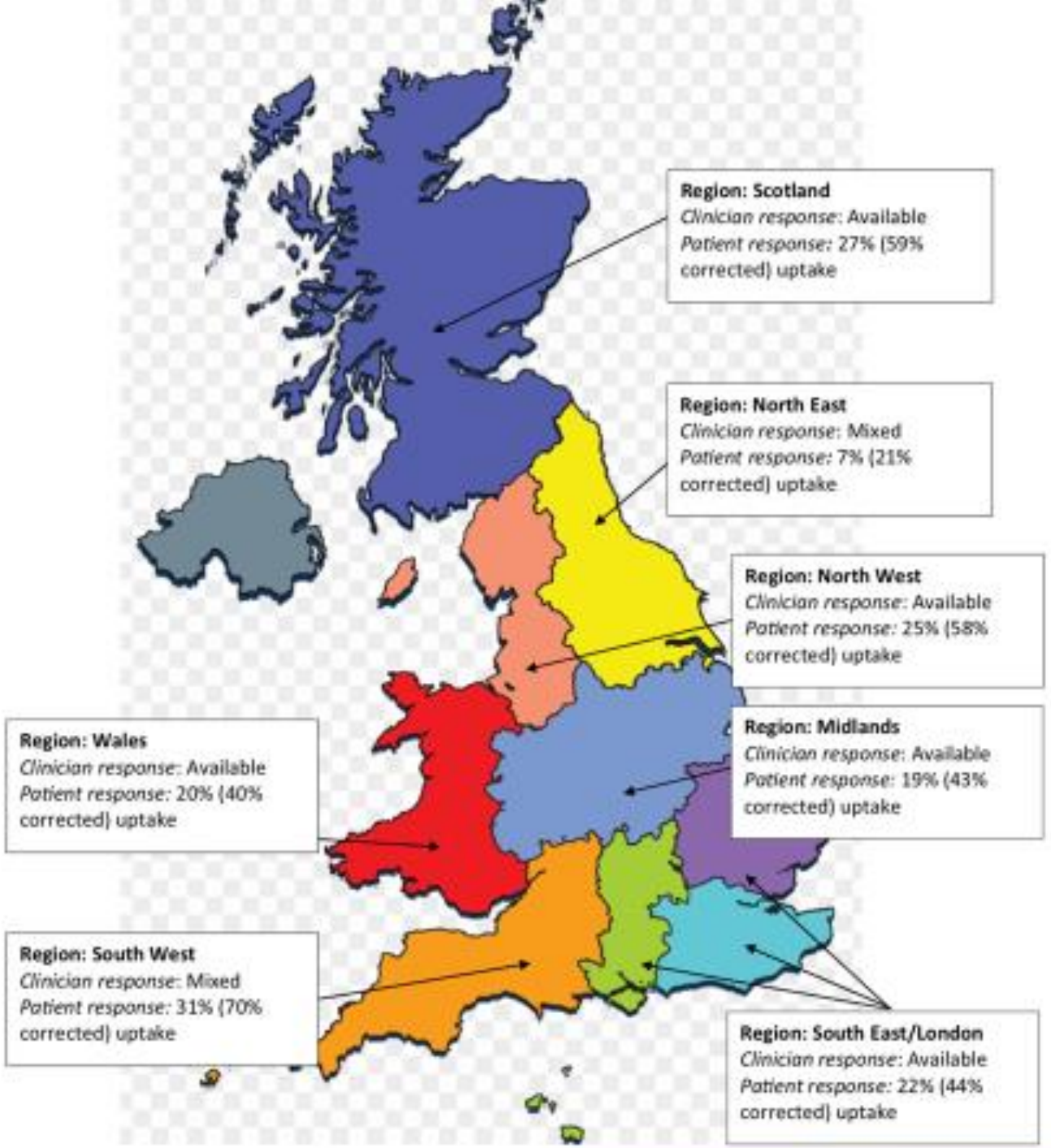
DOI: 10.1111/1471-0528.16432
www.bjog.org

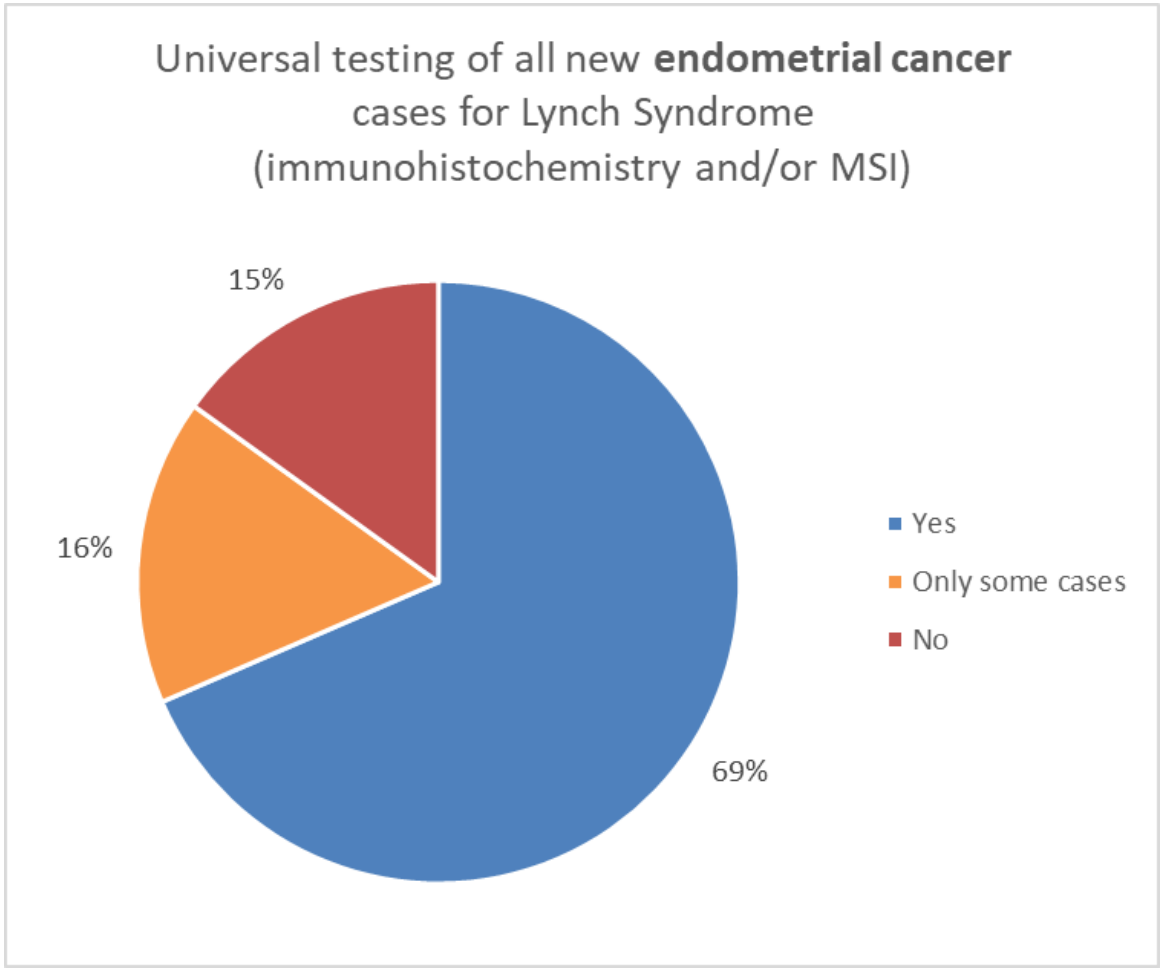
Original Article
Gynaecological oncology

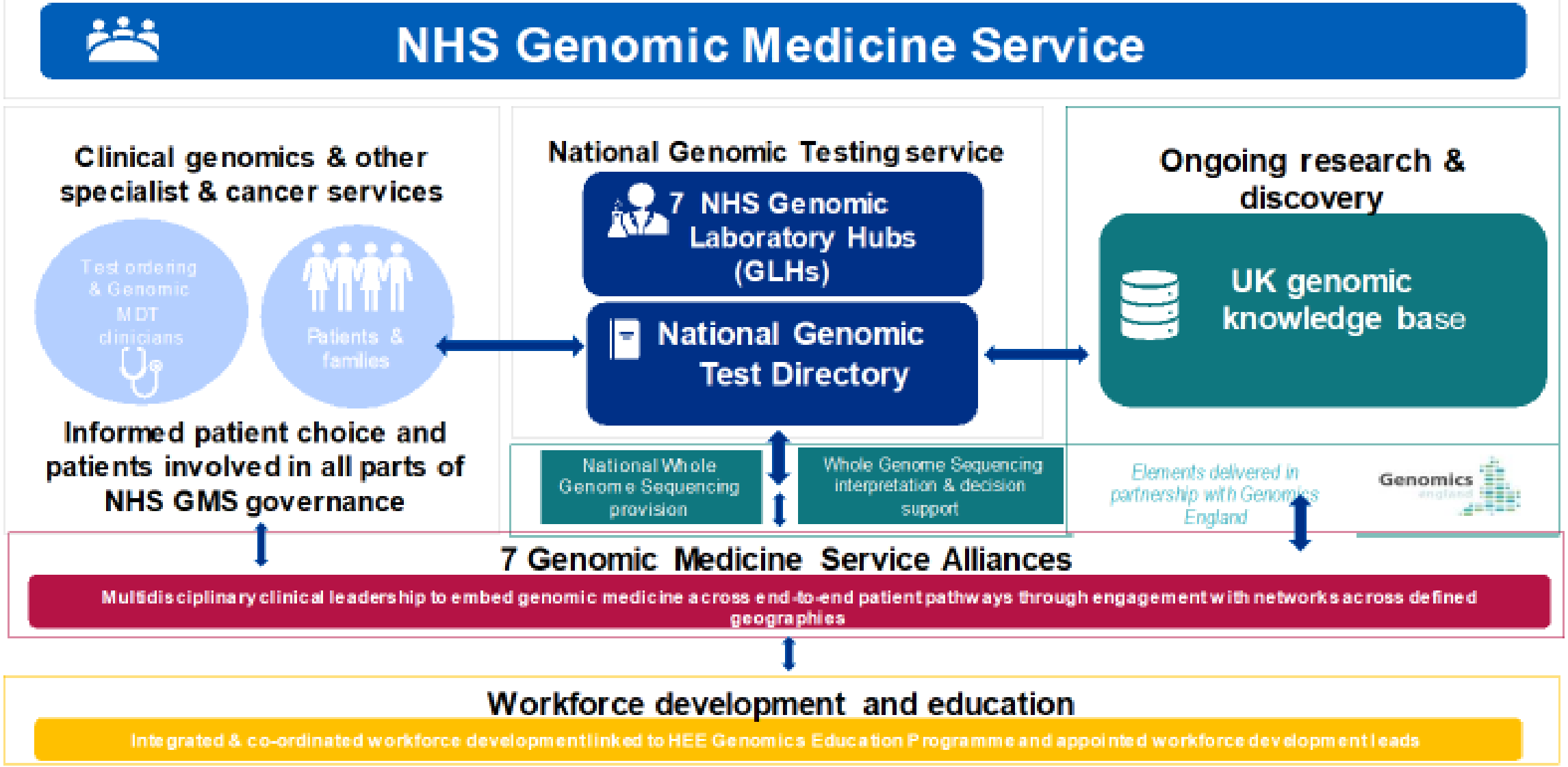
A mismatch in care: results of a United Kingdom-wide patient and clinician survey of gynaecological services for women with Lynch syndrome

NAJ Ryan,[a,b] M Nobes,[c] D Sedgewick,[d] S-N Teoh,[e] DG Evans,[a,f] EJ Crosbie[b,g]

- 20% of GO didn't known LS was associated with OC
- 18% of GO didn't agree with the universal LS screening in EC
- <5% of Cancer Centers we carrying out universal screening in EC
- The management of women with LS was far from uniform




Universal testing of all new **endometrial cancer** cases for Lynch Syndrome (immunohistochemistry and/or MSI)
15%
16%
69%
Yes
Only some cases
No

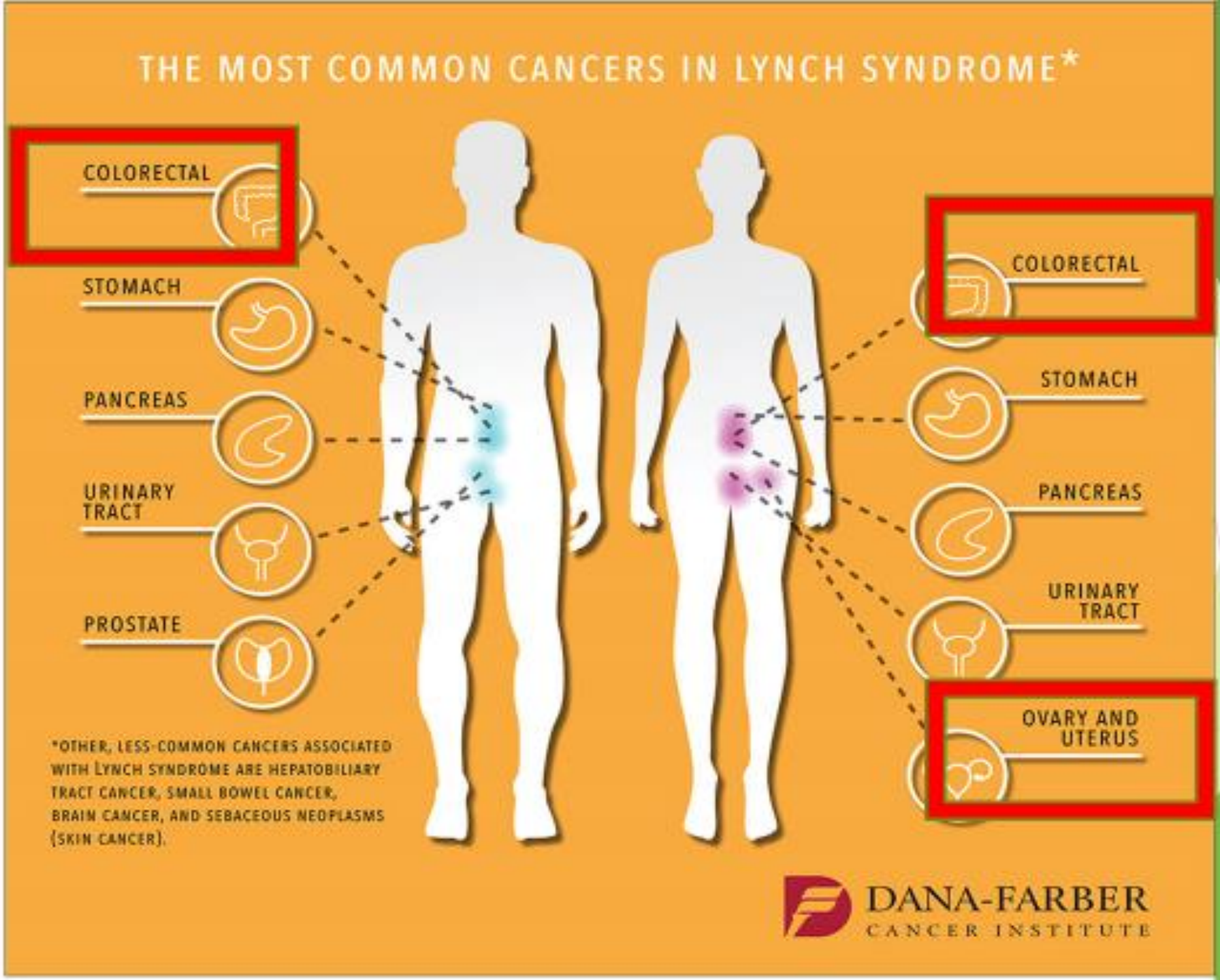

NHS Genomic Medicine Service
Clinical genomics & other specialist & cancer services
Test ordering & Genomic MDT clinicians
Patients & families
Informed patient choice and patients involved in all parts of NHS GMS governance
National Genomic Testing service
7 NHS Genomic Laboratory Hubs (GLHs)
National Genomic Test Directory
National Whole Genome Sequencing provision
Whole Genome Sequencing interpretation & decision support
Ongoing research & discovery
UK genomic knowledge base
Elements delivered in partnership with Genomics England
Genomics england
7 Genomic Medicine Service Alliances
Multidisciplinary clinical leadership to embed genomic medicine across end-to-end patient pathways through engagement with networks across defined geographies
Workforce development and education
Integrated & co-ordinated workforce development linked to HEE Genomics Education Programme and appointed workforce development leads

GMS Alliance national projects

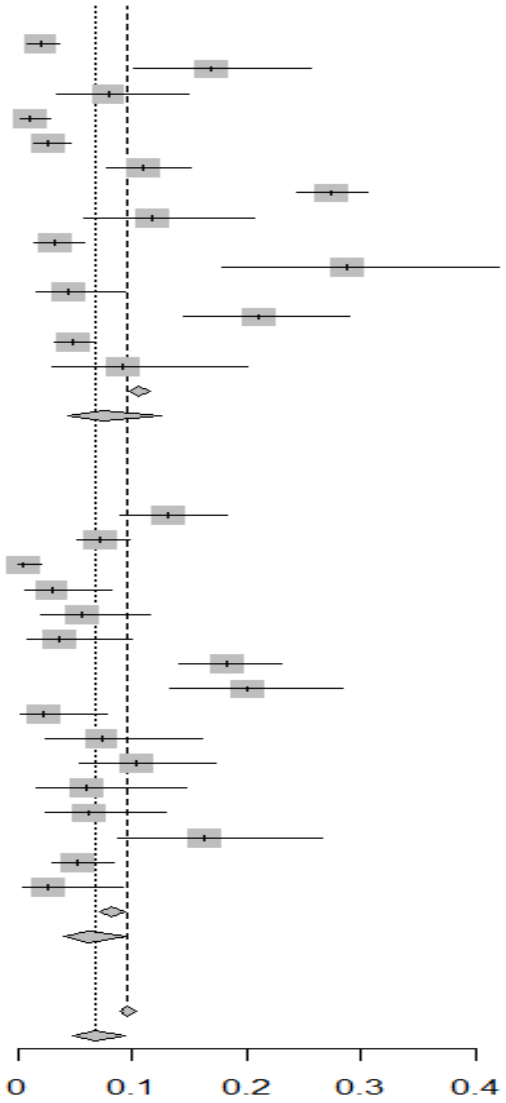
Project area	Key objectives
DPYD	• Review of testing and implementation, identify barriers to equitable access, standardised MDT pathways and data collection • Review of electronic systems to inform informatics/decision support projects • Characterisation of additional relevant DPYD variants • Scope availability of therapeutic drug monitoring
Familial Hypercholesterolaemia	• Supporting primary care teams to increase the detection of FH in the community, in line with the NHS Long Term Plan commitment • Drive improvement of genomic understanding and implementation of genomic test requesting in primary care through education of General Practitioners and other primary health care professionals, and support for pathway transformation in PCNs, focusing on FH as an exemplar [illegible] • Assess the effectiveness of remote approaches to family cascade screening
Lynch Syndrome	• Determine geographical variation and barriers to access to testing pathways across all relevant providers in the geography • Embed ubiquitous testing for Lynch Syndrome in colorectal and endometrial cancer patients across the geography • Demonstrate clinical impact of testing pathways on access to personalised/stratified care following a cancer diagnosis • Develop and embed infrastructure to support pathway transformation and quality improvement in patient care working towards regional Lynch syndrome networks linking primary, secondary and tertiary care
Pathology	• Engagement with pathology [illegible] blended learning package for clinical interpretation of tests in the Test Directory. • Assessment, mapping and development of pathways - identify areas where delays and barriers exist, agreement model tissue pathway for genomic analysis to meet cancer TATs
Sudden Cardiac Death	• Support for BHF pilot to introduce genomic testing pathway for SCD
Monogenic diabetes	• Embed monogenic diabetes into clinical practice through trained medical and nursing lead for monogenic diabetes in Trusts • Local improvement support via existing trained Genetic Diabetes Nurses, embedded in the GMS Alliances
Nursing and midwifery	• Use roadmap and tools developed by Global Genomics Nursing Alliance (G2NA), to ensure focus is maintained on a systematic and coordinated approach to embedding genomics in nursing and midwifery practice


WE NEED
YOU!

Future directions


THE MOST COMMON CANCERS IN LYNCH SYNDROME*
COLORECTAL
STOMACH
PANCREAS
URINARY TRACT
PROSTATE
COLORECTAL
STOMACH
PANCREAS
URINARY TRACT
OVARY AND UTERUS
*OTHER, LESS-COMMON CANCERS ASSOCIATED WITH LYNCH SYNDROME ARE HEPATOBILIARY TRACT CANCER, SMALL BOWEL CANCER, BRAIN CANCER, AND SEBACEOUS NEOPLASMS (SKIN CANCER).
DANA-FARBER
CANCER INSTITUTE

Study	Events	Total	Proportion	95%-CI
Selected = Unselected				
Fraune 2020	9	478	0.019	[0.009; 0.035]
Carnevali 2019	17	101	0.168	[0.101; 0.256]
Geisler 2000	8	102	0.078	[0.034; 0.149]
Tajima Y 2018	3	305	0.010	[0.002; 0.028]
Xue 2018	11	419	0.026	[0.013; 0.046]
Zhai 2008	34	310	0.110	[0.077; 0.150]
Lee 2014	228	834	0.273	[0.243; 0.305]
Niskakowski 2013	10	85	0.118	[0.058; 0.206]
Lu 2012	9	290	0.031	[0.014; 0.058]
Permuth-Wey 2009	17	59	0.288	[0.178; 0.421]
Yamashita 2019	6	136	0.044	[0.016; 0.094]
Brandt 2017	28	133	0.211	[0.145; 0.290]
Rambau 2016	29	612	0.047	[0.032; 0.067]
Catasus 2004	5	55	0.091	[0.030; 0.200]
Common effect model		3919	0.106	[0.096; 0.116]
Random effects model			0.074	[0.043; 0.124]
Heterogeneity: $I^2 = 96\%$, $\tau^2 = 1.1090$, $p < 0.01$				
Selected = Selected				
Kim 2020	28	215	0.130	[0.088; 0.183]
Leskela 2020	36	502	0.072	[0.051; 0.098]
Schmoeckel 2019	1	288	0.003	[0.000; 0.019]
Bennet 2019	3	104	0.029	[0.006; 0.082]
Bennet 2016	6	109	0.055	[0.020; 0.116]
Vierkoetter 2014	3	86	0.035	[0.007; 0.099]
Coppola 2012	55	301	0.183	[0.141; 0.231]
Zhu 2019	24	120	0.200	[0.133; 0.283]
Parra-Herran 2019	2	90	0.022	[0.003; 0.078]
Parra-Herran 2017	5	69	0.072	[0.024; 0.161]
Keleman 2017	12	117	0.103	[0.054; 0.172]
Stewart 2013	4	67	0.060	[0.017; 0.146]
Domanska 2007	6	98	0.061	[0.023; 0.129]
Liu 2004	12	74	0.162	[0.087; 0.266]
Hodan 2020	16	308	0.052	[0.030; 0.083]
Lin 2020	2	76	0.026	[0.003; 0.092]
Common effect model		2624	0.082	[0.072; 0.093]
Random effects model			0.062	[0.039; 0.095]
Heterogeneity: $I^2 = 83\%$, $\tau^2 = 0.7239$, $p < 0.01$				
Common effect model		**6543**	**0.096**	**[0.089; 0.104]**
Random effects model			**0.067**	**[0.047; 0.094]**



Heterogeneity: $I^2 = 93\%$, $\tau^2 = 0.9321$, $p < 0.01$
Test for subgroup differences (fixed effect): $\chi^2_1 = 10.11$, df = 1 ($p < 0.01$)
Test for subgroup differences (random effects): $\chi^2_1 = 0.26$, df = 1 ($p = 0.61$)

nature COMMUNICATIONS

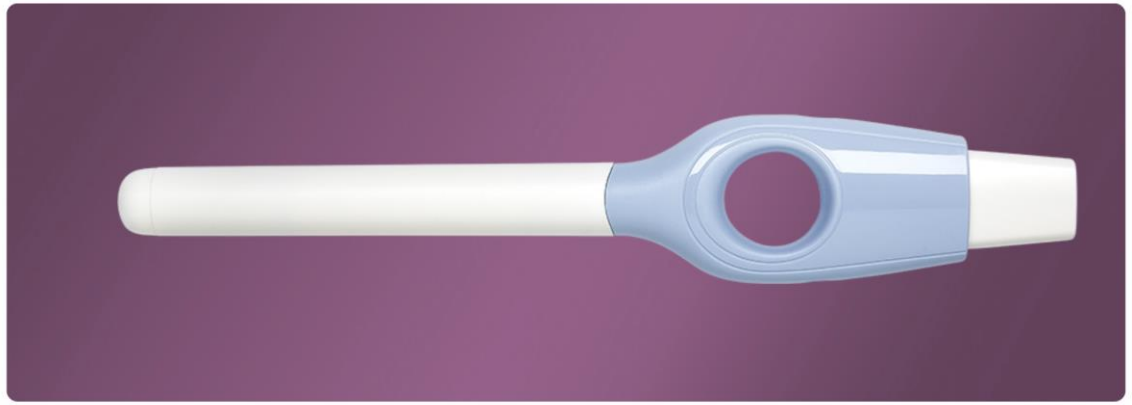
ARTICLE

Check for updates

https://doi.org/10.1038/s41467-021-21257-6 OPEN

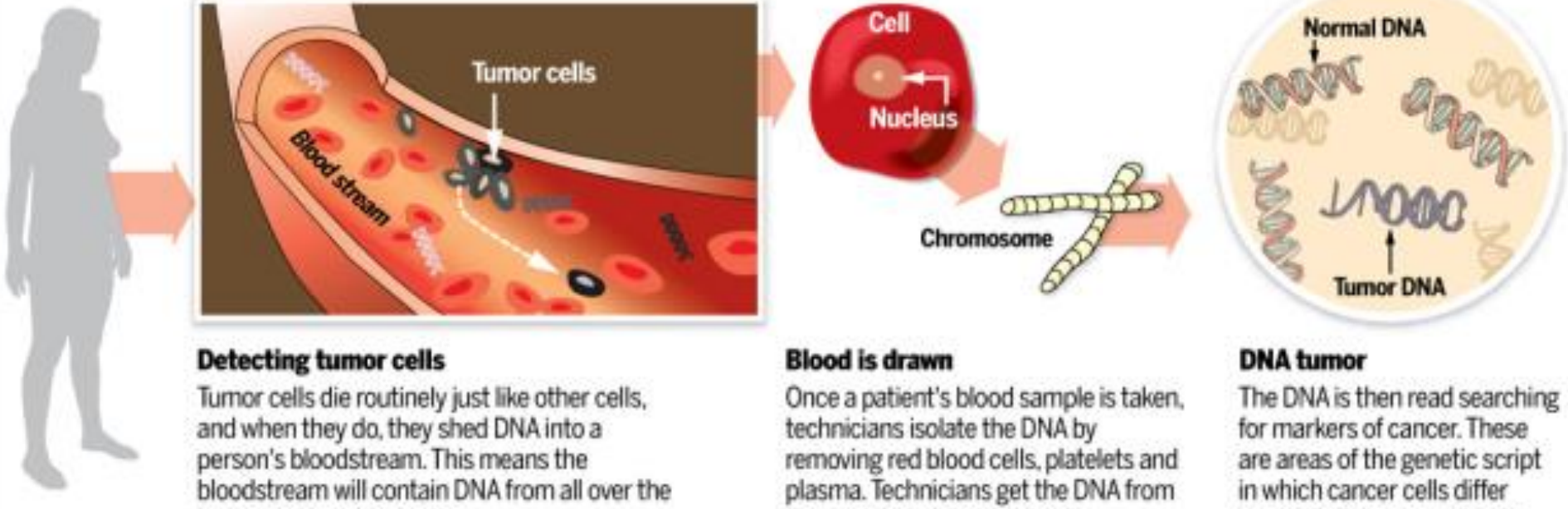
Diagnostic accuracy of cytology for the detection of endometrial cancer in urine and vaginal samples

Helena O'Flynn[1], Neil A. J. Ryan[1], Nadira Narine[2], David Shelton[2], Durgesh Rana[2] & Emma J. Crosbie[1,3]✉



How 'liquid biopsies' work

Different sections of a tumor have different genetic scripts. Taking a biopsy from the tumor itself will tell you only about the DNA in one part of the tumor.



Detecting tumor cells

Tumor cells die routinely just like other cells, and when they do, they shed DNA into a person's bloodstream. This means the bloodstream will contain DNA from all over the tumor, not just one section.

Blood is drawn

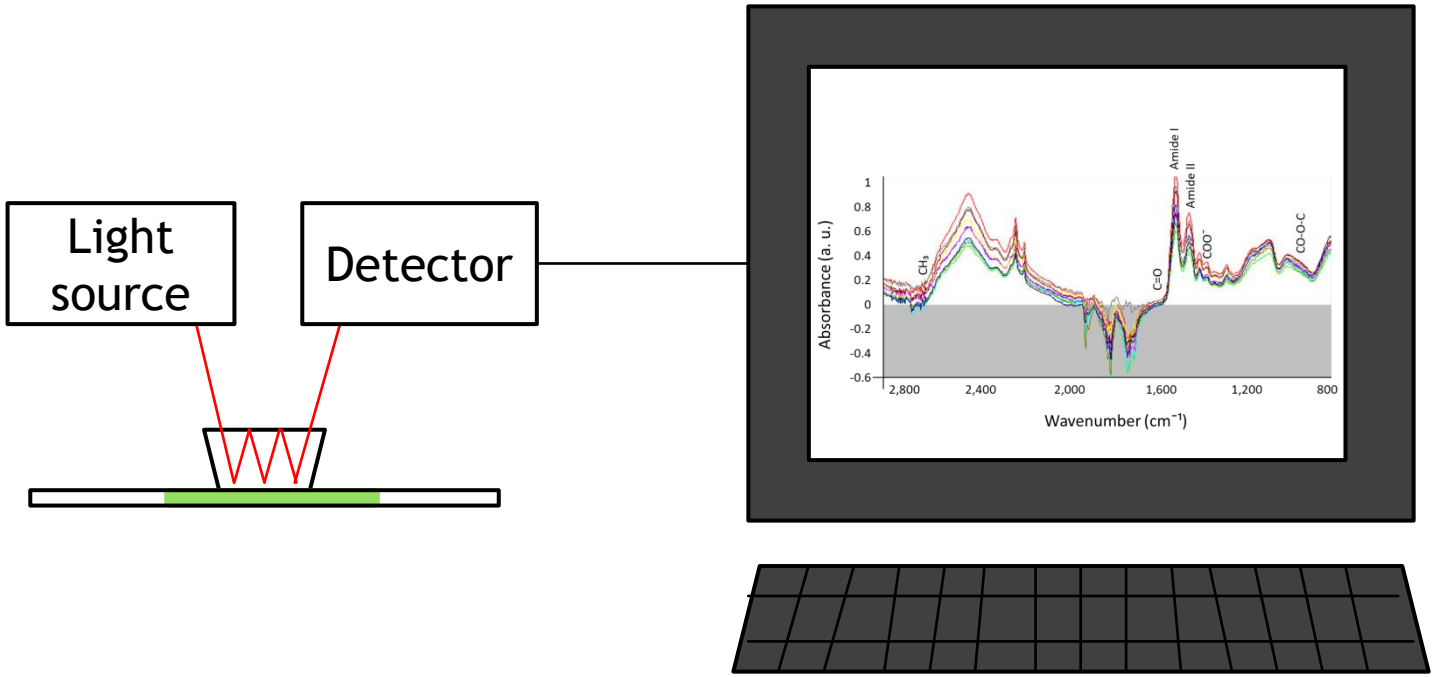
Once a patient's blood sample is taken, technicians isolate the DNA by removing red blood cells, platelets and plasma. Technicians get the DNA from the nuclei of white blood cells.

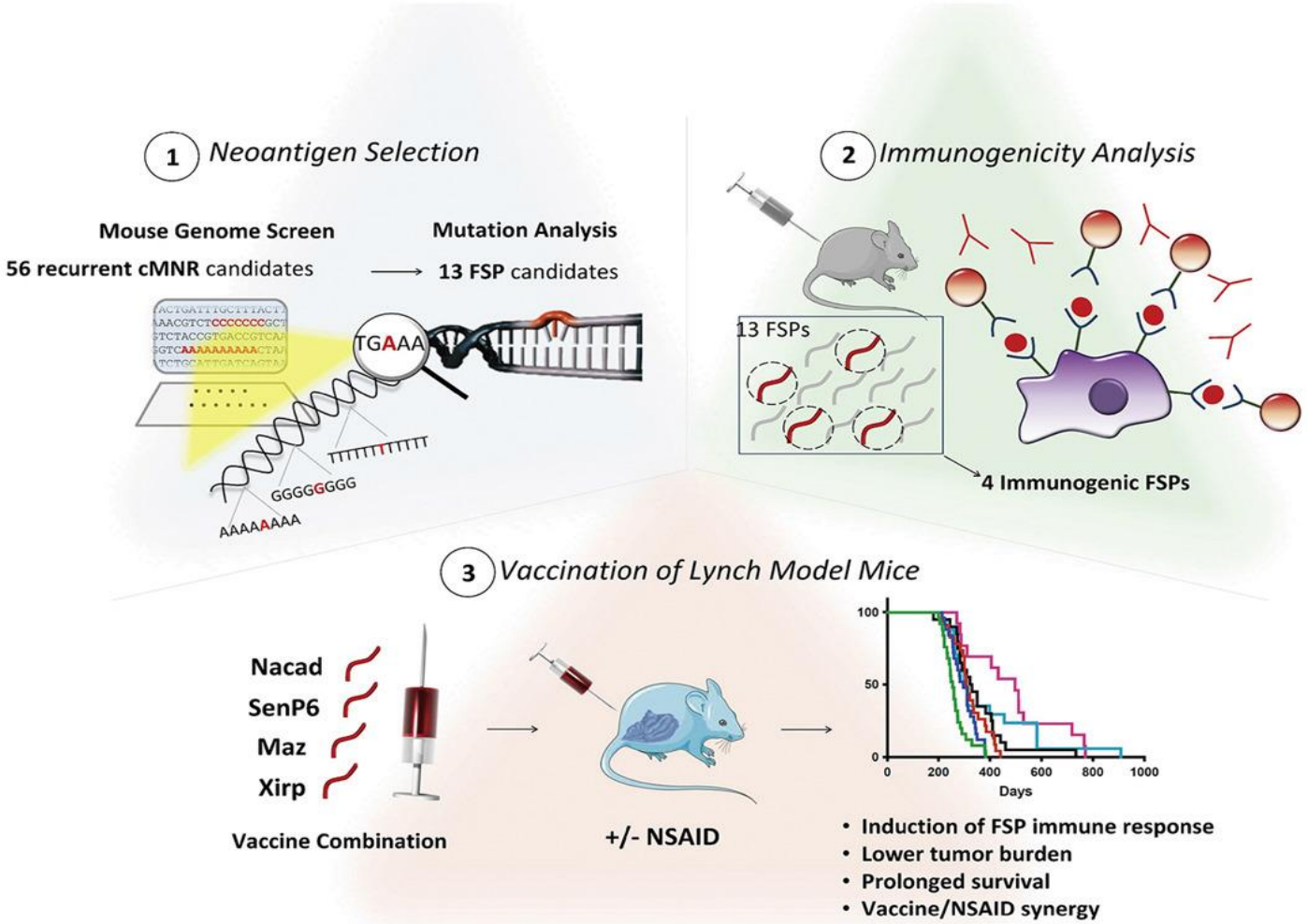
DNA tumor

The DNA is then read searching for markers of cancer. These are areas of the genetic script in which cancer cells differ markedly from normal cells.

Source: Qiagen

Journal Sentinel


Light source
Detector
Absorbance (a. u.)
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
2,800
2,400
2,000
1,600
1,200
800
Wavenumber (cm⁻¹)
CH₃
C=O
Amide I
Amide II
COO⁻
CO-O-C



Gastroenterology

Learning

RM Partners
West London Cancer Alliance
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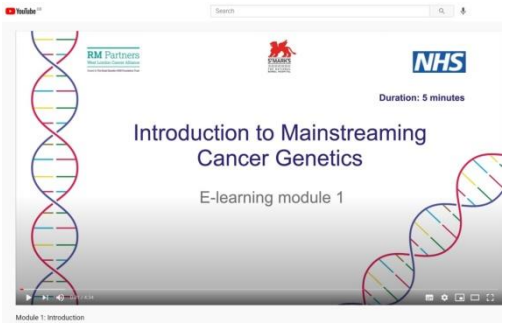
Lynch Syndrome Early Diagnosis Pathway

One aim of the NHS Long Term Plan is that 75% of cancers will be diagnosed at an early stage. This can be achieved through targeted screening and personalised surveillance of those most at risk of developing cancer, such as those with Lynch syndrome.

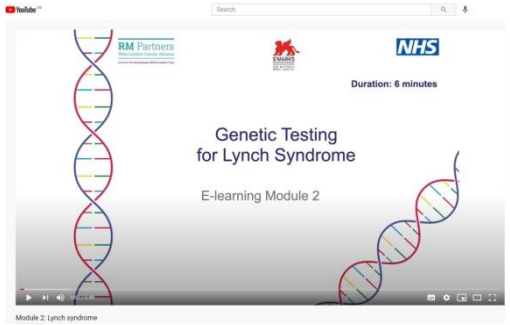
Each year, 1,100 colorectal cancers are caused by Lynch syndrome, making it the most common form of hereditary colorectal cancer. An estimated 175,000 people have Lynch syndrome in the UK, but fewer than 5% of individuals know they have the condition (Bowel Cancer UK).

Training Resources

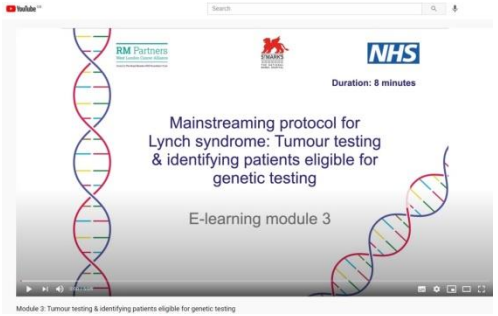
- **Module 1: Introduction**
  Click here to take the test
- **Module 2: Lynch syndrome**
  Click here to take the test
- **Module 3: Tumour testing & identifying patients eligible for genetic testing**



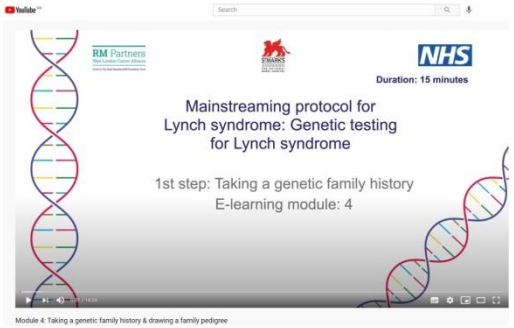
Introduction: 5 minutes



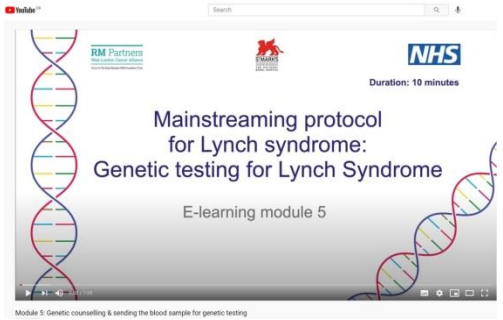
Introduction LS: 6 minutes



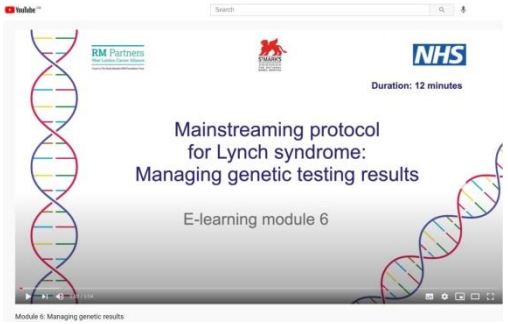
Identifying LS: 8 minutes



Family Pedigree: 15 minutes



Genetic counselling: 10 minutes



Genetic Results: 12 minutes

DOI: 10.1111/tog.12706
2021;23:9–20
The Obstetrician & Gynaecologist
http://onlinetog.org

Review

Lynch syndrome for the gynaecologist

Neil AJ Ryan PhD MRCS(Eng),[a] **Raymond FT McMahon** MD FRCPath,[b] **Neal C Ramchander** MBChB,[c] **Mourad W Seif** PhD FRCOG,[d] **D Gareth Evans** MD FRCP,[e] **Emma J Crosbie** PhD FRCOG*[f]

Screening and diagnosis

The National Institute for Health and Care Excellence now recommends that all women with endometrial cancer are screened for Lynch syndrome

Tumour-based testing

Tumour-based testing does not identify people with Lynch syndrome; it stratifies their risk for the condition.

Immunohistochemistry

Immunohistochemistry tests for loss of MMR protein expression (MMR deficiency). There is a relative lack of specificity, associated with somatic loss of MMR expression.

Microsatellite instability analysis

Microsatellites are repeated DNA motifs. Instability is a marker of hypermutation, as seen in Lynch syndrome-associated tumours. If microsatellite instability is high, Lynch syndrome is more likely.

Germline testing

Involving genomic testing of the patient, germline testing is the only way in which a Lynch syndrome diagnosis can be made. It is done using next-generation sequencing, is expensive and can only be done in specialist centres.

Risk-reducing strategies

Hysterectomy

The lifetime risk of gynaecological cancer is sufficiently high to offer total hysterectomy +/- bilateral salpingo-oophorectomy for women with Lynch syndrome who have completed childbearing.

Hormone therapy

The oral contraceptive pill reduces the risk of sporadic ovarian and endometrial cancer, and the levonorgestrel-releasing intrauterine system reduces the risk of endometrial cancer in the general population, so it is thought these may also reduce cancer risk in Lynch syndrome.

Aspirin

Aspirin has been shown to reduce the risk of cancer in Lynch syndrome. Trials to determine the best dose of aspirin for cancer prevention are ongoing.

Lifestyle modifications

While few studies have specifically explored the effect of lifestyle choices on cancer risk in Lynch syndrome, smoking cessation, maintaining a healthy body mass index and increased exercise are thought sensible.

Gynaecological surveillance

There is currently no strong evidence to support gynaecological surveillance for the early detection of gynaecological cancer in Lynch syndrome.

The future...

Novel strategies are being tested to harness the Lynch syndrome patient's own immune system to prevent cancers through vaccination. Novel diagnostic methods, with the potential for complete automation, are in development; such technologies would simplify and reduce the costs of Lynch syndrome screening and diagnostic pathways.

This is a summary of a review published in TOG. For further details on Lynch syndrome, please read the full article:
Ryan NAJ, McMahon RFT, Ramchander NC, Seif MW, Evans DG, Crosbie EJ. Lynch syndrome for the gynaecologist. The Obstetrician & Gynaecologist 2021; https://doi.org/10.1111/tog.12706

onlinetog.org

Questions?

- neilryan@nhs.net