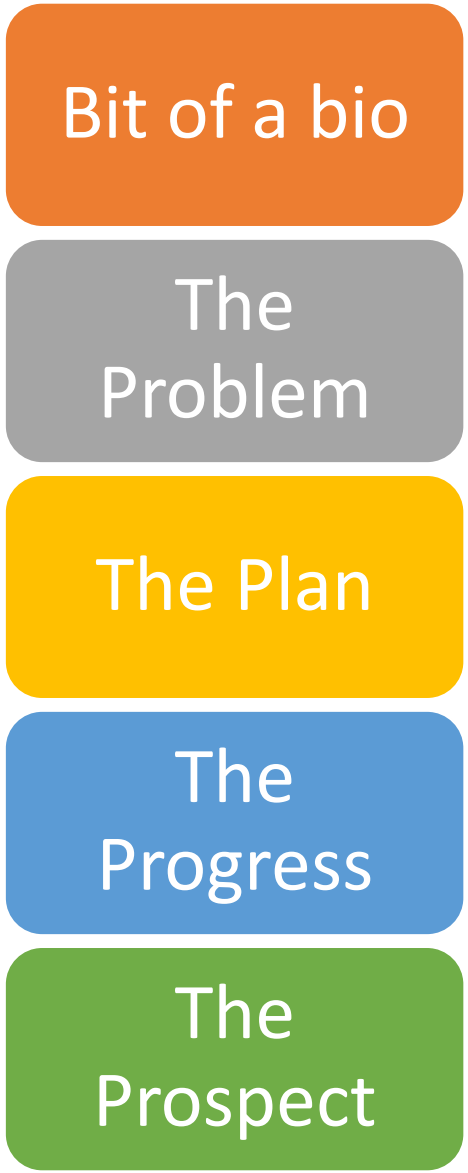
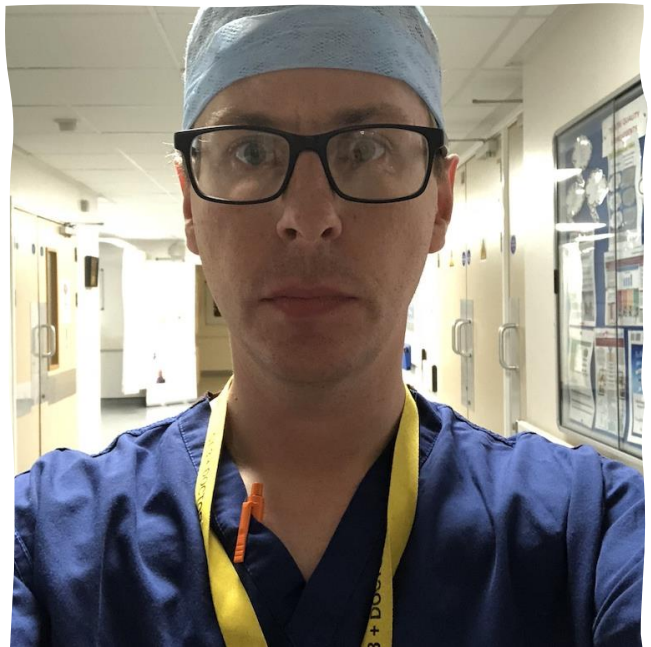
Lynch syndrome and female cancer: PETALS, BOLT, UP, MOSAIC - turning gibberish into knowledge

Neil Ryan
PhD MRCS(Eng) MRCOG FHEA
Email: neilryan@nhs.net Twitter: @neilajryan

Overview





Mini Bio

- London
- Bristol Medical School
- Foundation London
- Army
- ENT training
- O&G number Bristol
- PhD Manchester
- ST in Bristol
- Gynaecology Oncology Fellow
- RCOG Oncology Subspecialty Fellow Edinburgh


LAKOTA
26th SEPT


The Royal Infirmary of Edinburgh
NHS

The problem

What is Lynch syndrome?

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

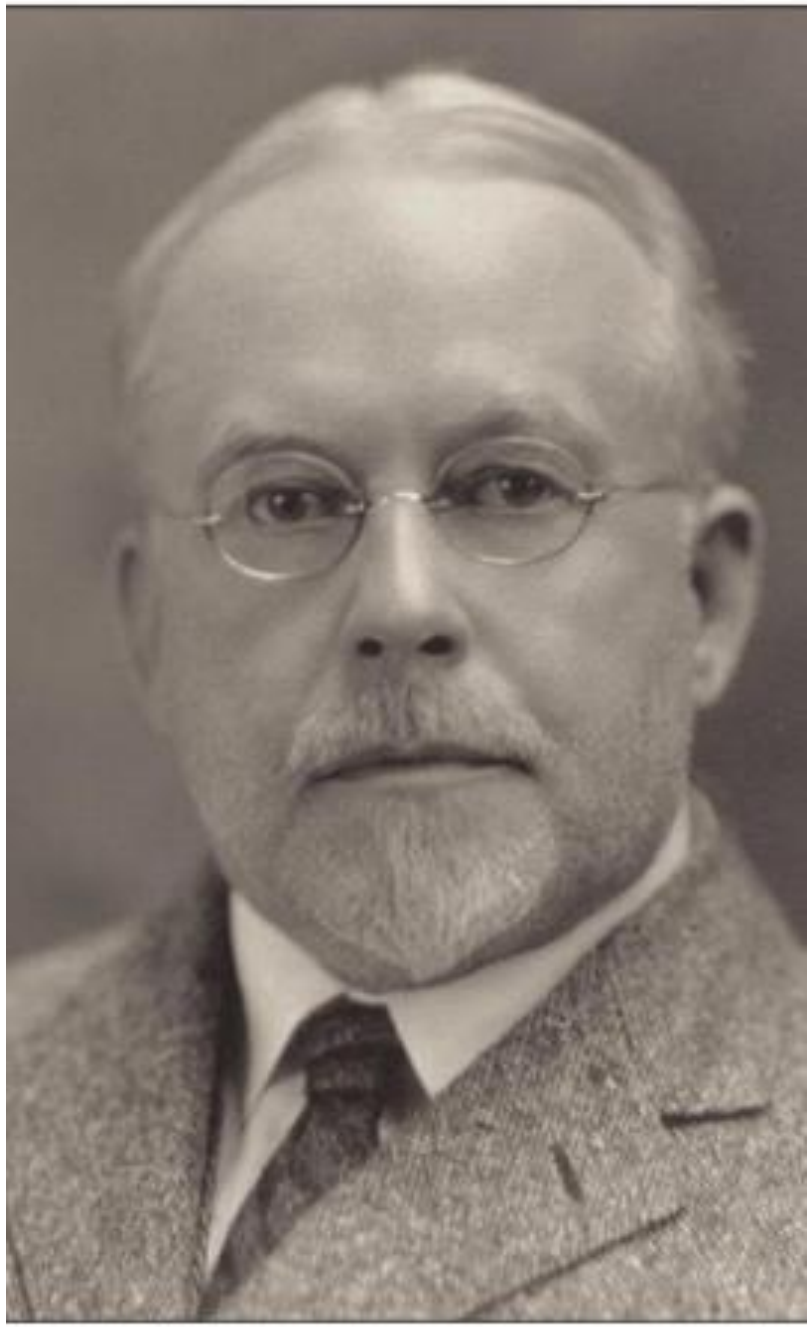
Up to 95% of Lynch syndrome carriers are unaware

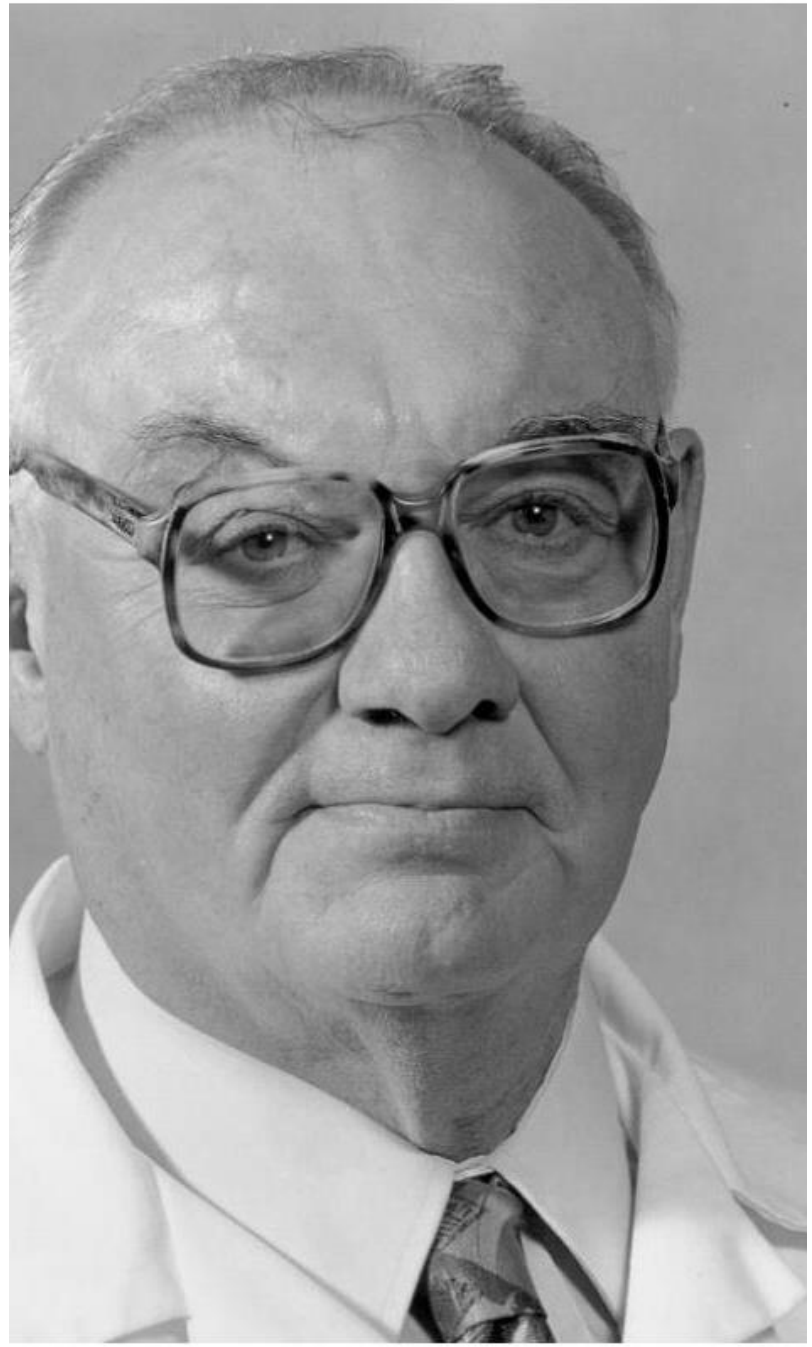
Lynch syndrome may occur in up to

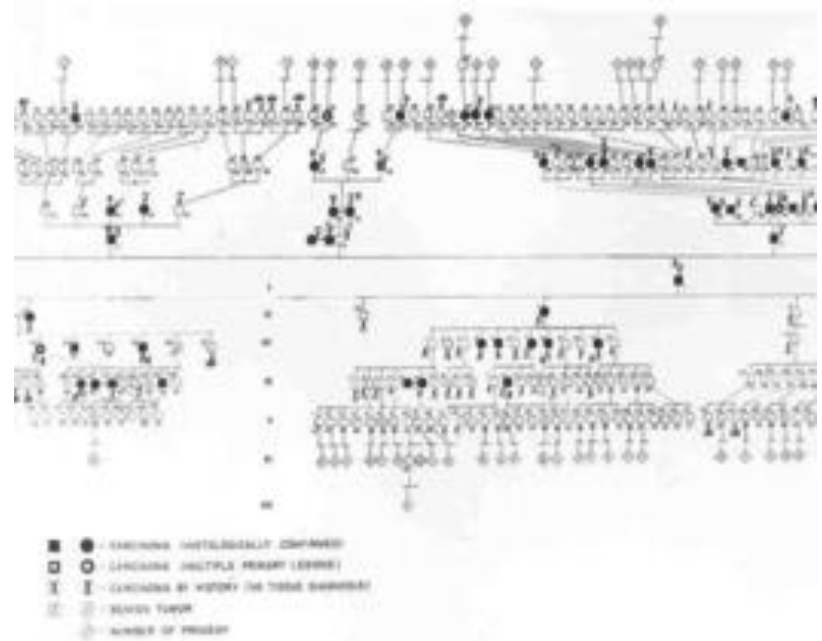
1 in 278

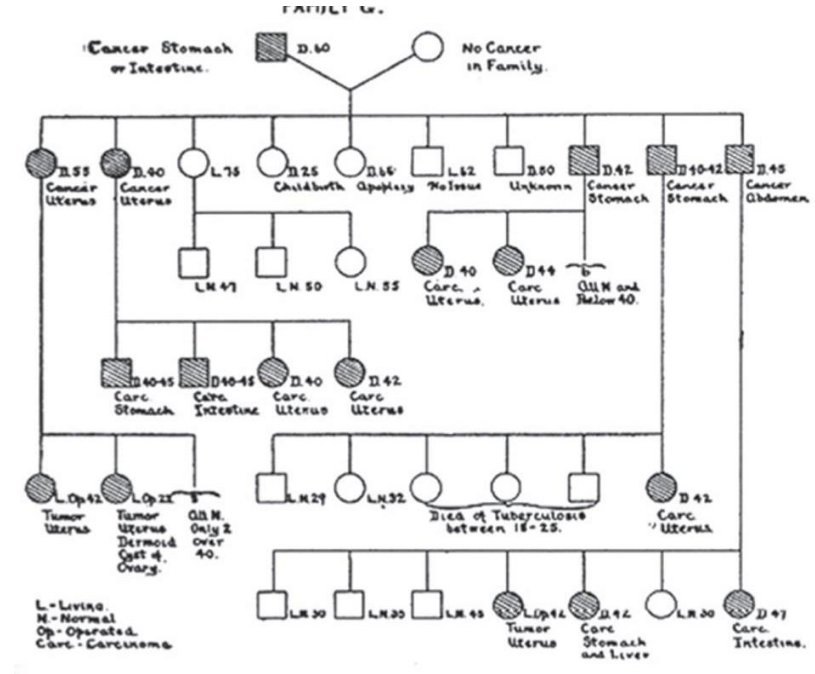
people

making it the most common inherited cause of cancer








Cancer Stomach or Intestine.
D.60
No Cancer in Family.
D.55 Cancer Uterus
D.40 Cancer Uterus
L.75
D.25 Childbirth
D.26 Apoplexy
L.42 No Issue
D.50 Unknown
D.42 Cancer Stomach
D.40-42 Cancer Stomach
D.45 Cancer Abdomen
L.N.47
L.N.50
L.N.55
D.40 Canc. Uterus.
D.44 Canc Uterus
6 Ch. N and Below 40.
D.40-45 Canc Stomach
D.40-45 Canc Intestine
D.40 Canc Uterus
D.42 Canc Uterus
L.Op.42 Tumor Uterus
L.Op.22 Tumor Uterus Dermoid Cyst of Ovary.
3 Ch. N. Only 2 over 40.
L.N.29
L.N.32
Died of Tuberculosis between 18-25.
D.42 Canc. Uterus
L.N.20
L.N.20
L.N.45
L.Op.42 Tumor Uterus
D.42 Canc Stomach and Liver
L.N.20
D.47 Canc. Intestine.
L - Living.
N - Normal
Op - Operated.
Canc - Carcinoma

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†

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*§

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

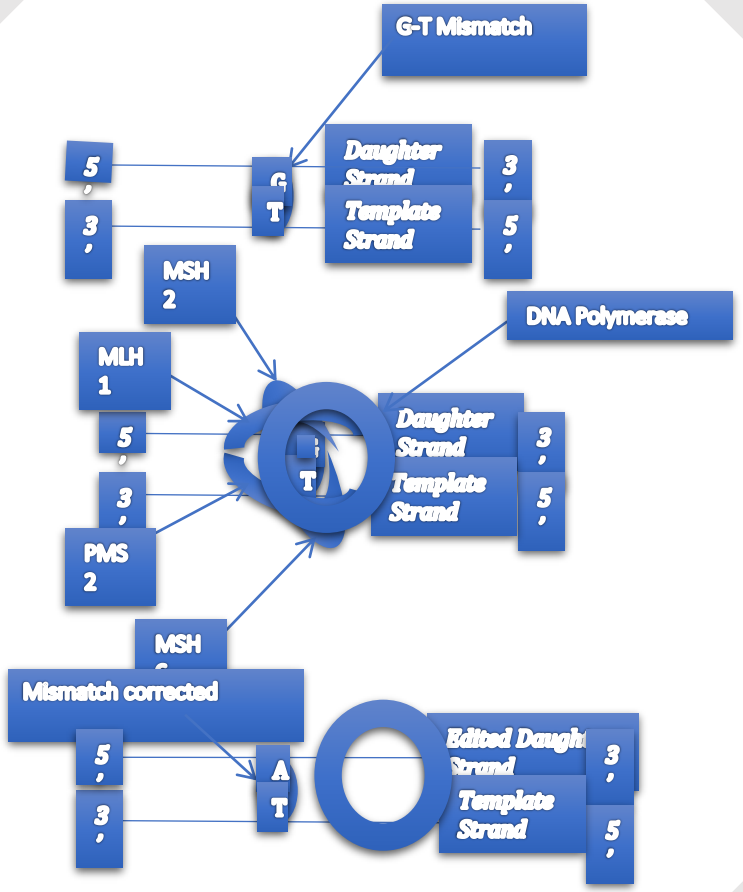
Clues to the Pathogenesis of Familial Colorectal Cancer

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†

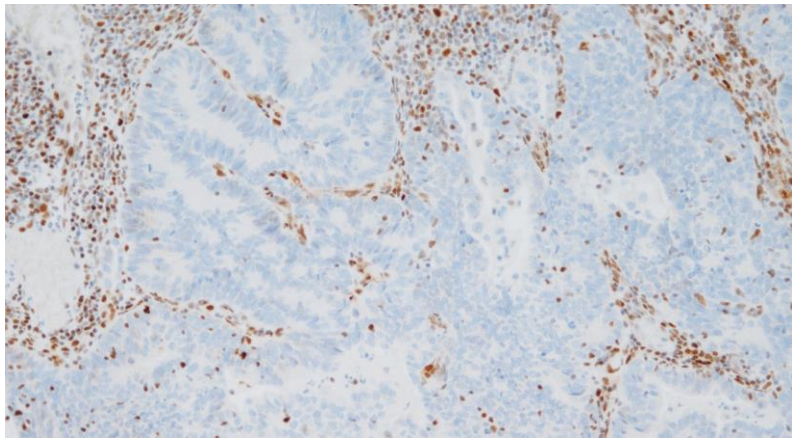
Mutation of a *mutL* Homolog in Hereditary Colon Cancer

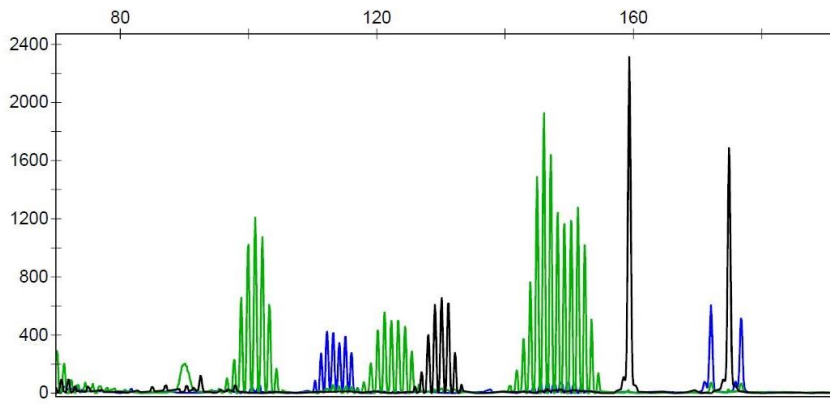
Nickolas Papadopoulos,* Nicholas C. Nicolaides,* Ying-Fei Wei, Steven M. Ruben, Kenneth C. Carter, Craig A. Rosen,

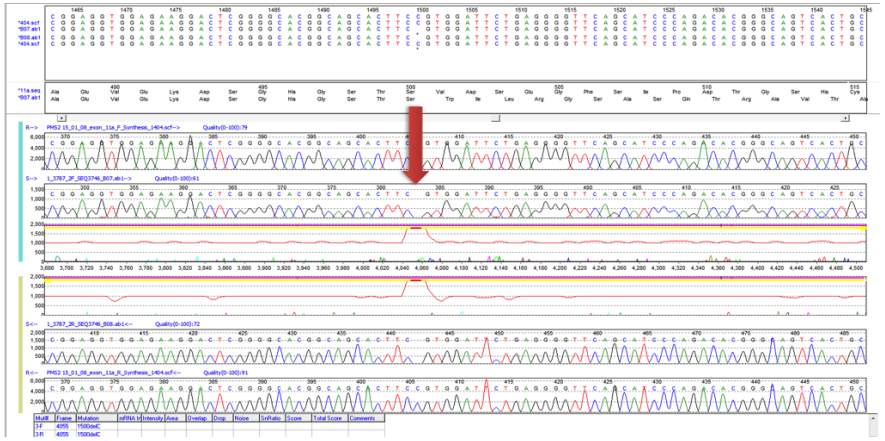
Mismatch repair (MMR) system

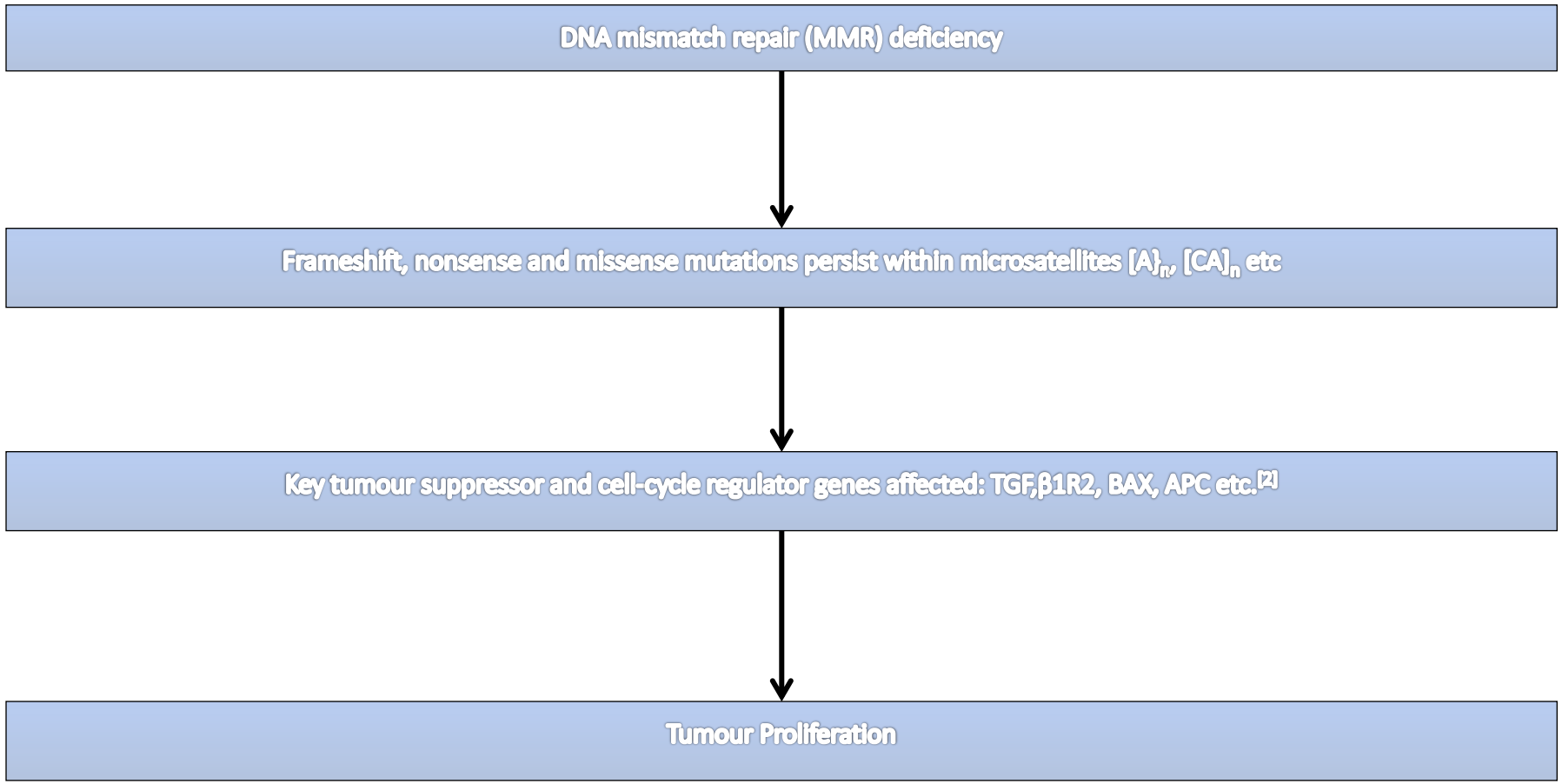


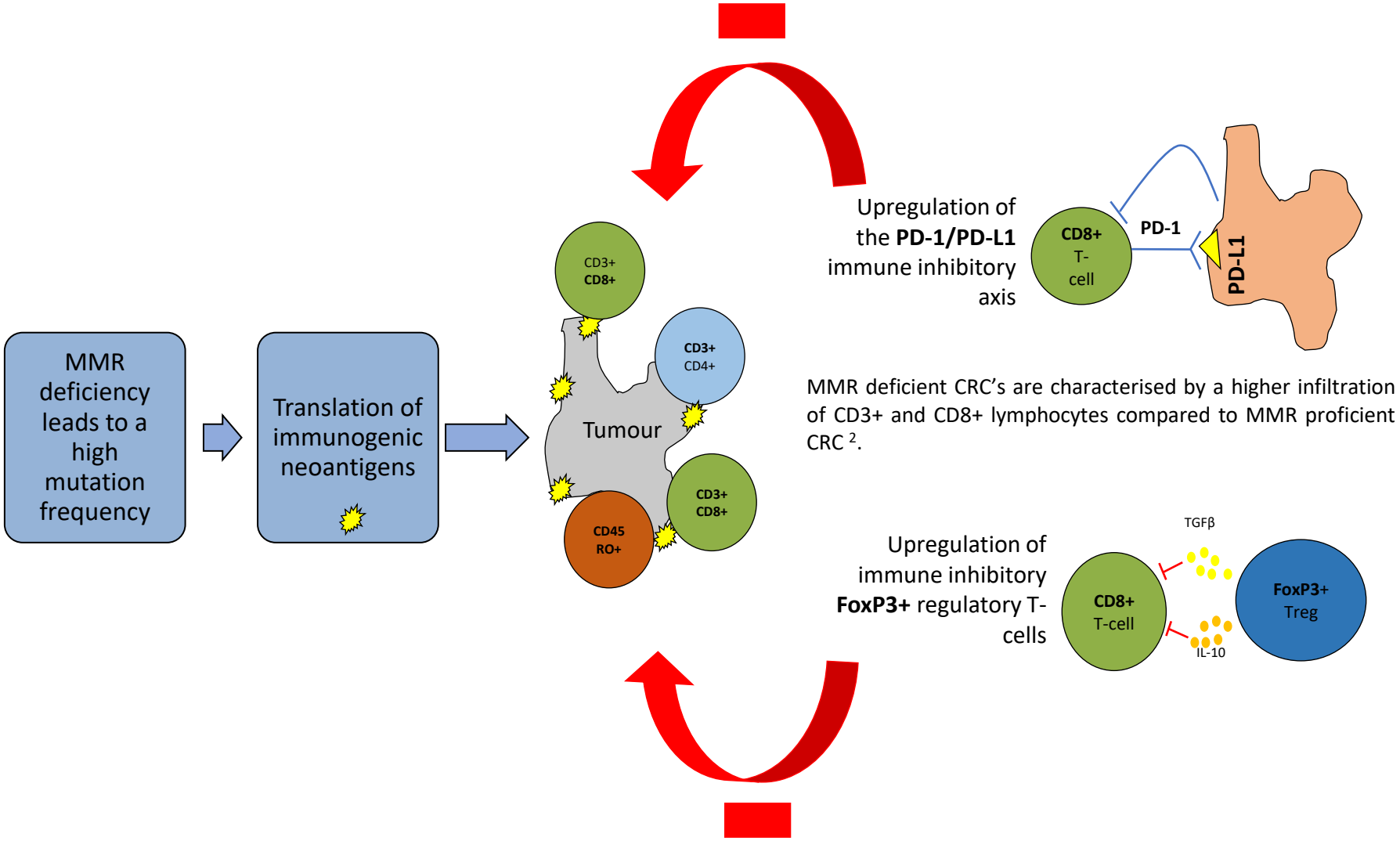
Courtesy of Dr N Ramchander

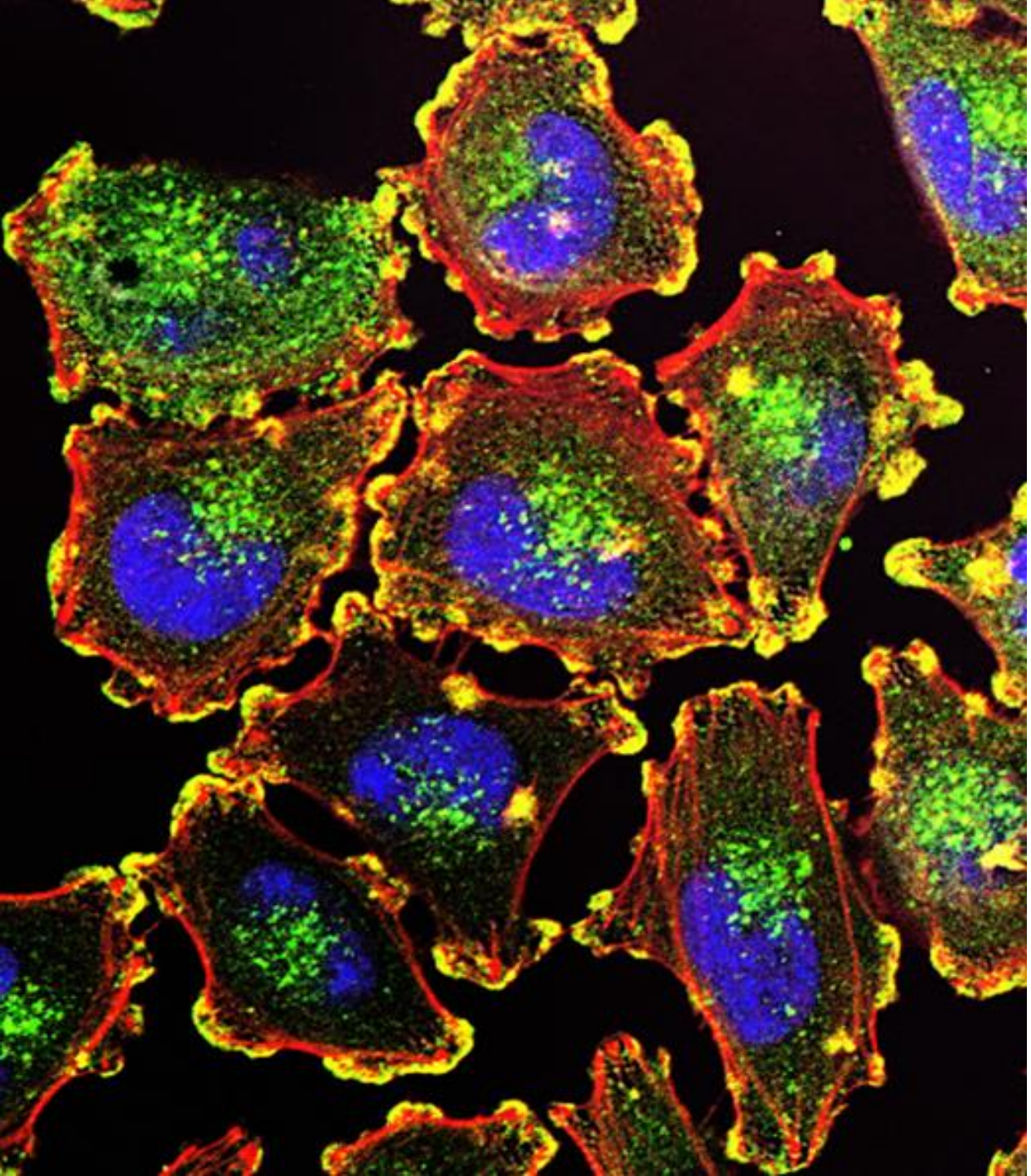



80
120
160
2400
2000
1600
1200
800
400
0



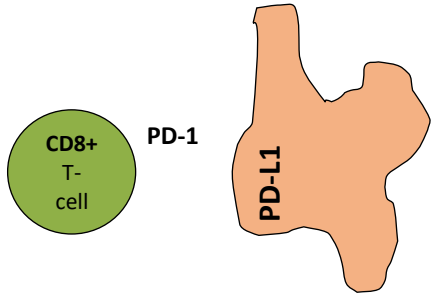

DNA mismatch repair (MMR) deficiency
Frameshift, nonsense and missense mutations persist within microsatellites $[A]_n$, $[CA]_n$ etc
Key tumour suppressor and cell-cycle regulator genes affected: TGFβ1R2, BAX, APC etc.[2]
Tumour Proliferation

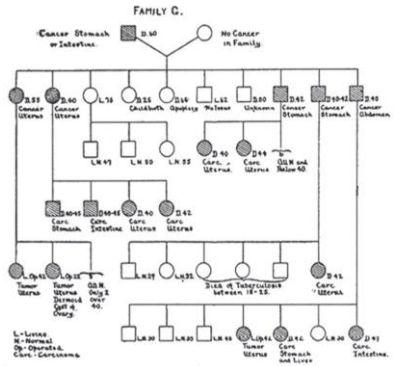

MMR deficiency leads to a high mutation frequency
Translation of immunogenic neoantigens
CD3+ CD8+
CD3+ CD4+
Tumour
CD3+ CD8+
CD45 RO+
Upregulation of the PD-1/PD-L1 immune inhibitory axis
CD8+ T-cell
PD-1
PD-L1
MMR deficient CRC's are characterised by a higher infiltration of CD3+ and CD8+ lymphocytes compared to MMR proficient CRC [2].
Upregulation of immune inhibitory FoxP3+ regulatory T-cells
TGFβ
CD8+ T-cell
FoxP3+ Treg
IL-10

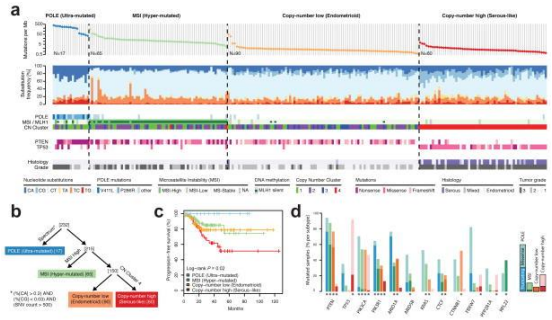


- Immune check point mechanisms can be targeted by mono-colonal antibody based therapies
- In 2000 Medarex launched its first clinical trials with a human Mab binding to CTLA-4.
- Approval of ipilimumab for the treatment of metastatic melanoma by the FDA in 2011.

Upregulation of the **PD-1/PD-L1** immune inhibitory axis







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

ORIGINAL ARTICLE

Genetic counseling and cascade genetic testing in Lynch syndrome

Heather Hampel[1]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prophylactic Surgery to Reduce the Risk of Gynecologic Cancers in the Lynch Syndrome

Kathleen M. Schmeler, M.D., Henry T. Lynch, M.D., Lee-may Chen, M.D., Mark F. Munsell, M.S., Pamela T. Soliman, M.D., Mary Beth Clark, M.S.W., Molly S. Daniels, M.S., Kristin G. White, B.S., Stephanie G. Boyd-Rogers, R.N., Peggy G. Conrad, M.S., Kathleen Y. Yang, M.D., Mary M. Rubin, Ph.D., Charlotte C. Sun, Dr.P.H., Brian M. Slomovitz, M.D., David M. Gershenson, M.D., and Karen H. Lu, M.D.

GASTROENTEROLOGY 2006;130:665–671

Decrease in Mortality in Lynch Syndrome Families Because of Surveillance

ANDREA E. DE JONG,*,† YVONNE M. C. HENDRIKS,§ JAN H. KLEIBEUKER,¶ SYBRAND Y. DE BOER,‖ ANNEMIEKE CATS,# GERRIT GRIFFIOEN,† FOKKO M. NAGENGAST,** FRITS G. NELIS,†† MATTI A. ROOKUS,§§ and HANS F. A. VASEN*,†

*The Netherlands Foundation for the Detection of Hereditary Tumors, †Department of Gastroenterology and §Department of Human and Clinical Genetics, Leiden University Medical Center, Leiden; ¶Department of Gastroenterology, University of Groningen and University Medical Center Groningen, Groningen; ‖Rijnstate Hospital Arnhem, Arnhem; #The Netherlands Cancer Institute, Amsterdam; **University Medical Center Nijmegen, Nijmegen; ††Sophia Hospital Zwolle, Zwolle; and §§Department of Epidemiology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

CURRENT CONCEPTS IN CLINICAL SURGERY

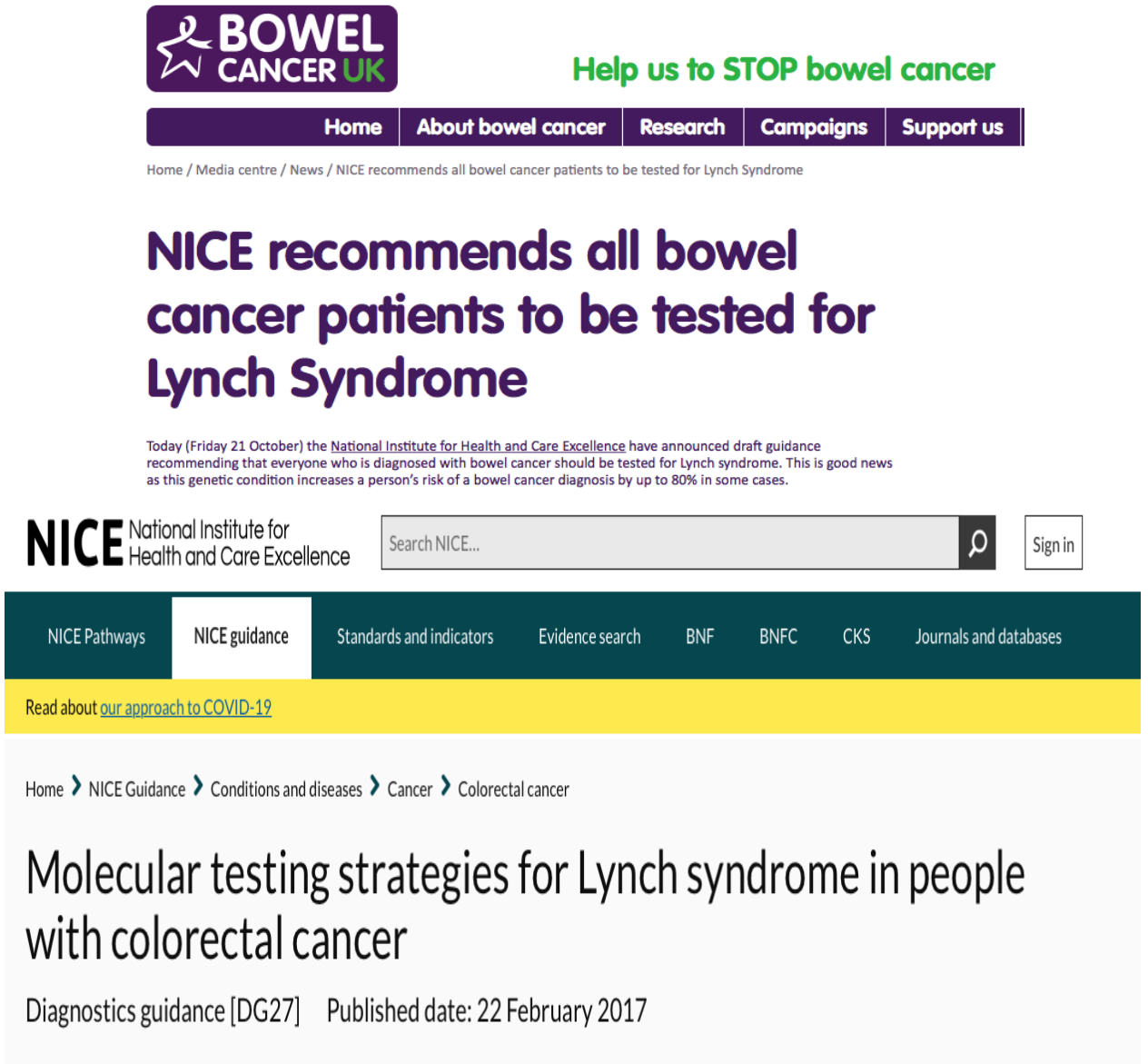
Preventive surgery for colon cancer in familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer syndrome

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

CANCER BIOMARKERS

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

In bowel cancer



BOWEL CANCER UK

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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.

NICE National Institute for Health and Care Excellence

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Read about our approach to COVID-19

Home › NICE Guidance › Conditions and diseases › Cancer › Colorectal cancer

Molecular testing strategies for Lynch syndrome in people with colorectal cancer

Diagnostics guidance [DG27] Published date: 22 February 2017

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 5, 2005 VOL. 352 NO. 18

Screening for the Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer)

Heather Hampel, M.S., Wendy L. Frankel, M.D., Edward Martin, M.D., Mark Arnold, M.D., Karamjit Khanduja, M.D., Philip Kuebler, M.D., Ph.D., Hidewaki Nakagawa, M.D., Ph.D., Kaisa Sotamaa, M.D., Thomas W. Prior, Ph.D., Judith Westman, M.D., Jenny Panescu, B.S., Dan Fix, B.S., Janet Lockman, B.S., Ilene Comeras, R.N., and Albert de la Chapelle, M.D., Ph.D.

n=1,066

This Issue | Views 8,007 | Citations 0 | Altmetric 366

Original Investigation

April 2017

More

Prevalence and Spectrum of Germline Cancer Susceptibility Gene Mutations Among Patients With Early-Onset Colorectal Cancer

Rachel Pearlman, MS, CGC[1]; Wendy L. Frankel, MD[2]; Benjamin Swanson, MD[2]; et al

Author Affiliations

JAMA Oncol. 2017;3(4):464-471. doi:10.1001/jamaoncol.2016.5194

n=450

ORIGINAL ARTICLE

Outcome of 24 years national surveillance in different hereditary colorectal cancer subgroups leading to more individualised surveillance

Lars Joachim Lindberg,[1] Steen Ladelund,[1] Birgitte Lidegaard Frederiksen,[1] Lars Smith-Hansen,[1] Inge Bernstein[1,2]

n=13,444 surveillance sessions

Identification of Lynch Syndrome Among Patients With Colorectal Cancer

Leticia Moreira, MD
Francese Balaguer, MD, PhD
Noralane Lindor, MD
Albert de la Chapelle, MD, PhD
Heather Hampel, MS
Lauri A. Aaltonen, MD, PhD
John L. Hopper, PhD
Loic Le Marchand, MD, PhD
Steven Gallinger, MD
Polly A. Newcomb, PhD, MPH

Context Lynch syndrome is the most common form of hereditary colorectal cancer (CRC) and is caused by germline mutations in DNA mismatch repair (MMR) genes. Identification of gene carriers currently relies on germline analysis in patients with MMR-deficient tumors, but criteria to select individuals in whom tumor MMR testing should be performed are unclear.

Objective To establish a highly sensitive and efficient strategy for the identification of MMR gene mutation carriers among CRC probands.

Design, Setting, and Patients Pooled-data analysis of 4 large cohorts of newly diagnosed CRC probands recruited between 1994 and 2010 (n=10 206) from the Co... lon Cancer Family Registry, the EPICOLON project, the Ohio Stat... the University of Helsinki examining personal, tumor-related, and fa... tics, as well as microsatellite instability, tumor MMR immunostainin... MMR mutational status data.

n=10,206

Clinical and Molecular Characteristics of Post-Colonoscopy Colorectal Cancer: A Population-based Study

Elena M. Stoffel,[1,2] Rune Erichsen,[2] Trine Frøslev,[2] Lars Pedersen,[2] Mogens Vyberg,[3] Erika Koeppe,[1] Seth D. Crockett,[5] Stanley R. Hamilton,[4] Henrik T. Sørensen,[2] and John A. Baron[5]

[1]Department of Internal Medicine, University of Michigan Health System, Ann Arbor, Michigan; [2]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [3]Institute of Pathology, Department of Clinical Medicine, Aalborg

n=10,365

Next-Generation Sequencing Panels for the Diagnosis of Colorectal Cancer and Polyposis Syndromes: A Cost-Effectiveness Analysis

Carlos J. Gallego, Brian H. Shirts, Caroline S. Bennette, Greg Guzauskas, Laura M. Amendola, Martha Horike-Pyne, Fuki M. Hisama, Colin C. Pritchard, William M. Grady, Wylie Burke, Gail P. Jarvik, and David L. Veenstra

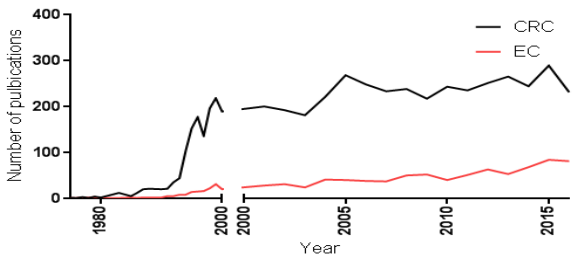
A B S T R A C T

A systematic review and economic evaluation of diagnostic strategies for Lynch syndrome

Tristan Snowsill,[1*] Nicola Huxley,[1] Martin Hoyle,[1] Tracey Jones-Hughes,[1] Helen Coelho,[1] Chris Cooper,[1] Chris Hyde[1]

Assessment Group (PenTAG), University of Exeter Medical School, ...netics, Cardiff University, Cardiff, UK

Crude comparison of publication number



Population-Based Molecular Detection of Heredi... Nonpolyposis Colorectal Cancer

By Reijo Salovaara, Anu Loukola, Paula Kristo, Helena Kääriäinen, Heikki Ahtola, Matti Eskelinen, Niilo... Risto Julkunen, Eero Kangas, Seppo Ojala, Jukka Tulikoura, Erkki Valkamo, Heikki Järvinen, Jukka-Pekk... Lauri A. Aaltonen, and Albert de la Chapelle

Purpose: Cancer morbidity and mortality can be dramatically reduced by colonoscopic screening of individuals with the hereditary nonpolyposis colorectal cancer (HNPCC) syndrome, creating a need to identify HNPCC. We studied how HNPCC identification should

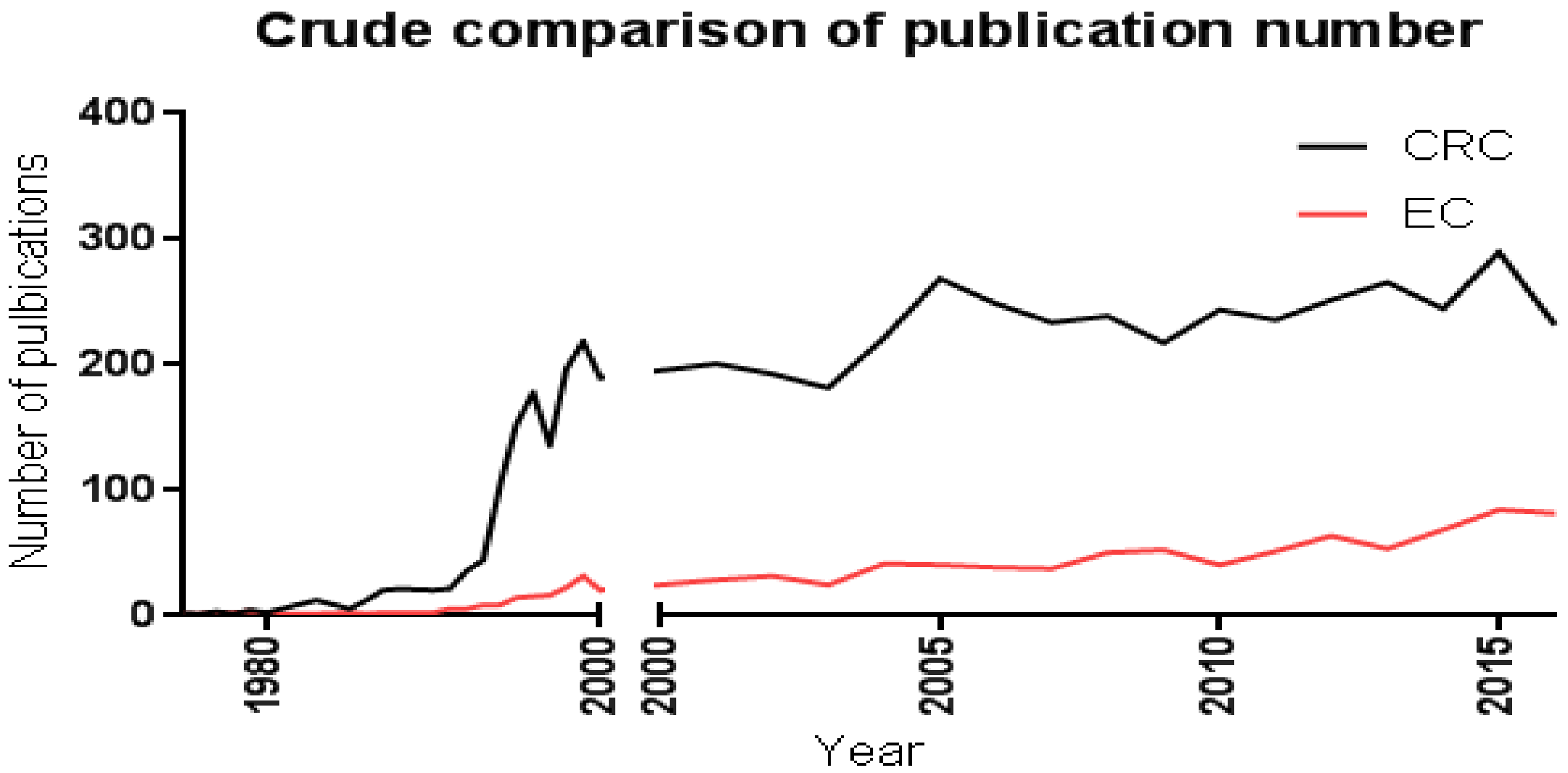
first-degree relative with colorectal or en... cer. Notably, 17 (94%) of 18 patients had... these three features, which were presen... 535 patients. Combining these data w... study of 509 patients, mutation-positi...

n=535

BRAF M... Frequently Present in Sporadic Colorectal Cancer ... ylated hMLH1, But Not in Hereditary Nonpoly... rectal Cancer

Guoren Deng, James Gum,[2] Brian A. Alle... Marvin H. Sl... zanne Crawley,[1] erdiman,[2] ruta,[2] Young S. Kim[1]

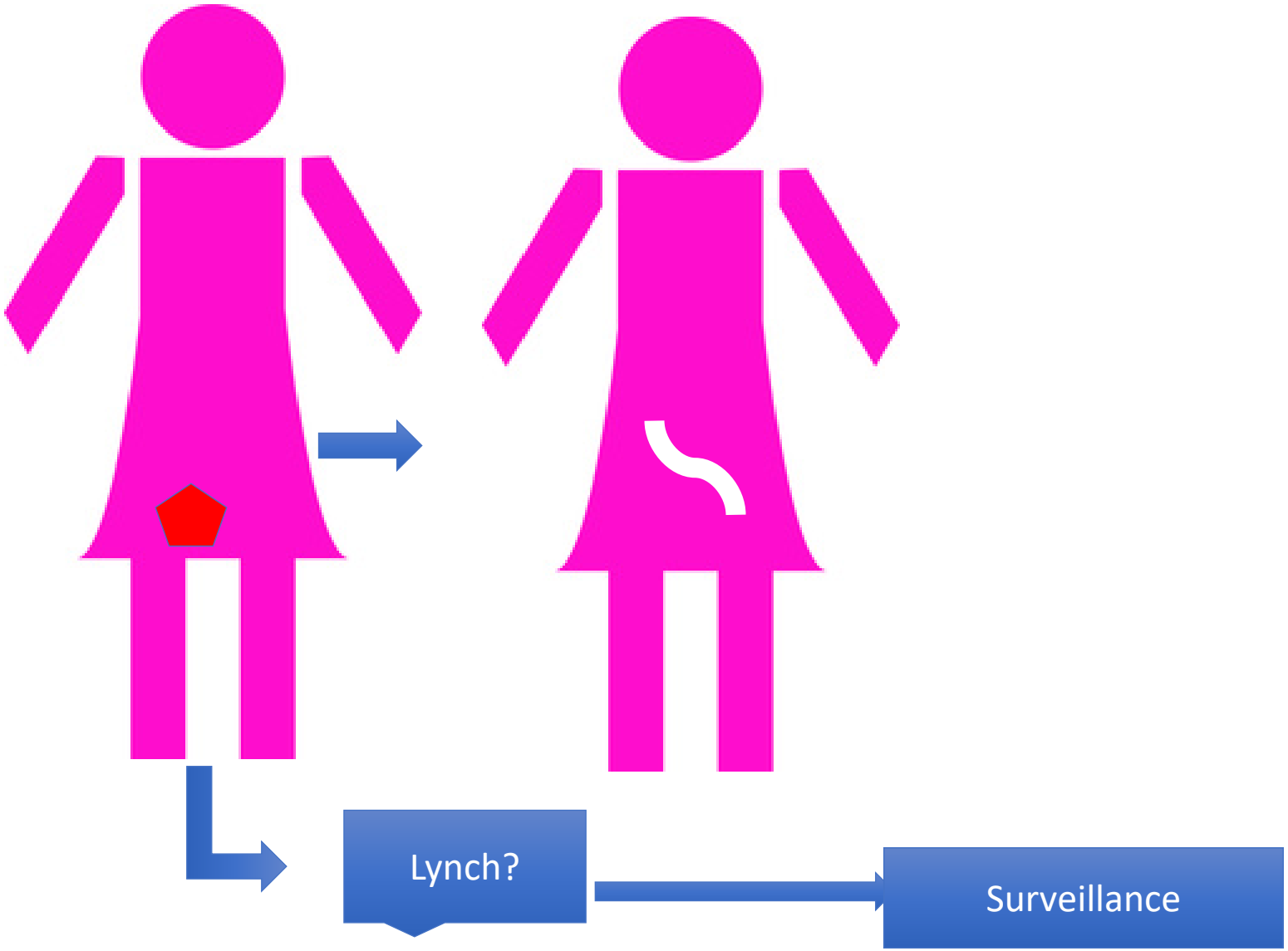
Conclusions: BRAF mutations are frequently present in sporadic colorectal cancer with methylated *hMLH1*, but not in HNPCC-related cancers. This discrepancy of *BRAF* mutations between sporadic MSI+ cancer and HNPCC might be used in a strategy for the detection of HNPCC families.



((((endometrial cancer) OR uterine) OR womb cancer) AND (Lynch syndrome OR HNPCC)

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


Lynch?
Surveillance

ORIGINAL ARTICLE

Prophylactic Surgery to Reduce the Risk of Gynecologic Cancers in the Lynch Syndrome

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ABSTRACT

Policy@Manchester Blogs: **All posts**

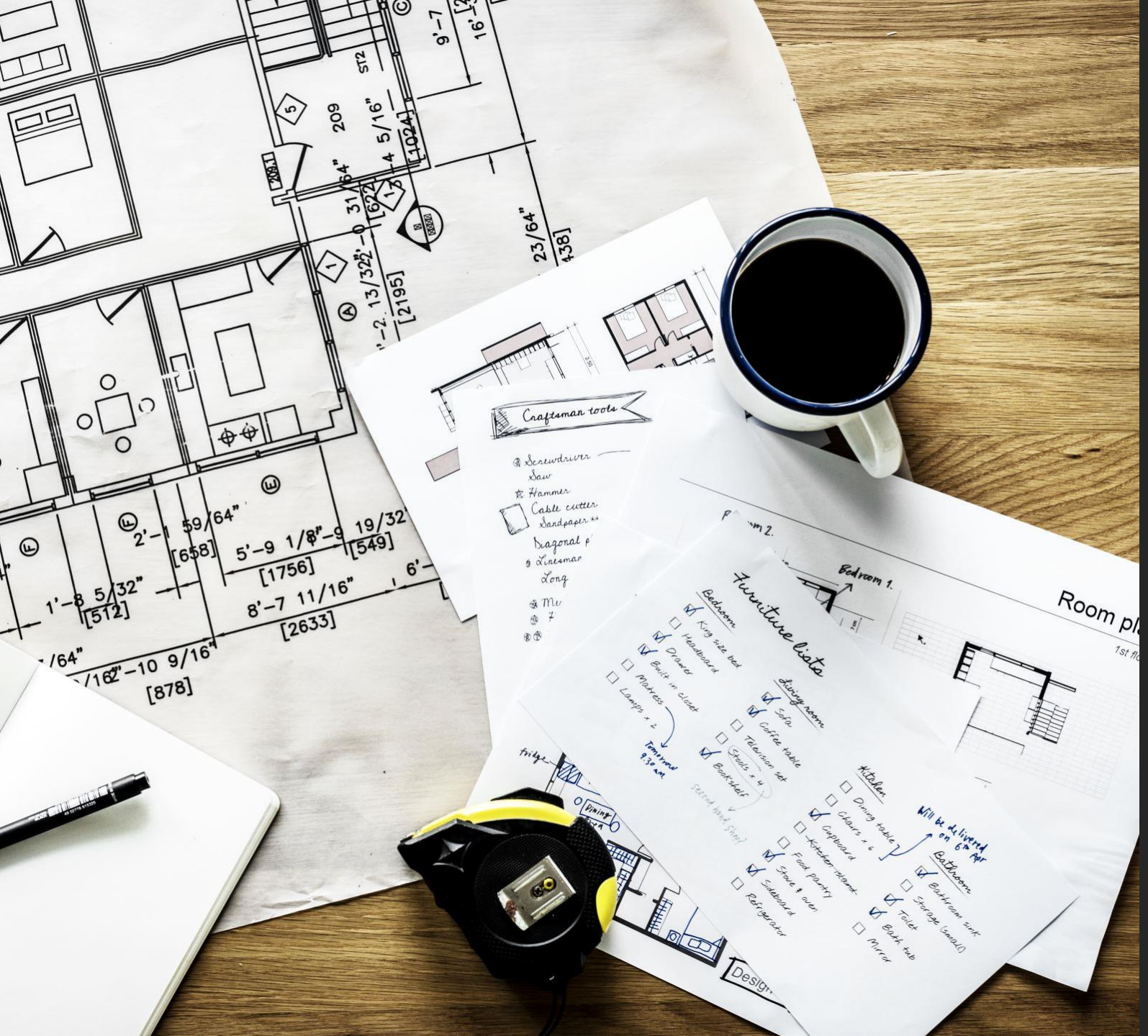
You are here: Home / All posts / Can cancer services be sexist? Rectifying a gender disparity in cancer screening practices.

Can cancer services be sexist? Rectifying a gender disparity in cancer screening practices.


By Emma Crosbie and Neil Ryan
Filed Under: All posts, Health and Social Care
Posted: February 7, 2018

The Questions

- What proportion of endometrial cancer has MMRd?
- What proportion of endometrial cancer is related to Lynch syndrome?
- What is the best way to screen endometrial cancer for MMRd?
- How feasible is it to screen all endometrial cancers for MMRd/Lynch syndrome?
- Does the aetiology of MMRd effect the immune response?


Craftsman tools
Screwdriver
Saw
Hammer
Cable cutter
Sandpaper
Furniture lists
Bedroom
King size bed
Headboard
Drawer
Built in closet
Mattress
Lamps x 2
Living room
Sofa
Coffee table
Television set
Chairs x 4
Bookshelf
Kitchen
Dining table
Chairs x 6
Cupboard
Kitchen island
Food pantry
Stove & oven
Sideboard
Refrigerator
Bathroom
Bathroom sink
Storage (small)
Toilet
Bath tub
Mirror
Will be delivered on 6th Apr
Bedroom 1.
Room pl
1st flo
Design

The plan

petals

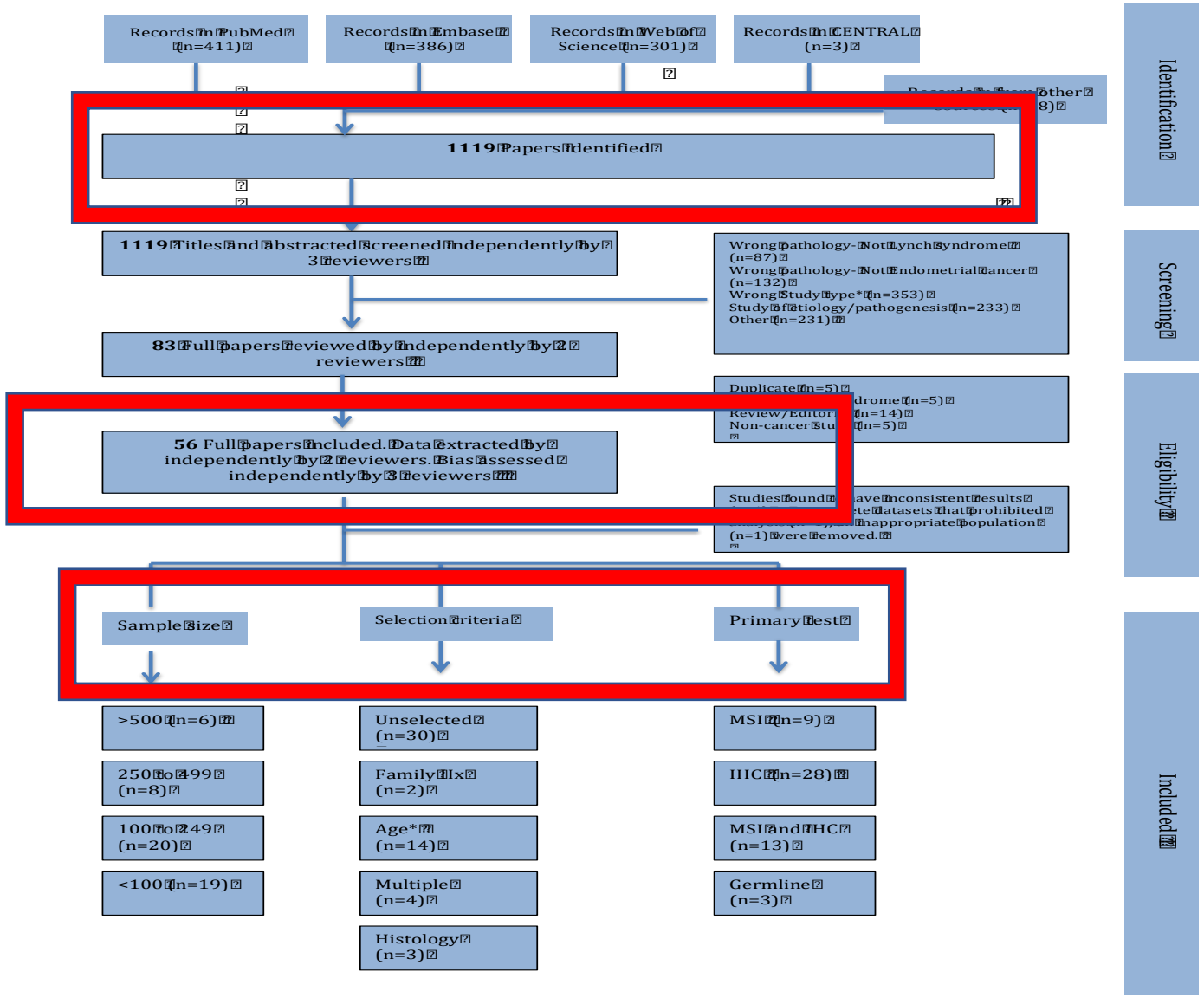
Proportion of Endometrial Tumours
Associated with Lynch Syndrome

SYSTEMATIC REVIEW | Genetics in Medicine

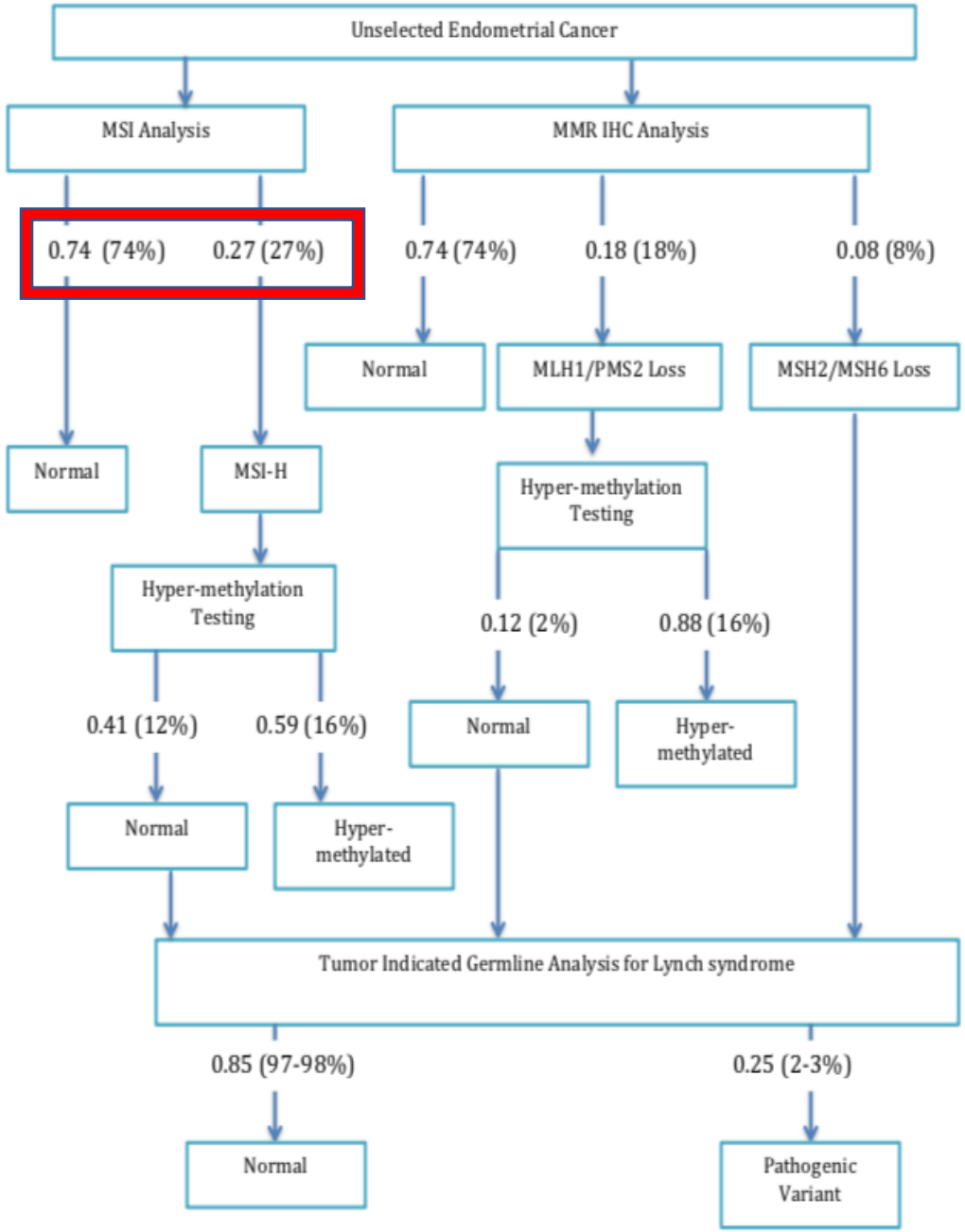
Open

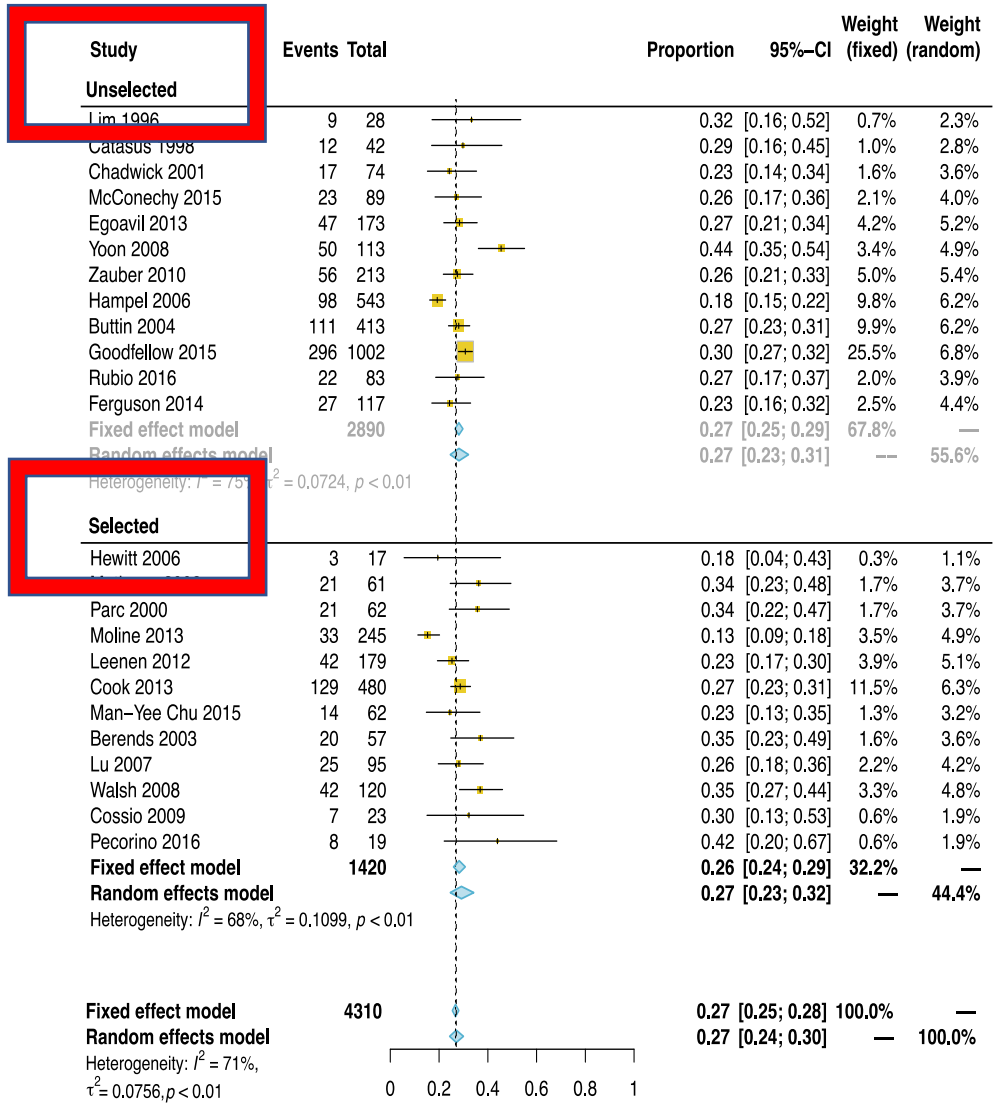
The proportion of endometrial cancers associated with Lynch syndrome: a systematic review of the literature and meta-analysis

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]



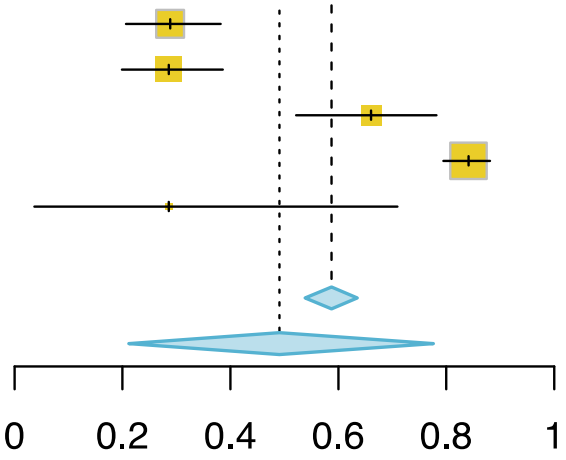
*Two studies selected on age <80yrs


Unselected Endometrial Cancer
MSI Analysis
MMR IHC Analysis
0.74 (74%)
0.27 (27%)
0.74 (74%)
0.18 (18%)
0.08 (8%)
Normal
MLH1/PMS2 Loss
MSH2/MSH6 Loss
Normal
MSI-H
Hyper-methylation Testing
Hyper-methylation Testing
0.12 (2%)
0.88 (16%)
0.41 (12%)
0.59 (16%)
Normal
Hyper-methylated
Normal
Hyper-methylated
Tumor Indicated Germline Analysis for Lynch syndrome
0.85 (97-98%)
0.25 (2-3%)
Normal
Pathogenic Variant

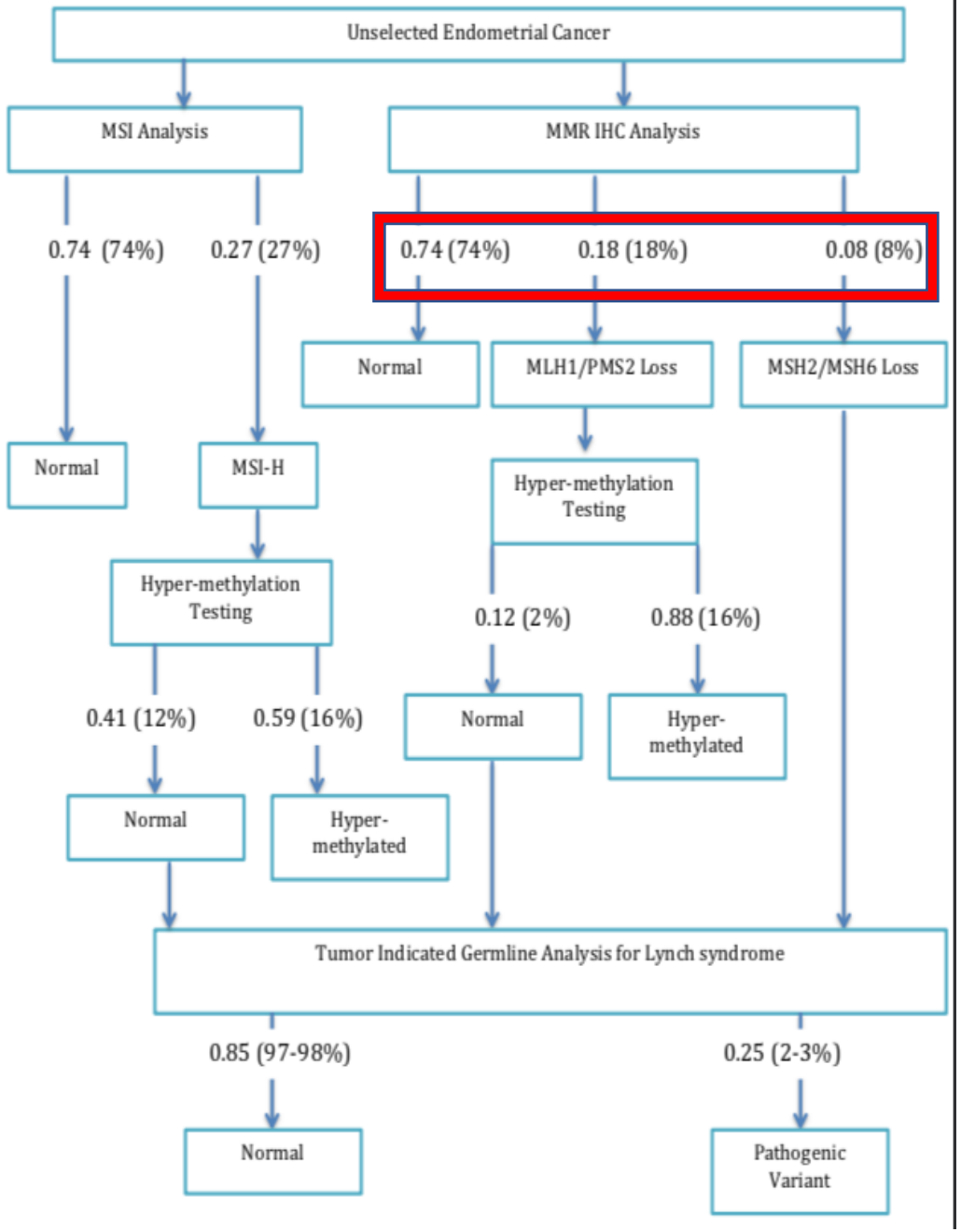

Study
Events Total
Proportion
95%–CI
Weight (fixed)
Weight (random)
Unselected
Lim 1996 9 28 0.32 [0.16; 0.52] 0.7% 2.3%
Catasus 1998 12 42 0.29 [0.16; 0.45] 1.0% 2.8%
Chadwick 2001 17 74 0.23 [0.14; 0.34] 1.6% 3.6%
McConechy 2015 23 89 0.26 [0.17; 0.36] 2.1% 4.0%
Egoavil 2013 47 173 0.27 [0.21; 0.34] 4.2% 5.2%
Yoon 2008 50 113 0.44 [0.35; 0.54] 3.4% 4.9%
Zauber 2010 56 213 0.26 [0.21; 0.33] 5.0% 5.4%
Hampel 2006 98 543 0.18 [0.15; 0.22] 9.8% 6.2%
Buttin 2004 111 413 0.27 [0.23; 0.31] 9.9% 6.2%
Goodfellow 2015 296 1002 0.30 [0.27; 0.32] 25.5% 6.8%
Rubio 2016 22 83 0.27 [0.17; 0.37] 2.0% 3.9%
Ferguson 2014 27 117 0.23 [0.16; 0.32] 2.5% 4.4%
Fixed effect model 2890 0.27 [0.25; 0.29] 67.8% —
Random effects model 0.27 [0.23; 0.31] — 55.6%
Heterogeneity: I^2 = 75%, τ^2 = 0.0724, p < 0.01
Selected
Hewitt 2006 3 17 0.18 [0.04; 0.43] 0.3% 1.1%
21 61 0.34 [0.23; 0.48] 1.7% 3.7%
Parc 2000 21 62 0.34 [0.22; 0.47] 1.7% 3.7%
Moline 2013 33 245 0.13 [0.09; 0.18] 3.5% 4.9%
Leenen 2012 42 179 0.23 [0.17; 0.30] 3.9% 5.1%
Cook 2013 129 480 0.27 [0.23; 0.31] 11.5% 6.3%
Man–Yee Chu 2015 14 62 0.23 [0.13; 0.35] 1.3% 3.2%
Berends 2003 20 57 0.35 [0.23; 0.49] 1.6% 3.6%
Lu 2007 25 95 0.26 [0.18; 0.36] 2.2% 4.2%
Walsh 2008 42 120 0.35 [0.27; 0.44] 3.3% 4.8%
Cossio 2009 7 23 0.30 [0.13; 0.53] 0.6% 1.9%
Pecorino 2016 8 19 0.42 [0.20; 0.67] 0.6% 1.9%
Fixed effect model 1420 0.26 [0.24; 0.29] 32.2% —
Random effects model 0.27 [0.23; 0.32] — 44.4%
Heterogeneity: I^2 = 68%, τ^2 = 0.1099, p < 0.01
Fixed effect model 4310 0.27 [0.25; 0.28] 100.0% —
Random effects model 0.27 [0.24; 0.30] — 100.0%
Heterogeneity: I^2 = 71%,
τ^2 = 0.0756, p < 0.01
0 0.2 0.4 0.6 0.8 1

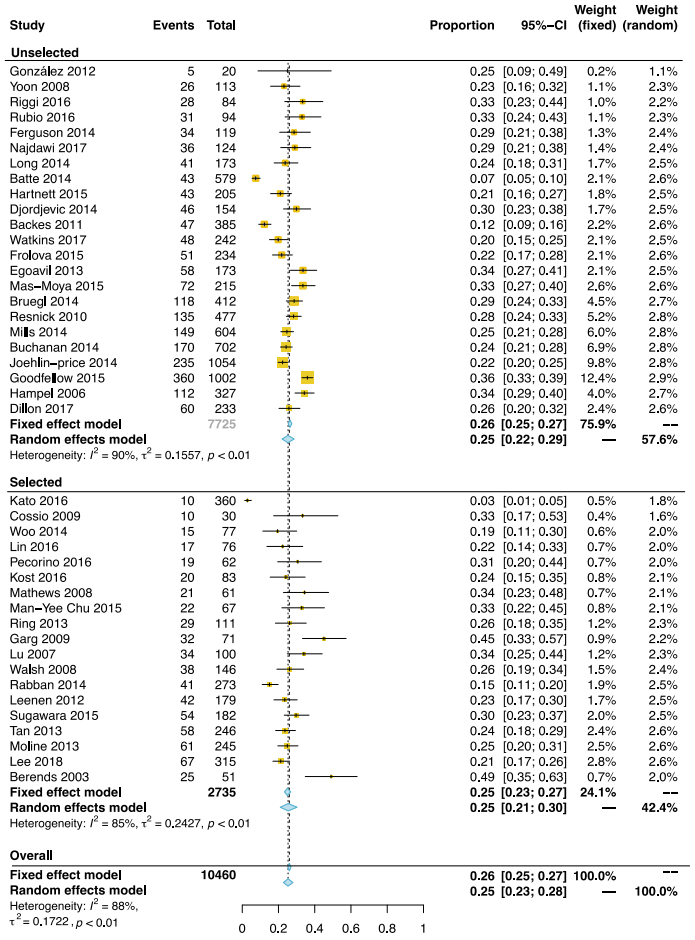

Unselected Endometrial Cancer
MSI Analysis
MMR IHC Analysis
0.74 (74%)
0.27 (27%)
0.74 (74%)
0.18 (18%)
0.08 (8%)
Normal
MLH1/PMS2 Loss
MSH2/MSH6 Loss
Normal
MSI-H
Hyper-methylation Testing
Hyper-methylation Testing
0.12 (2%)
0.88 (16%)
0.41 (12%)
0.59 (16%)
Normal
Hyper-methylated
Normal
Hyper-methylated
Tumor Indicated Germline Analysis for Lynch syndrome
0.85 (97-98%)
0.25 (2-3%)
Normal
Pathogenic Variant

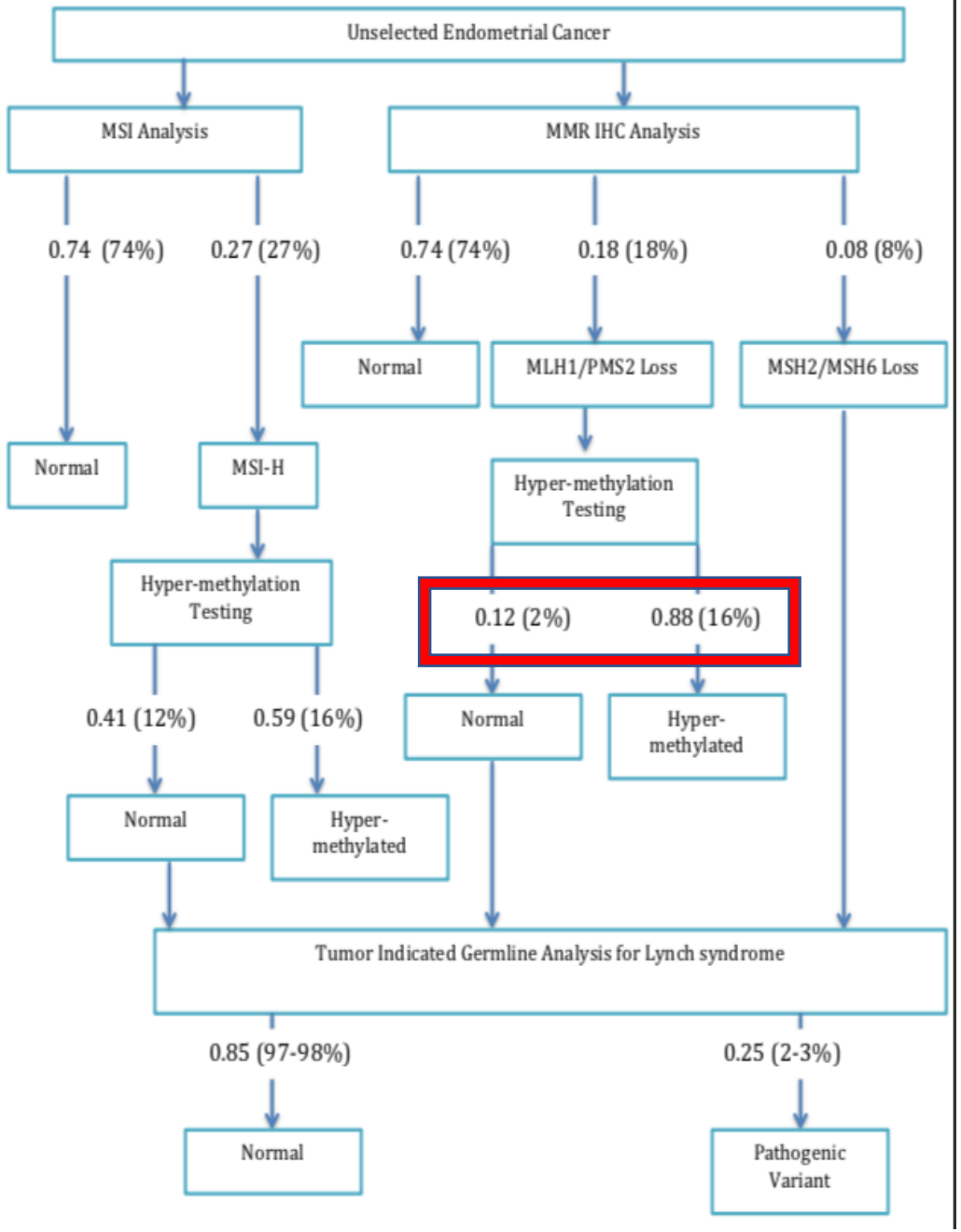
Study	Events	Total	Proportion	95%–CI	Weight (fixed)	Weight (random)
Buttin 2004	32	111	0.29	[0.21; 0.38]	23.7%	21.1%
Hampel 2006	28	98	0.29	[0.20; 0.39]	20.8%	21.0%
Zauber 2010	37	56	0.66	[0.52; 0.78]	13.0%	20.7%
Goodfellow 2015	249	296	0.84	[0.79; 0.88]	41.1%	21.3%
Cassio 2009	2	7	0.29	[0.04; 0.71]	1.5%	15.9%
Fixed effect model		**568**	**0.59**	**[0.54; 0.63]**	**100.0%**	**––**
Random effects model			**0.49**	**[0.21; 0.78]**	**––**	**100.0%**

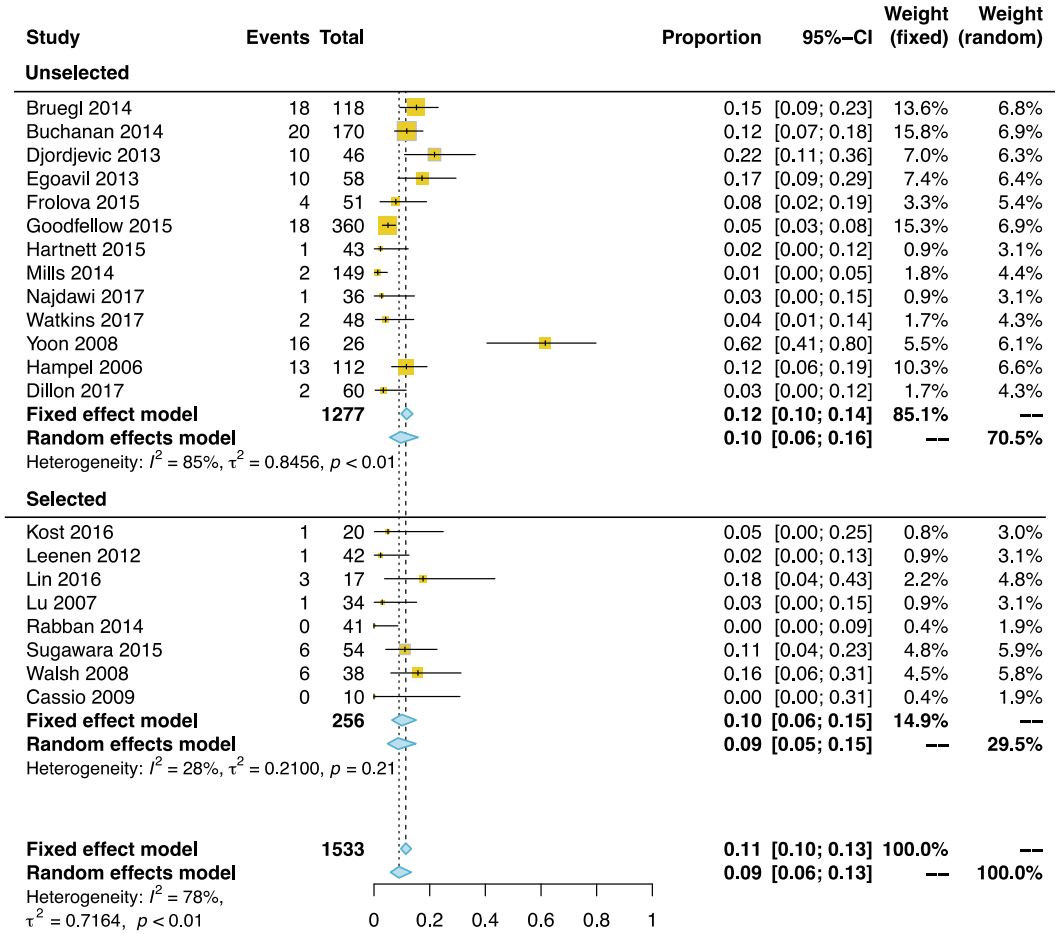


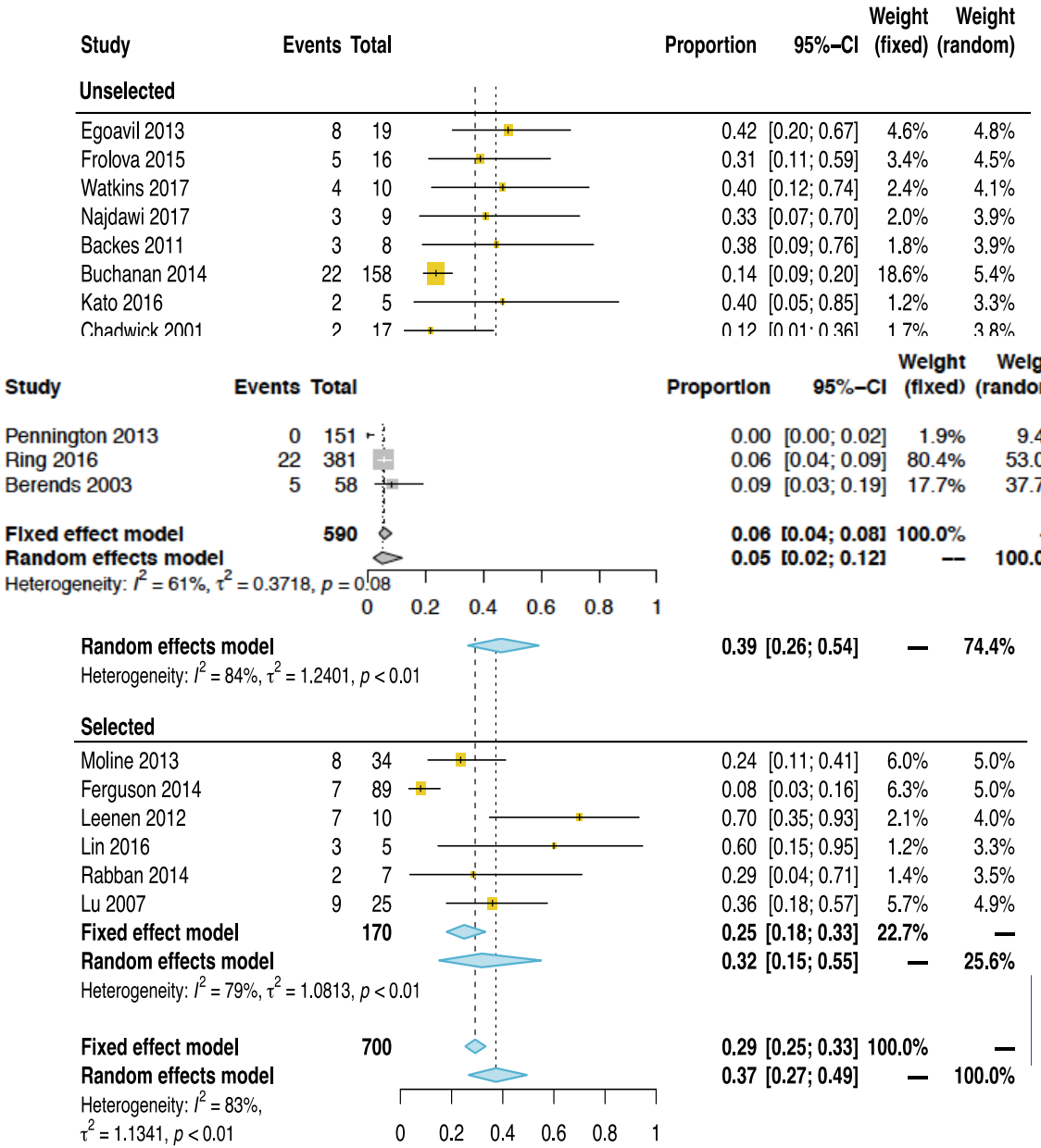
Heterogeneity: $I^2 = 97\%$,
$\tau^2 = 1.9753, p < 0.01$


Unselected Endometrial Cancer
MSI Analysis
MMR IHC Analysis
0.74 (74%)
0.27 (27%)
0.74 (74%)
0.18 (18%)
0.08 (8%)
Normal
MLH1/PMS2 Loss
MSH2/MSH6 Loss
Normal
MSI-H
Hyper-methylation Testing
Hyper-methylation Testing
0.12 (2%)
0.88 (16%)
0.41 (12%)
0.59 (16%)
Normal
Hyper-methylated
Normal
Hyper-methylated
Tumor Indicated Germline Analysis for Lynch syndrome
0.85 (97-98%)
0.25 (2-3%)
Normal
Pathogenic Variant


Study
Events
Total
Proportion
95%−CI
Weight (fixed)
Weight (random)
Unselected
González 2012 5 20 0.25 [0.09; 0.49] 0.2% 1.1%
Yoon 2008 26 113 0.23 [0.16; 0.32] 1.1% 2.3%
Riggi 2016 28 84 0.33 [0.23; 0.44] 1.0% 2.2%
Rubio 2016 31 94 0.33 [0.24; 0.43] 1.1% 2.3%
Ferguson 2014 34 119 0.29 [0.21; 0.38] 1.3% 2.4%
Najdawi 2017 36 124 0.29 [0.21; 0.38] 1.4% 2.4%
Long 2014 41 173 0.24 [0.18; 0.31] 1.7% 2.5%
Batte 2014 43 579 0.07 [0.05; 0.10] 2.1% 2.6%
Hartnett 2015 43 205 0.21 [0.16; 0.27] 1.8% 2.5%
Djordjevic 2014 46 154 0.30 [0.23; 0.38] 1.7% 2.5%
Backes 2011 47 385 0.12 [0.09; 0.16] 2.2% 2.6%
Watkins 2017 48 242 0.20 [0.15; 0.25] 2.1% 2.5%
Frolova 2015 51 234 0.22 [0.17; 0.28] 2.1% 2.6%
Egoavil 2013 58 173 0.34 [0.27; 0.41] 2.1% 2.5%
Mas−Moya 2015 72 215 0.33 [0.27; 0.40] 2.6% 2.6%
Bruegl 2014 118 412 0.29 [0.24; 0.33] 4.5% 2.7%
Resnick 2010 135 477 0.28 [0.24; 0.33] 5.2% 2.8%
Mills 2014 149 604 0.25 [0.21; 0.28] 6.0% 2.8%
Buchanan 2014 170 702 0.24 [0.21; 0.28] 6.9% 2.8%
Joehlin−price 2014 235 1054 0.22 [0.20; 0.25] 9.8% 2.8%
Goodfellow 2015 360 1002 0.36 [0.33; 0.39] 12.4% 2.9%
Hampel 2006 112 327 0.34 [0.29; 0.40] 4.0% 2.7%
Dillon 2017 60 233 0.26 [0.20; 0.32] 2.4% 2.6%
Fixed effect model 7725 0.26 [0.25; 0.27] 75.9% --
Random effects model 0.25 [0.22; 0.29] -- 57.6%
Heterogeneity: I^2 = 90%, τ^2 = 0.1557, p < 0.01
Selected
Kato 2016 10 360 0.03 [0.01; 0.05] 0.5% 1.8%
Cossio 2009 10 30 0.33 [0.17; 0.53] 0.4% 1.6%
Woo 2014 15 77 0.19 [0.11; 0.30] 0.6% 2.0%
Lin 2016 17 76 0.22 [0.14; 0.33] 0.7% 2.0%
Pecorino 2016 19 62 0.31 [0.20; 0.44] 0.7% 2.0%
Kost 2016 20 83 0.24 [0.15; 0.35] 0.8% 2.1%
Mathews 2008 21 61 0.34 [0.23; 0.48] 0.7% 2.1%
Man−Yee Chu 2015 22 67 0.33 [0.22; 0.45] 0.8% 2.1%
Ring 2013 29 111 0.26 [0.18; 0.35] 1.2% 2.3%
Garg 2009 32 71 0.45 [0.33; 0.57] 0.9% 2.2%
Lu 2007 34 100 0.34 [0.25; 0.44] 1.2% 2.3%
Walsh 2008 38 146 0.26 [0.19; 0.34] 1.5% 2.4%
Rabban 2014 41 273 0.15 [0.11; 0.20] 1.9% 2.5%
Leenen 2012 42 179 0.23 [0.17; 0.30] 1.7% 2.5%
Sugawara 2015 54 182 0.30 [0.23; 0.37] 2.0% 2.5%
Tan 2013 58 246 0.24 [0.18; 0.29] 2.4% 2.6%
Moline 2013 61 245 0.25 [0.20; 0.31] 2.5% 2.6%
Lee 2018 67 315 0.21 [0.17; 0.26] 2.8% 2.6%
Berends 2003 25 51 0.49 [0.35; 0.63] 0.7% 2.0%
Fixed effect model 2735 0.25 [0.23; 0.27] 24.1% --
Random effects model 0.25 [0.21; 0.30] -- 42.4%
Heterogeneity: I^2 = 85%, τ^2 = 0.2427, p < 0.01
Overall
Fixed effect model 10460 0.26 [0.25; 0.27] 100.0% --
Random effects model 0.25 [0.23; 0.28] -- 100.0%
Heterogeneity: I^2 = 88%, τ^2 = 0.1722 , p < 0.01
0
0.2
0.4
0.6
0.8
1

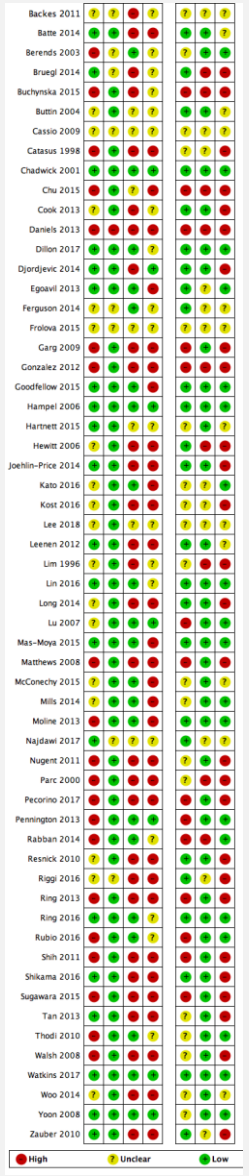

Unselected Endometrial Cancer
MSI Analysis
MMR IHC Analysis
0.74 (74%)
0.27 (27%)
0.74 (74%)
0.18 (18%)
0.08 (8%)
Normal
MSI-H
Normal
MLH1/PMS2 Loss
MSH2/MSH6 Loss
Hyper-methylation Testing
Hyper-methylation Testing
0.12 (2%)
0.88 (16%)
0.41 (12%)
0.59 (16%)
Normal
Hyper-methylated
Normal
Hyper-methylated
Normal
Tumor Indicated Germline Analysis for Lynch syndrome
0.85 (97-98%)
0.25 (2-3%)
Normal
Pathogenic Variant


Study
Events
Total
Proportion
95%−CI
Weight (fixed)
Weight (random)
Unselected
Bruegl 2014 18 118 0.15 [0.09; 0.23] 13.6% 6.8%
Buchanan 2014 20 170 0.12 [0.07; 0.18] 15.8% 6.9%
Djordjevic 2013 10 46 0.22 [0.11; 0.36] 7.0% 6.3%
Egoavil 2013 10 58 0.17 [0.09; 0.29] 7.4% 6.4%
Frolova 2015 4 51 0.08 [0.02; 0.19] 3.3% 5.4%
Goodfellow 2015 18 360 0.05 [0.03; 0.08] 15.3% 6.9%
Hartnett 2015 1 43 0.02 [0.00; 0.12] 0.9% 3.1%
Mills 2014 2 149 0.01 [0.00; 0.05] 1.8% 4.4%
Najdawi 2017 1 36 0.03 [0.00; 0.15] 0.9% 3.1%
Watkins 2017 2 48 0.04 [0.01; 0.14] 1.7% 4.3%
Yoon 2008 16 26 0.62 [0.41; 0.80] 5.5% 6.1%
Hampel 2006 13 112 0.12 [0.06; 0.19] 10.3% 6.6%
Dillon 2017 2 60 0.03 [0.00; 0.12] 1.7% 4.3%
Fixed effect model 1277 0.12 [0.10; 0.14] 85.1% –
Random effects model 0.10 [0.06; 0.16] – 70.5%
Heterogeneity: I^2 = 85%, τ^2 = 0.8456, p < 0.01
Selected
Kost 2016 1 20 0.05 [0.00; 0.25] 0.8% 3.0%
Leenen 2012 1 42 0.02 [0.00; 0.13] 0.9% 3.1%
Lin 2016 3 17 0.18 [0.04; 0.43] 2.2% 4.8%
Lu 2007 1 34 0.03 [0.00; 0.15] 0.9% 3.1%
Rabban 2014 0 41 0.00 [0.00; 0.09] 0.4% 1.9%
Sugawara 2015 6 54 0.11 [0.04; 0.23] 4.8% 5.9%
Walsh 2008 6 38 0.16 [0.06; 0.31] 4.5% 5.8%
Cassio 2009 0 10 0.00 [0.00; 0.31] 0.4% 1.9%
Fixed effect model 256 0.10 [0.06; 0.15] 14.9% –
Random effects model 0.09 [0.05; 0.15] – 29.5%
Heterogeneity: I^2 = 28%, τ^2 = 0.2100, p = 0.21
Fixed effect model 1533 0.11 [0.10; 0.13] 100.0% –
Random effects model 0.09 [0.06; 0.13] – 100.0%
Heterogeneity: I^2 = 78%,
τ^2 = 0.7164, p < 0.01
0
0.2
0.4
0.6
0.8
1


Study
Events
Total
Proportion
95%−CI
Weight (fixed)
Weight (random)
Unselected
Egoavil 2013 8 19 0.42 [0.20; 0.67] 4.6% 4.8%
Frolova 2015 5 16 0.31 [0.11; 0.59] 3.4% 4.5%
Watkins 2017 4 10 0.40 [0.12; 0.74] 2.4% 4.1%
Najdawi 2017 3 9 0.33 [0.07; 0.70] 2.0% 3.9%
Backes 2011 3 8 0.38 [0.09; 0.76] 1.8% 3.9%
Buchanan 2014 22 158 0.14 [0.09; 0.20] 18.6% 5.4%
Kato 2016 2 5 0.40 [0.05; 0.85] 1.2% 3.3%
Chadwick 2001 2 17 0.12 [0.01; 0.36] 1.7% 3.8%
Pennington 2013 0 151 0.00 [0.00; 0.02] 1.9% 9.4%
Ring 2016 22 381 0.06 [0.04; 0.09] 80.4% 53.0%
Berends 2003 5 58 0.09 [0.03; 0.19] 17.7% 37.7%
Fixed effect model 590 0.06 [0.04; 0.08] 100.0% —
Random effects model 0.05 [0.02; 0.12] — 100.0%
Heterogeneity: I^2 = 61%, τ^2 = 0.3718, p = 0.08
0 0.2 0.4 0.6 0.8 1
Random effects model 0.39 [0.26; 0.54] — 74.4%
Heterogeneity: I^2 = 84%, τ^2 = 1.2401, p < 0.01
Selected
Moline 2013 8 34 0.24 [0.11; 0.41] 6.0% 5.0%
Ferguson 2014 7 89 0.08 [0.03; 0.16] 6.3% 5.0%
Leenen 2012 7 10 0.70 [0.35; 0.93] 2.1% 4.0%
Lin 2016 3 5 0.60 [0.15; 0.95] 1.2% 3.3%
Rabban 2014 2 7 0.29 [0.04; 0.71] 1.4% 3.5%
Lu 2007 9 25 0.36 [0.18; 0.57] 5.7% 4.9%
Fixed effect model 170 0.25 [0.18; 0.33] 22.7% —
Random effects model 0.32 [0.15; 0.55] — 25.6%
Heterogeneity: I^2 = 79%, τ^2 = 1.0813, p < 0.01
Fixed effect model 700 0.29 [0.25; 0.33] 100.0% —
Random effects model 0.37 [0.27; 0.49] — 100.0%
Heterogeneity: I^2 = 83%,
τ^2 = 1.1341, p < 0.01
0 0.2 0.4 0.6 0.8 1

But

- Quality of available studies was very poor
- Few studies tested all eligible patients
- No studies compared all testing strategies
- All studies in private health care setting



PLOS MEDICINE

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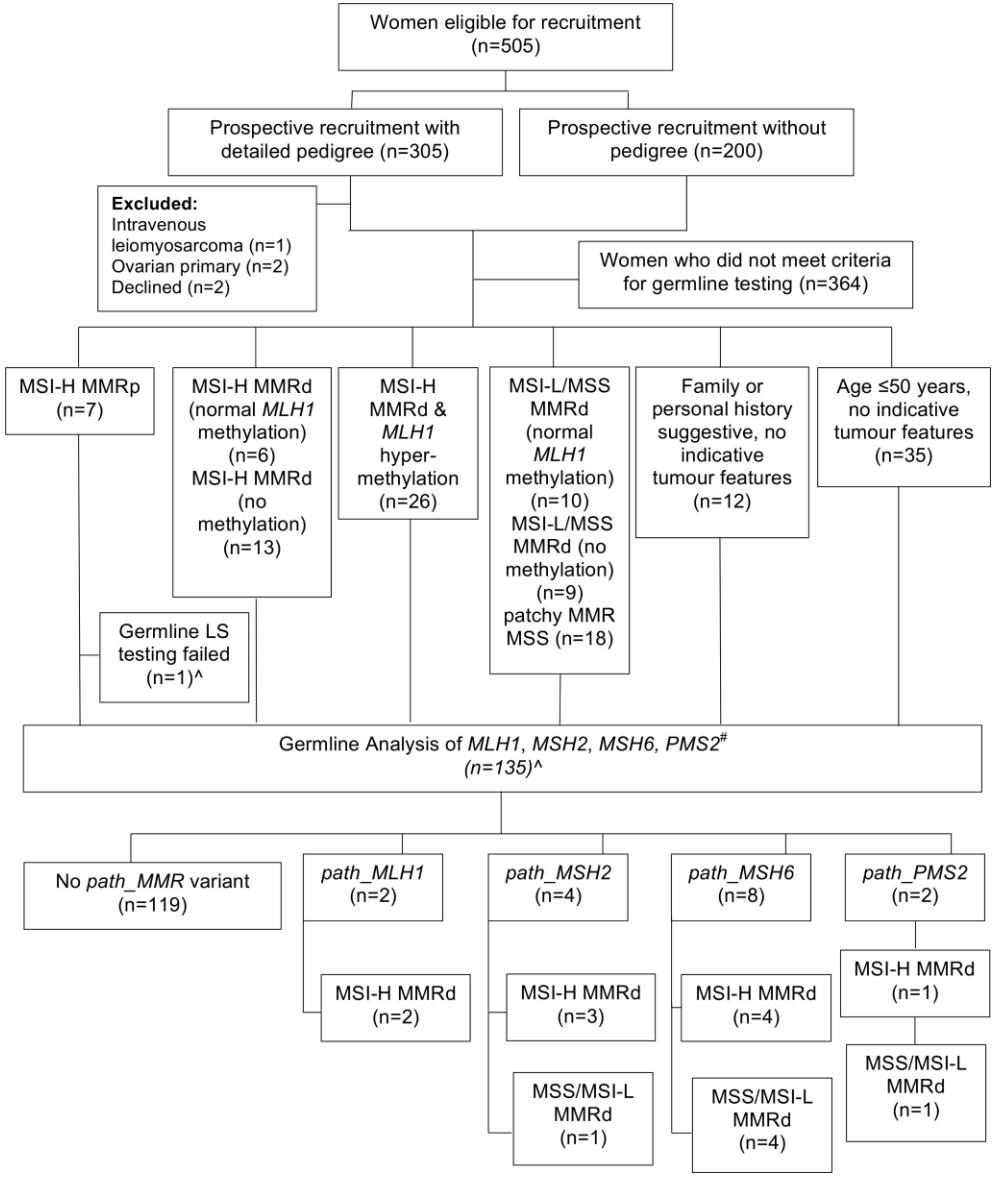
RESEARCH ARTICLE

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]

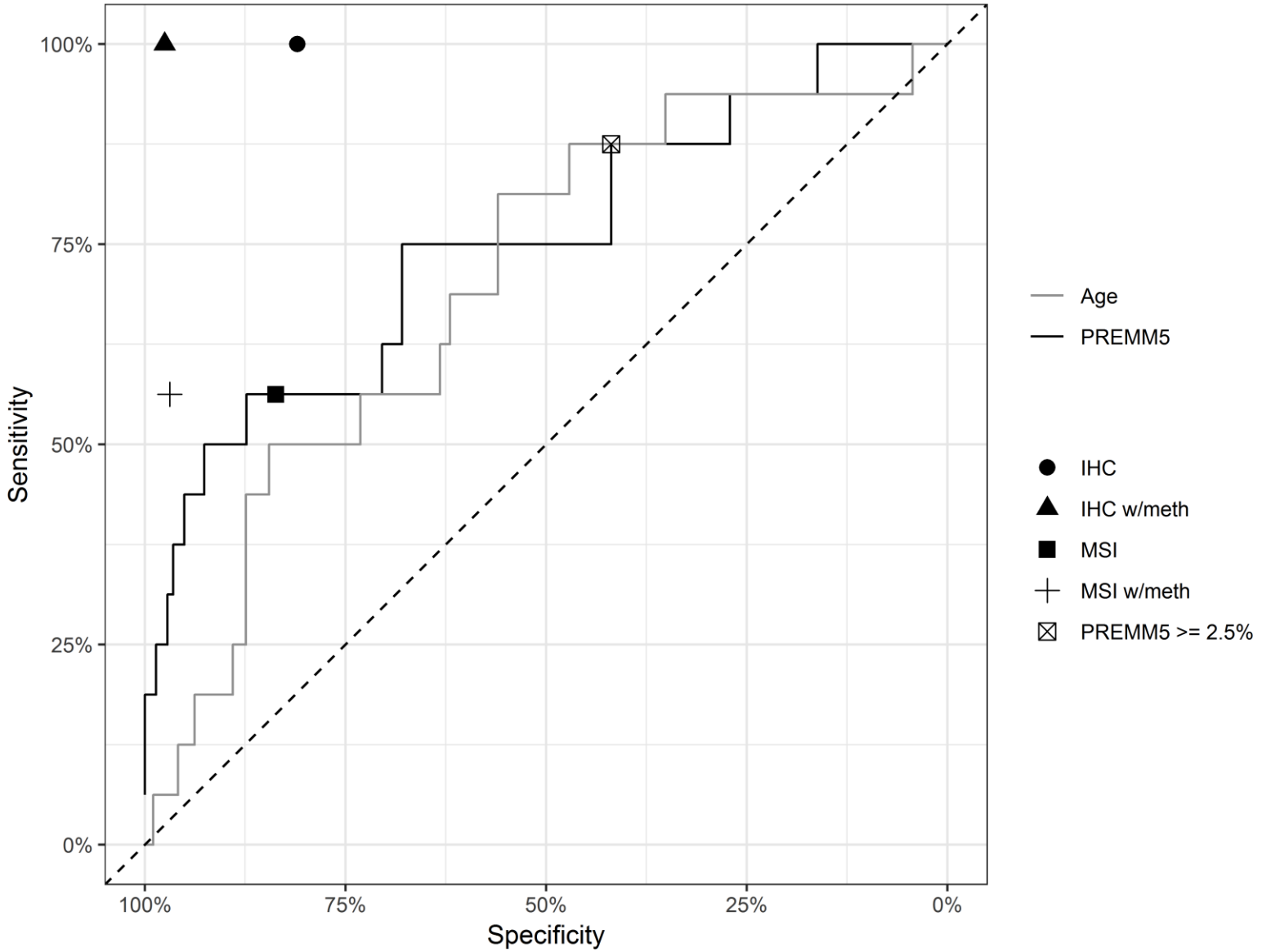
Published: September 17, 2020 • https://doi.org/10.1371/journal.pmed.1003263

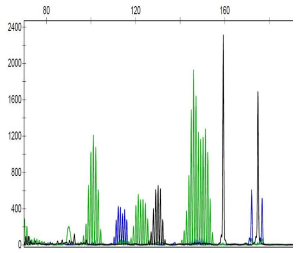

Women eligible for recruitment (n=505)
Prospective recruitment with detailed pedigree (n=305)
Prospective recruitment without pedigree (n=200)
Excluded: Intravenous leiomyosarcoma (n=1) Ovarian primary (n=2) Declined (n=2)
Women who did not meet criteria for germline testing (n=364)
MSI-H MMRp (n=7)
MSI-H MMRd (normal MLH1 methylation) (n=6) MSI-H MMRd (no methylation) (n=13)
MSI-H MMRd & MLH1 hyper-methylation (n=26)
MSI-L/MSS MMRd (normal MLH1 methylation) (n=10) MSI-L/MSS MMRd (no methylation) (n=9) patchy MMR MSS (n=18)
Family or personal history suggestive, no indicative tumour features (n=12)
Age ≤50 years, no indicative tumour features (n=35)
Germline LS testing failed (n=1)^
Germline Analysis of MLH1, MSH2, MSH6, PMS2# (n=135)^
No path_MMR variant (n=119)
path_MLH1 (n=2)
path_MSH2 (n=4)
path_MSH6 (n=8)
path_PMS2 (n=2)
MSI-H MMRd (n=2)
MSI-H MMRd (n=3)
MSS/MSI-L MMRd (n=1)
MSI-H MMRd (n=4)
MSS/MSI-L MMRd (n=4)
MSI-H MMRd (n=1)
MSS/MSI-L MMRd (n=1)

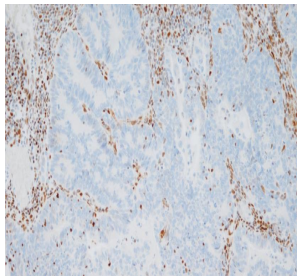
Clinicopathological variable	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
MMR deficiency by IHC	100 (79.4–100)	80.6 (76.8–84.0)	14.5 (8.5–22.5)	100 (99.1–100)
With *MLH1*-methylation testing	100 (79.4–100)	96.7 (94.7–98.1)	50.0 (31.9–68.1)	100 (99.2–100)
MSI-H	56.3 (29.9–80.2)	83.5 (79.9–86.7)	10.1 (4.7–18.3)	98.3 (96.5–99.3)
With *MLH1*-methylation testing	56.3 (29.9–80.2)	96.7 (94.7–98.1)	36.0 (18.0–57.5)	98.5 (97.0–99.4)
MMR deficiency or MSI-H	100 (79.4–100)	79.1 (75.2–82.7)	13.7 (8.0–21.5)	100 (99.0–100)
With *MLH1*-methylation testing	100 (79.4–100)	95.5 (93.2–97.1)	42.1 (26.3–59.2)	100 (99.2–100)
Age				
<50 years	43.8 (19.8–70.1)	87.4 (84.1–90.2)	10.3 (4.2–20.1)	97.9 (96.1–99.0)
<60 years	56.3 (29.9–80.2)	65.7 (61.3–69.9)	5.1 (2.4–9.5)	97.8 (95.6–99.1)
<70 years	93.8 (69.8–99.8)	35.1 (30.9–39.6)	4.6 (2.6–7.4)	99.4 (96.8–100.0)
BMI <35 kg/m^2	86.7 (59.5–98.3)	37.7 (33.3–42.2)	4.1 (2.2–7.0)	98.9 (96.1–99.9)
<50 years	33.3 (11.8–61.6)	94.8 (92.5–96.6)	16.7 (5.6–34.7)	97.9 (96.1–99.0)
<60 years	46.7 (21.3–73.4)	82.0 (78.3–85.3)	7.4 (3.0–14.7)	98.0 (96.1–99.1)
<70 years	80.0 (51.9–95.7)	64.0 (59.5–68.3)	6.5 (3.4–11.0)	99.0 (97.2–99.8)
PREMM$_5$ score	84.6 (54.6–98.1)	46.5 (40.6–52.5)	6.7 (3.4–11.7)	98.5 (94.8–99.8)
Amsterdam II Criteria	30.8 (9.1–61.4)	99.0 (97.0–99.8)	57.1 (18.4–90.1)	96.9 (94.2–98.6)
Revised Bethesda Guidelines	38.5 (13.9–68.4)	98.6 (96.5–99.6)	55.6 (21.2–86.3)	97.3 (94.7–98.8)
Endometrioid histopathology	68.8 (41.3–88.9)	29.8 (25.7–34.0	3.1 (1.6–5.5)	96.6 (92.3–98.9)
High TILs	93.8 (69.8–99.8)	76.7 (72.6–80.4)	11.7 (6.7–18.6)	99.7 (98.5–100)

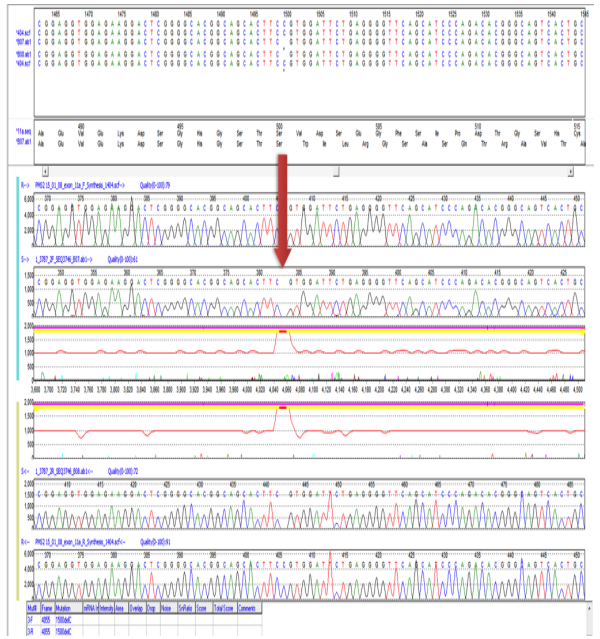
Abbreviations: BMI, body mass index; IHC, immunohistochemistry; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, microsatellite instability-high; NPV, negative predictive value; PPV, positive predictive value; PREMM, PREdiction Model for gene Mutations; TIL, tumour-infiltrating lymphocyte

https://doi.org/10.1371/journal.pmed.1003263.t003


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







88%

n=9

frontiers in Oncology

Front Oncol. 2019; 9: 61.

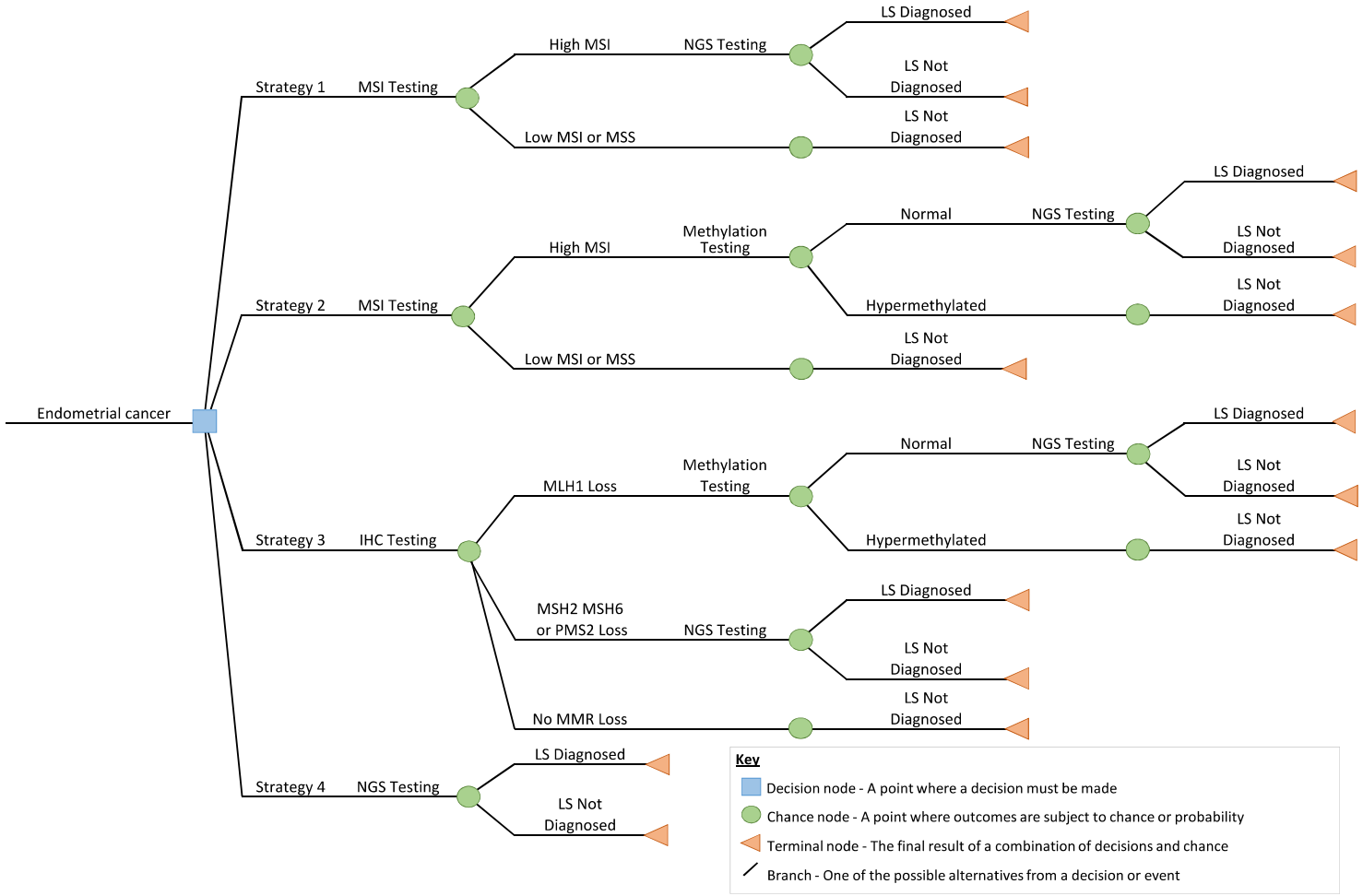
Published online 2019 Feb 26. doi: 10.3389/fonc.2019.00061

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,*]


Endometrial cancer
Strategy 1
MSI Testing
High MSI
NGS Testing
LS Diagnosed
LS Not Diagnosed
Low MSI or MSS
LS Not Diagnosed
Strategy 2
MSI Testing
High MSI
Methylation Testing
Normal
NGS Testing
LS Diagnosed
LS Not Diagnosed
Hypermethylated
LS Not Diagnosed
Low MSI or MSS
LS Not Diagnosed
Strategy 3
IHC Testing
MLH1 Loss
Methylation Testing
Normal
NGS Testing
LS Diagnosed
LS Not Diagnosed
Hypermethylated
LS Not Diagnosed
MSH2 MSH6 or PMS2 Loss
NGS Testing
LS Diagnosed
LS Not Diagnosed
No MMR Loss
LS Not Diagnosed
Strategy 4
NGS Testing
LS Diagnosed
LS Not Diagnosed
Key
Decision node - A point where a decision must be made
Chance node - A point where outcomes are subject to chance or probability
Terminal node - The final result of a combination of decisions and chance
Branch - One of the possible alternatives from a decision or event

Strategy	Cost per tumour
IHC & methylation	£45.68
MSI	£78.95
MSI & methylation	£42.01
Direct germline sequencing	£176.24

Journal List > J Clin Med > v.9(6); 2020 Jun > PMC7356917

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

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

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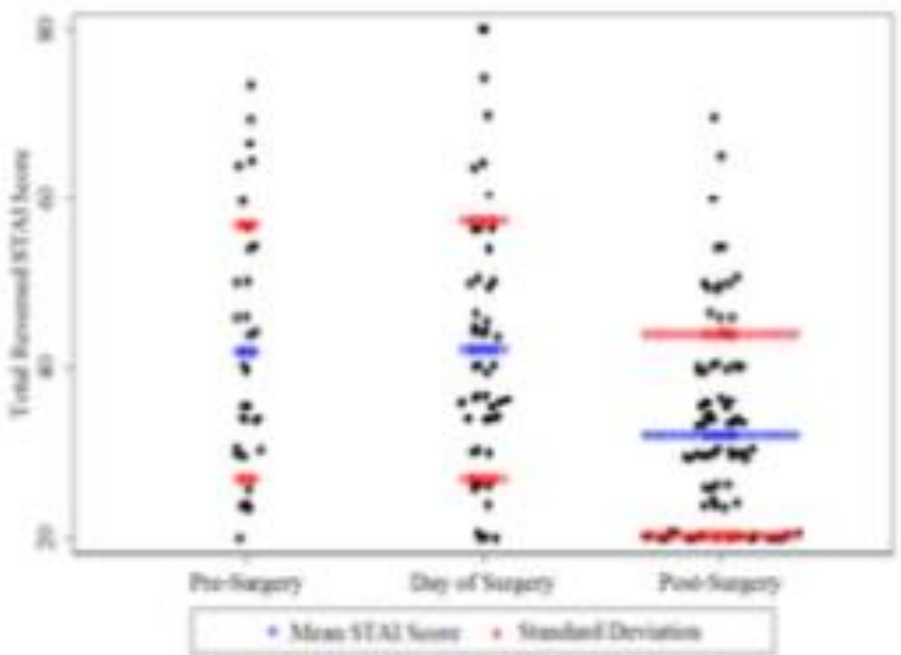
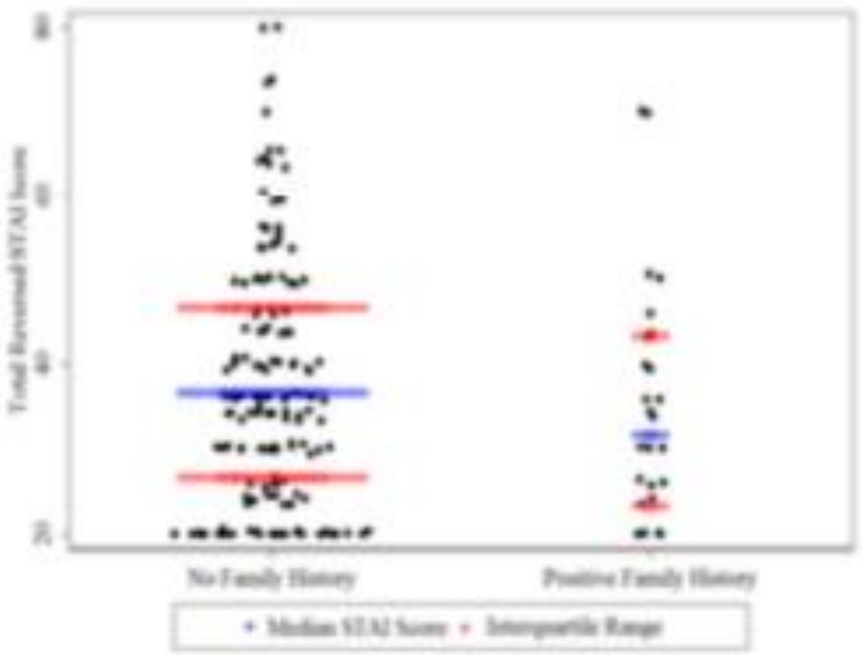
Open Access Article

Feasibility of Gynaecologist Led Lynch Syndrome Testing in Women with Endometrial Cancer

by Neil A. J. Ryan [1,2], Louise Donnelly [3,4], Katie Stocking [5], D. Gareth Evans [1,3,6] and Emma J. Crosbie [2,7,*]



(A)



(B)

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.11902

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/s41436-019-0489-y

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

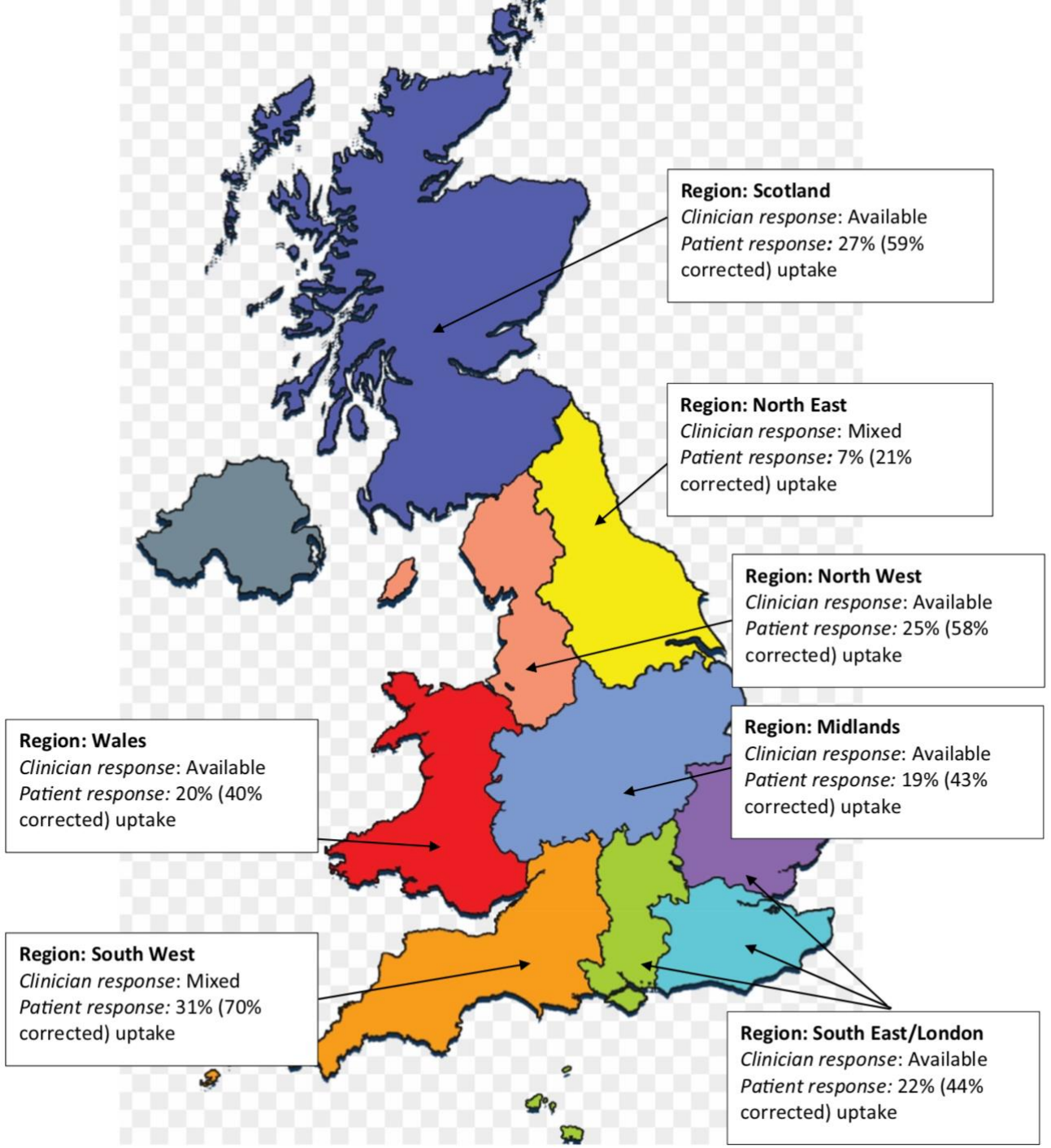

UP

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



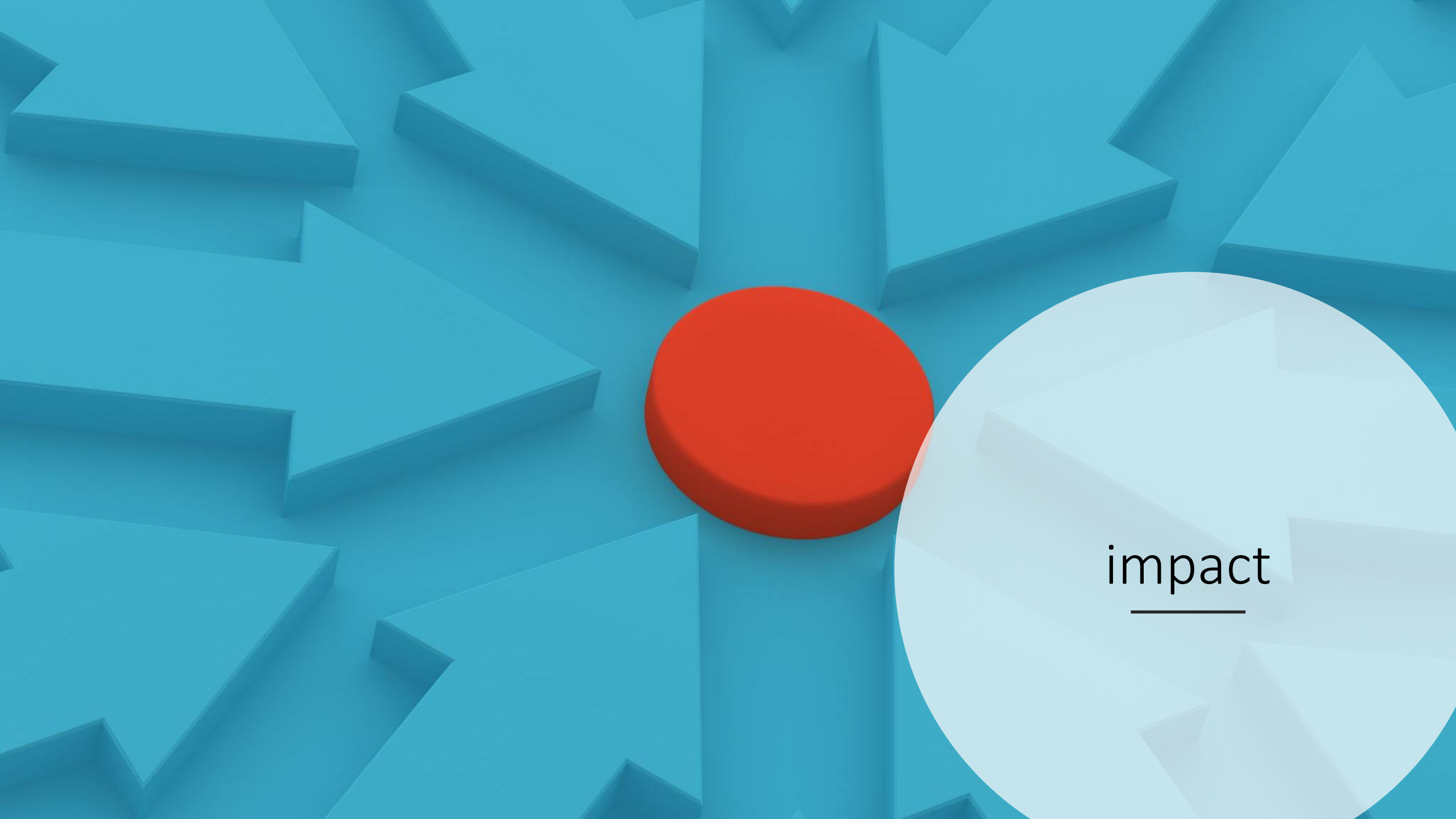
- Survey of BAGP and ISGyP (n=36 and 44)
- 90% aware of LS association with EC
- 36% carried out universal screening
- 36% thought consent was needed before tumour testing
- All respondents wanted a standardised terminology for reporting

Histopathology

Histopathology 2019, **75**, 813–824. DOI: 10.1111/his.13925

Lynch syndrome screening in gynaecological cancers: results of an international survey with recommendations for uniform reporting terminology for mismatch repair immunohistochemistry results

Neil Ryan,[1] Johanna Wall,[2] Emma J Crosbie,[1] Mark Arends,[3] Tjalling Bosse,[4] Saimah Arif,[5] Asma Faruqi,[2] Ian Frayling,[6] Raji Ganesan,[7] Ye L Hock,[8] Raymond McMahon,[9] Ranjit Manchanda,[10] W Glenn McCluggage,[11] Pinias Mukonoweshuro,[12] GerhardvanSchalkwyk,[13] Lucy Side,[14] John H Smith,[15] Bruce Tanchel,[16] D Gareth Evans,[17] C Blake Gilks[18] & Naveena Singh[2]


impact

NICE National Institute for Health and Care Excellence

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Testing strategies for Lynch syndrome in people with endometrial cancer

Diagnostics guidance [DG42] Published date: 28 October 2020 Register as a stakeholder

Draft SW pathway for MMR IHC for endometrial cancer (DG42)

For the identification of patients with Lynch syndrome

NICE National Institute for Health and Care Excellence

NICE guidance

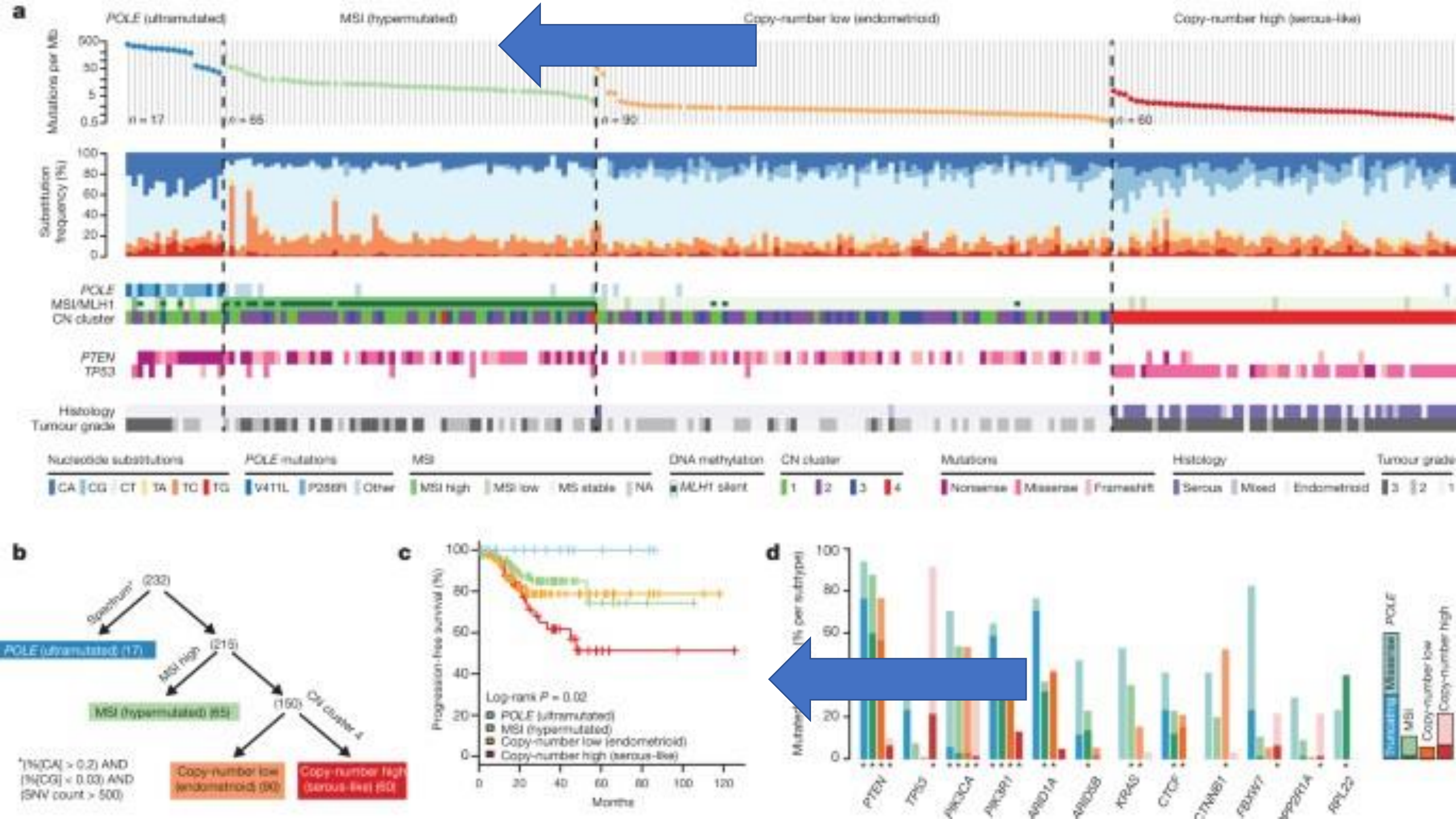
Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency

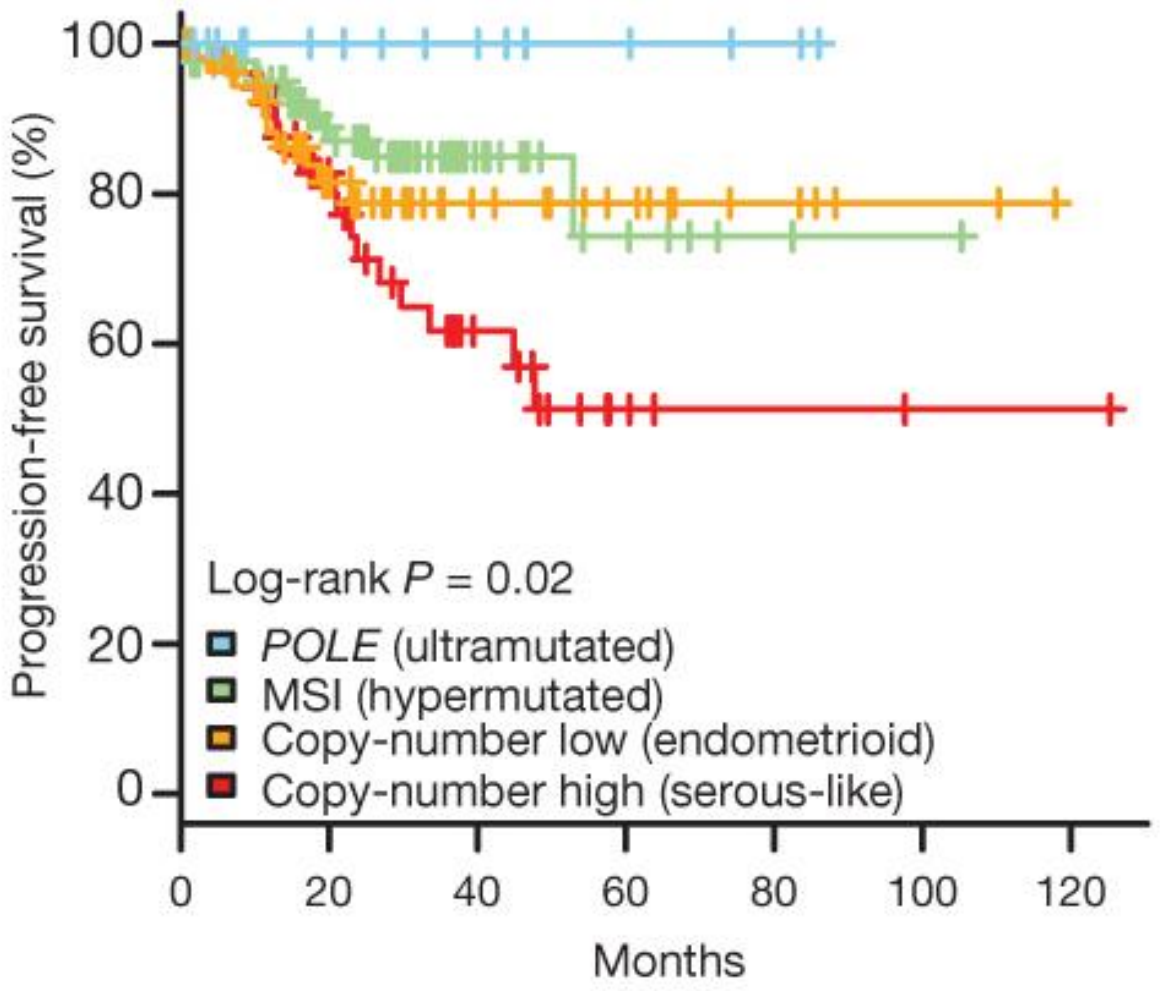
Technology appraisal guidance
Published: 16 March 2022
www.nice.org.uk/guidance/ta779

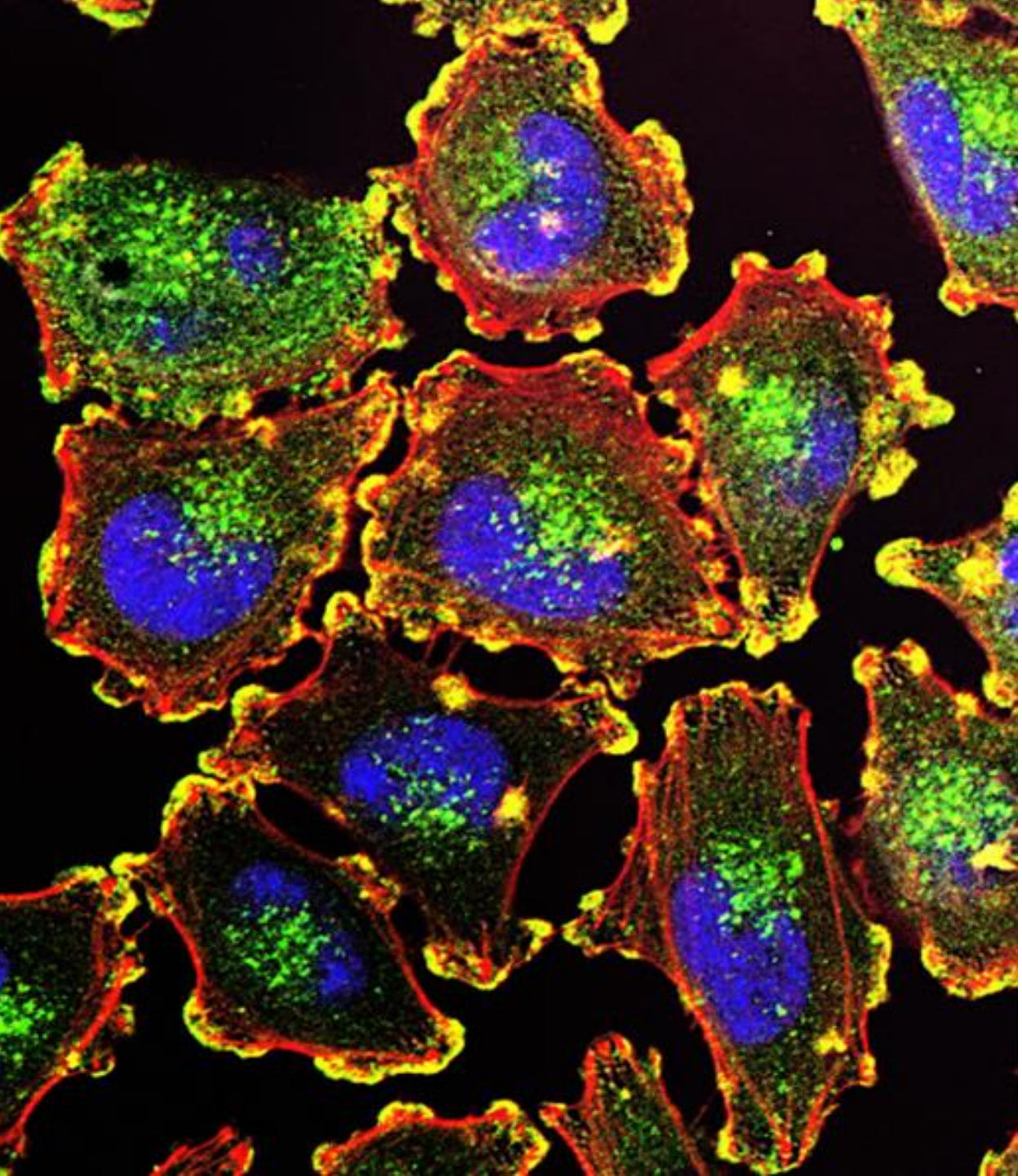
BRITISH
GYNAECOLOGICAL
CANCER
SOCIETY

BOLT

Biomarkers of Lynch Tumours

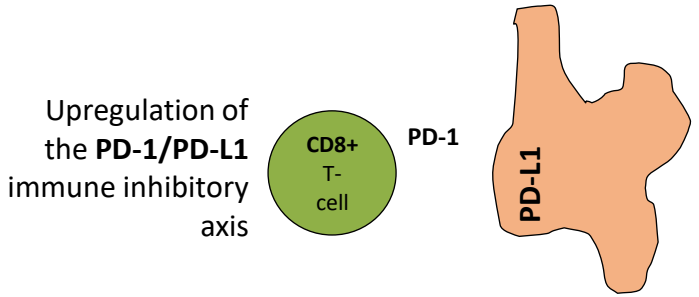

a
POLE (ultramutated)
MSI (hypermutated)
Copy-number low (endometrioid)
Copy-number high (serous-like)
Mutations per Mb
n = 17
n = 65
n = 90
n = 60
Substitution frequency (%)
POLE
MSI/MLH1
CN cluster
P7EN
TP53
Histology
Tumour grade
Nucleotide substitutions
CA CG CT TA TC TG
POLE mutations
V411L P286R 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
Mutation
Missense


Progression-free survival (%)
100
80
60
40
20
0
Log-rank P = 0.02
POLE (ultramutated)
MSI (hypermutated)
Copy-number low (endometrioid)
Copy-number high (serous-like)
0
20
40
60
80
100
120
Months



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.



Lynch Syndrome

+/-

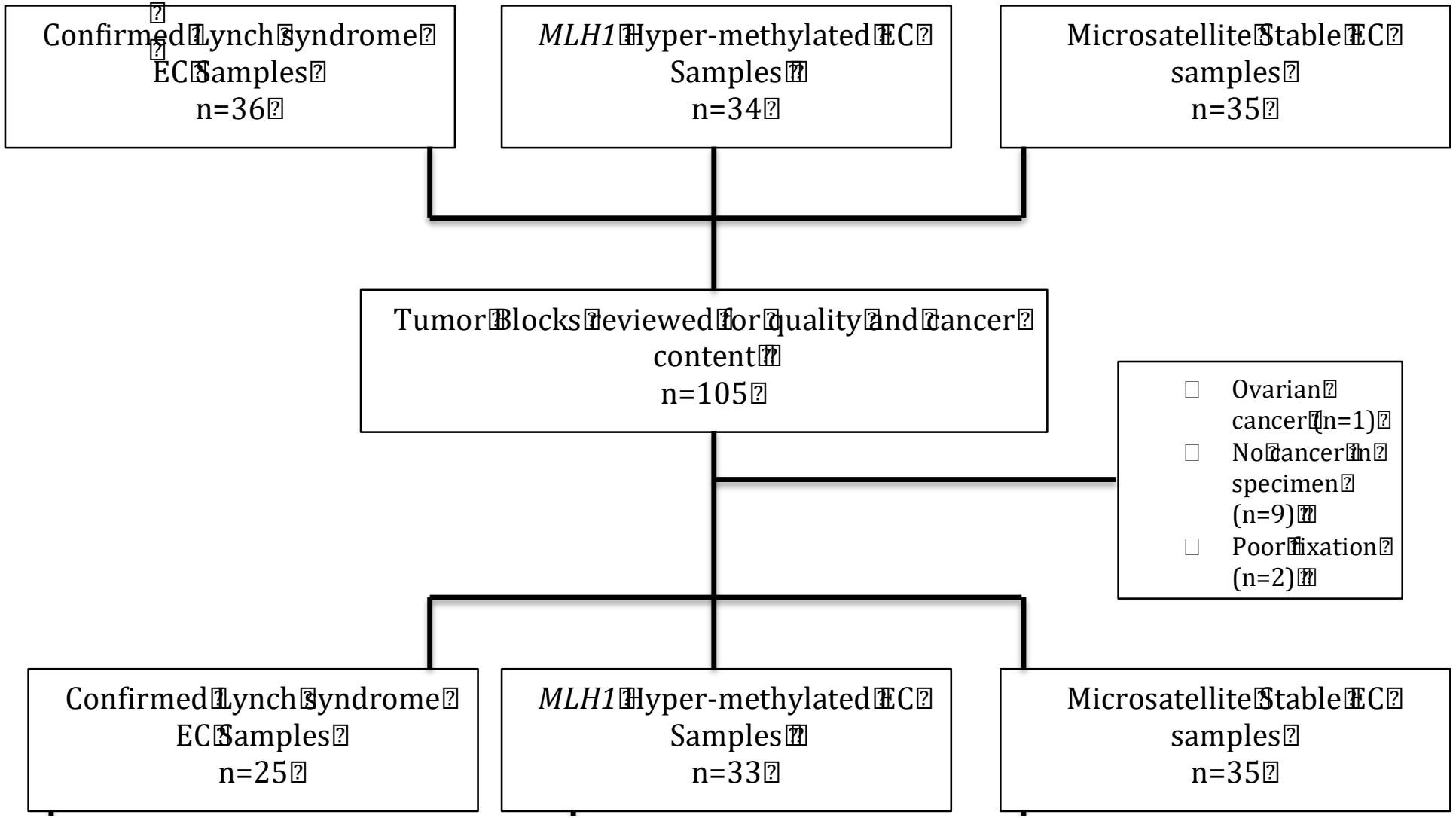
-/-

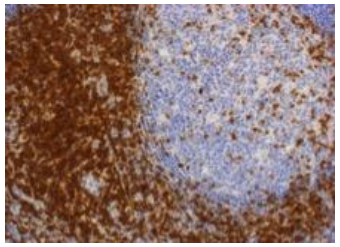
Somatic MMR loss

+/+

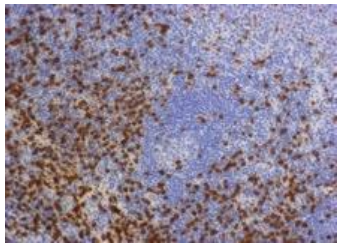
+/-

-/-

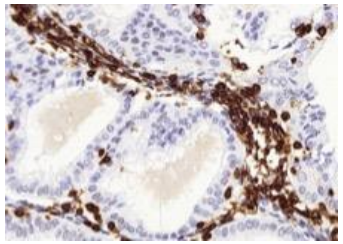

Confirmed Lynch syndrome EC Samples n=36
MLH1 Hyper-methylated EC Samples n=34
Microsatellite Stable EC samples n=35
Tumor Blocks reviewed for quality and cancer content n=105
Ovarian cancer (n=1)
No cancer in specimen (n=9)
Poor fixation (n=2)
Confirmed Lynch syndrome EC Samples n=25
MLH1 Hyper-methylated EC Samples n=33
Microsatellite Stable EC samples n=35



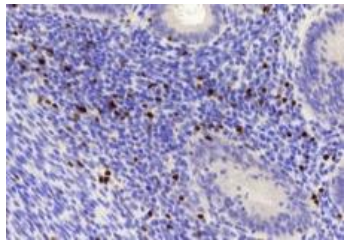
CD3



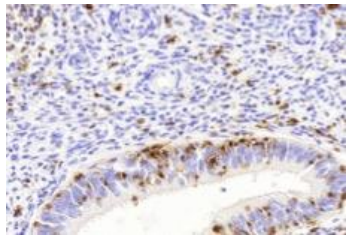
CD8



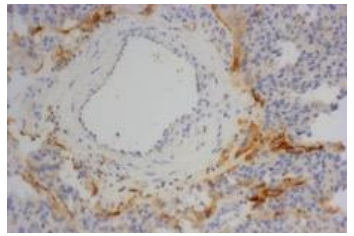
CD45R0



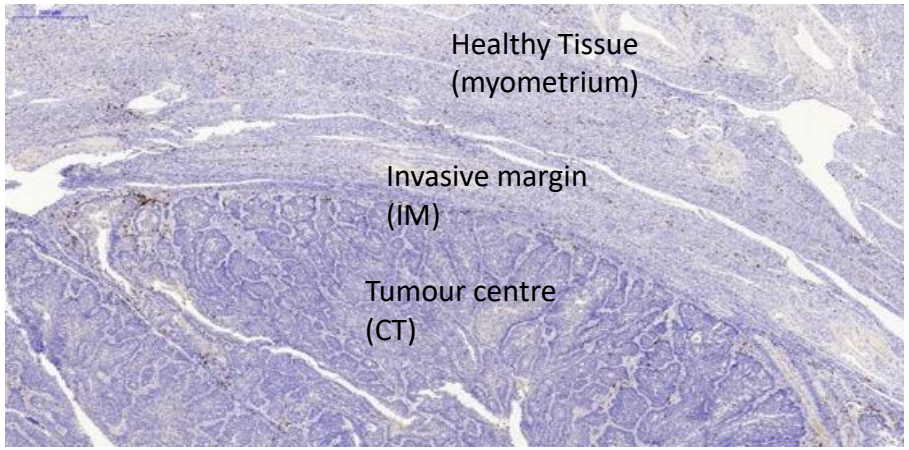
FOXP3

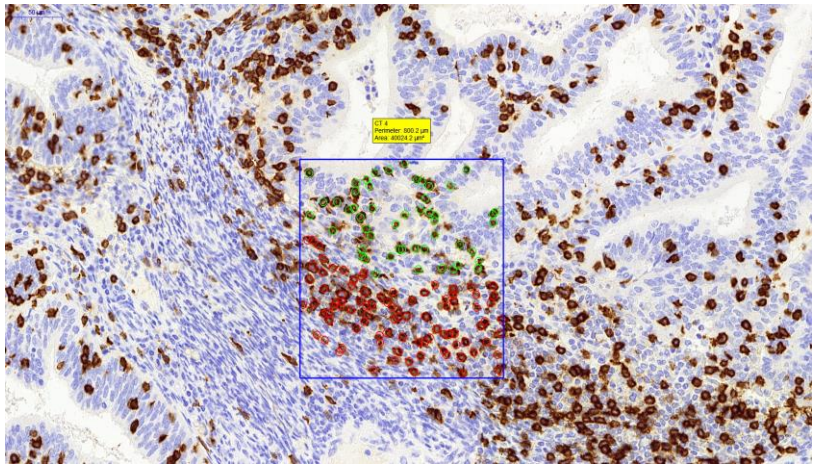


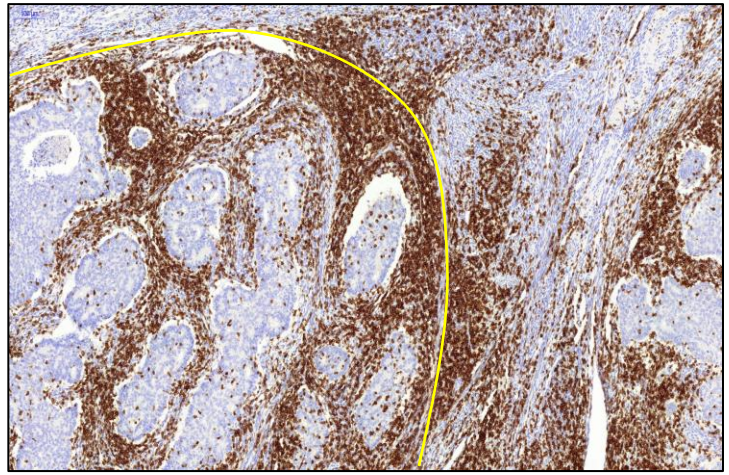
PD-1

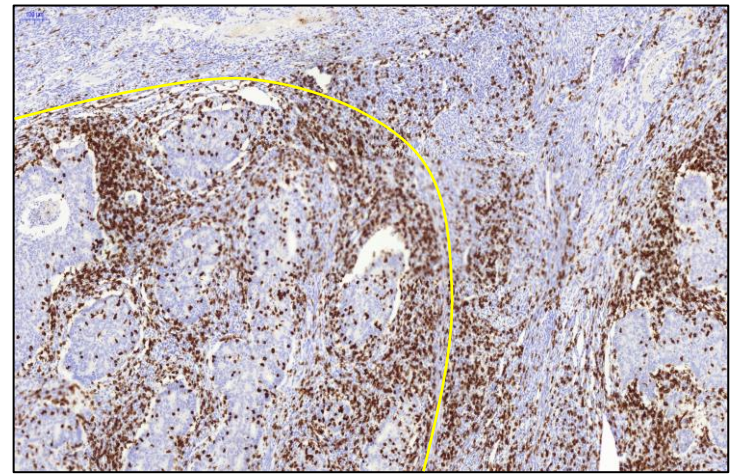


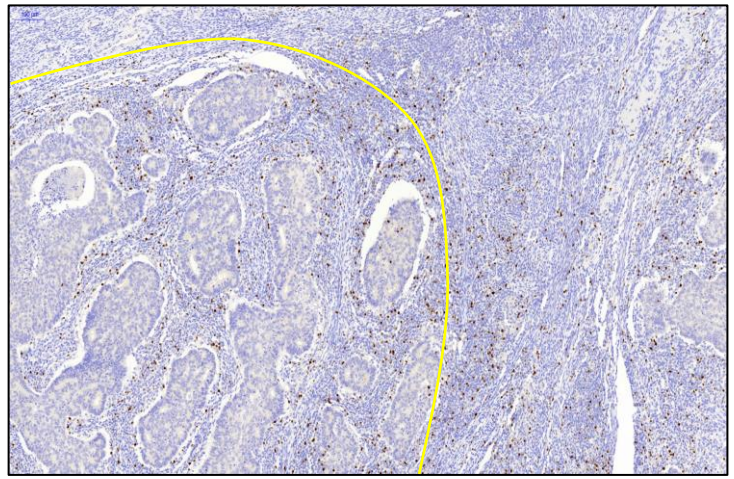
PD-L1

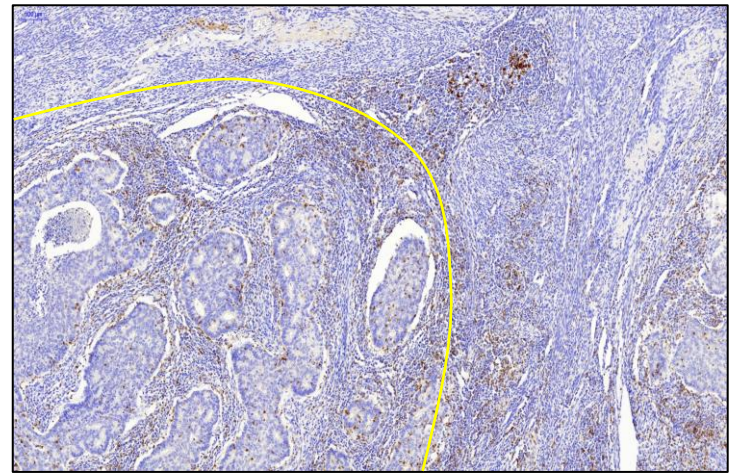








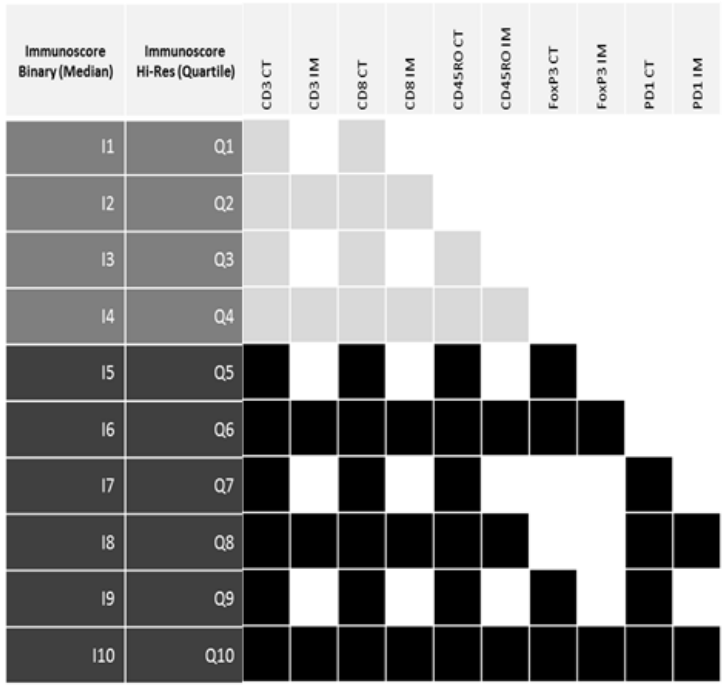




20 single-feature cohorts:
Immunoscores I1:I10 & Q1:Q10

Three-class or Two-class response variable

0.7:0.3 Train : Test Partition



Method used

- Multinomial Regression
- Neural Networks
- Support Vector Machines
  - Linear & Tuned
  - Radial & Tuned
- Discriminant Analyses
  - LDA
  - QDA
  - MDA
  - FDA
  - RDA

Train-control

- 5x 10-fold CV
- LOOCV
- LGOCV

Model Validation

- Accuracy
- Confusion Matrices
- ROC AUCs

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]*

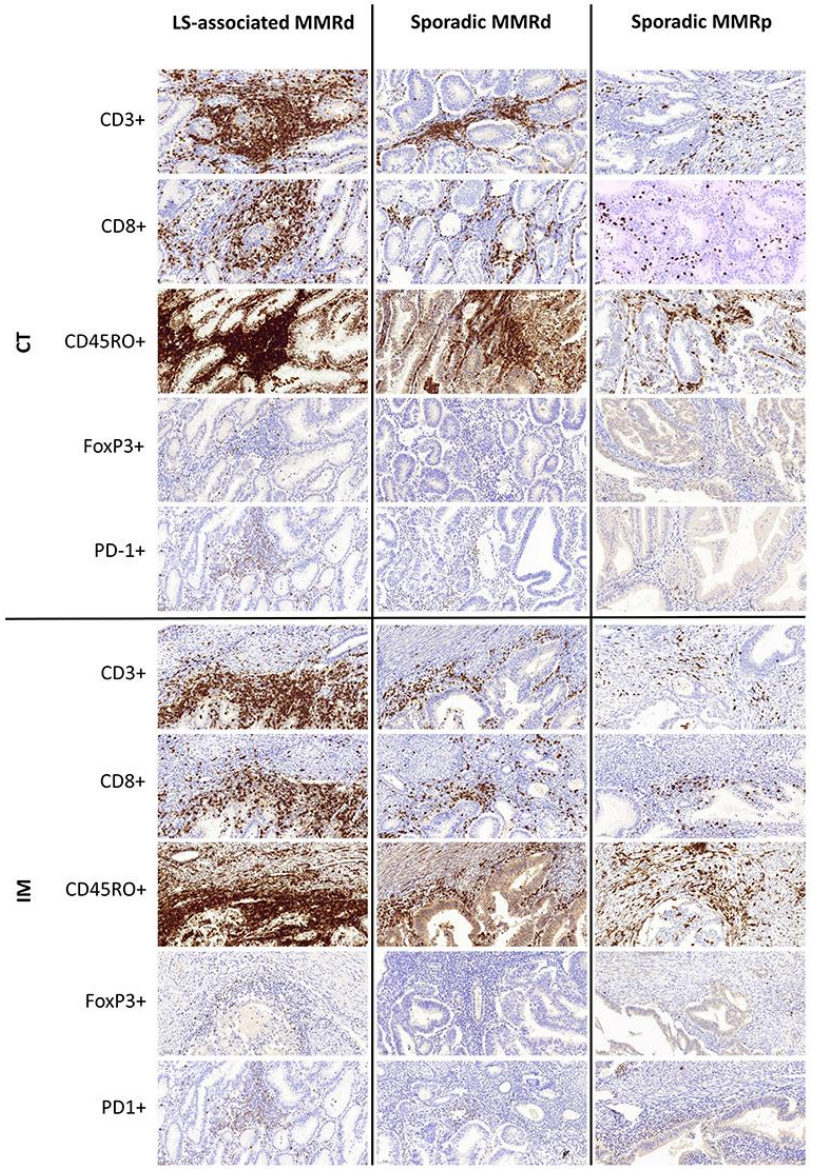


TABLE 3 | The difference in immune-profile expression by molecular group and location within the tumor.

Molecular subgroup	Marker	*p*-value		
		Overall	**Tumor center**	**Invasive margin**
Overall (LS-associated MMRd vs. Sporadic MMRd vs. MMRp)	CD3	**<0.0001**	**<0.0001**	**<0.0001**
LS-associated vs. sporadic MMRd	CD3	0.09	0.4	0.054
LS-associated vs. MMRp	CD3	**0.0001**	**0.002**	**<0.0001**
Sporadic MMRd vs. MMRp	CD3	**0.0024**	**0.003**	**0.006**
Overall (LS-associated MMRd vs. Sporadic MMRd vs. MMRp)	CD8	**<0.0001**	**<0.0001**	**<0.0001**
LS-associated vs. sporadic MMRd	CD8	**0.04**	0.2	**0.02**
LS-associated vs. MMRp	CD8	**<0.0001**	**<0.0001**	**<0.0001**
Sporadic MMRd vs. MMRp	CD8	**0.001**	**0.001**	**0.004**
Overall (LS-associated MMRd vs. Sporadic MMRd vs. MMRp)	CD45RO	**<0.0001**	0.08	**<0.0001**
LS-associated vs. sporadic MMRd	CD45RO	**0.008**	0.2	**0.0007**
LS-associated vs. MMRp	CD45RO	**<0.0001**	**0.04**	**0.0004**
Sporadic MMRd vs. MMRp	CD45RO	**0.04**	0.1	0.1
Overall (LS-associated MMRd vs. Sporadic MMRd vs. MMRp)	FoxP3	**<0.0001**	**<0.0001**	**<0.0001**
LS-associated vs. sporadic MMRd	FoxP3	**0.04**	0.08	0.08
LS-associated vs. MMRp	FoxP3	**0.0002**	**0.0009**	**0.0006**
Sporadic MMRd vs. MMRp	FoxP3	**0.02**	**0.02**	**0.03**
Overall (LS-associated MMRd vs. Sporadic MMRd vs. MMRp)	PD-1	**<0.0001**	**<0.0001**	**<0.0001**
LS-associated vs. sporadic MMRd	PD-1	**0.002**	**0.04**	**0.005**
LS-associated vs. MMRp	PD-1	**<0.0001**	**0.0007**	**0.0001**
Sporadic MMRd vs. MMRp	PD-1	0.09	0.05	0.1

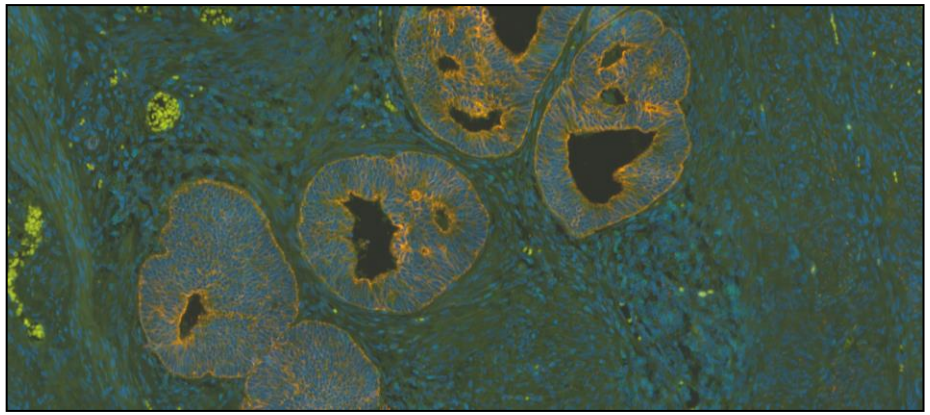
LS-associated MMRd, Lynch Syndrome-associated mismatch repair deficient; Sporadic MMRd, Sporadic mismatch repair deficient; MMRp, mismatch repair proficient. Unless otherwise stated p values represent Kruskal Wallis with Dunn post hoc, controlled for by Benjamini-Hochberg FDR.
All statistically significant results ($p < 0.05$) are in bold.

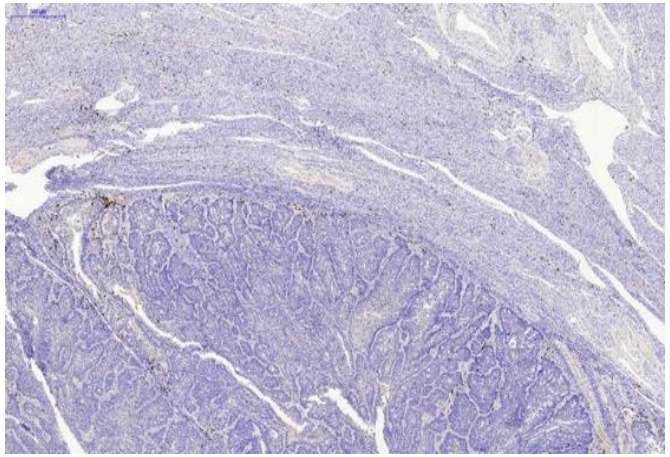
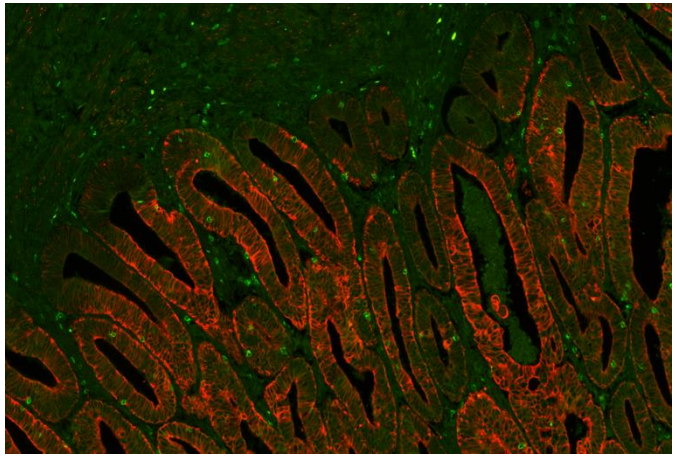
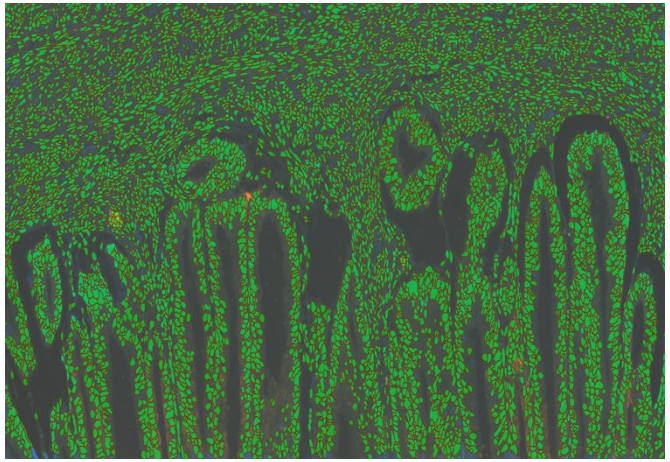
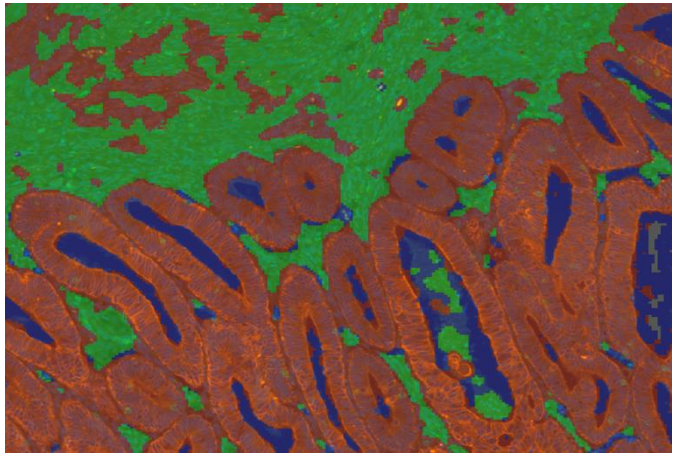
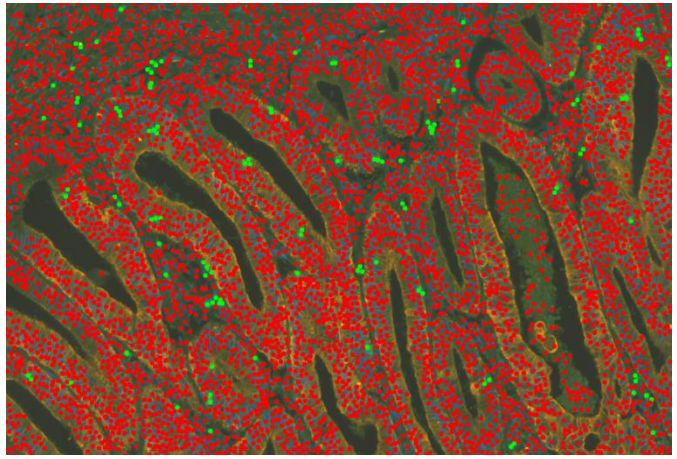
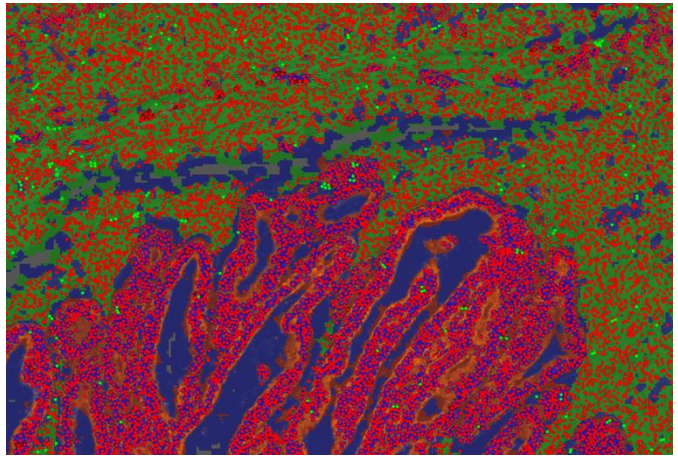
PORTEC 4a

BOLT
Biomarkers of Lynch Tumours

Endometrial Cancer
(n=585)

- NSMP (n=413)
- Suspected LS (n=25)
- *MLH1* Methylation (n=96)
- Somatic *POLE* (n=23)
- Lynch (n=50)
- MMRd &POLE (n=4)



cancers

MDPI

Article

Histological and Somatic Mutational Profiles of Mismatch Repair Deficient Endometrial Tumours of Different Aetiologies

Neil A. J. Ryan [1,2], Thomas D. J. Walker [1], James Bolton [3], Natalja ter Haar [4], Tom Van Wezel [4], Mark A. Glaire [5], David N. Church [5,6], D. Gareth Evans [2,7], Tjalling Bosse [4] and Emma J. Crosbie [1,8,*]

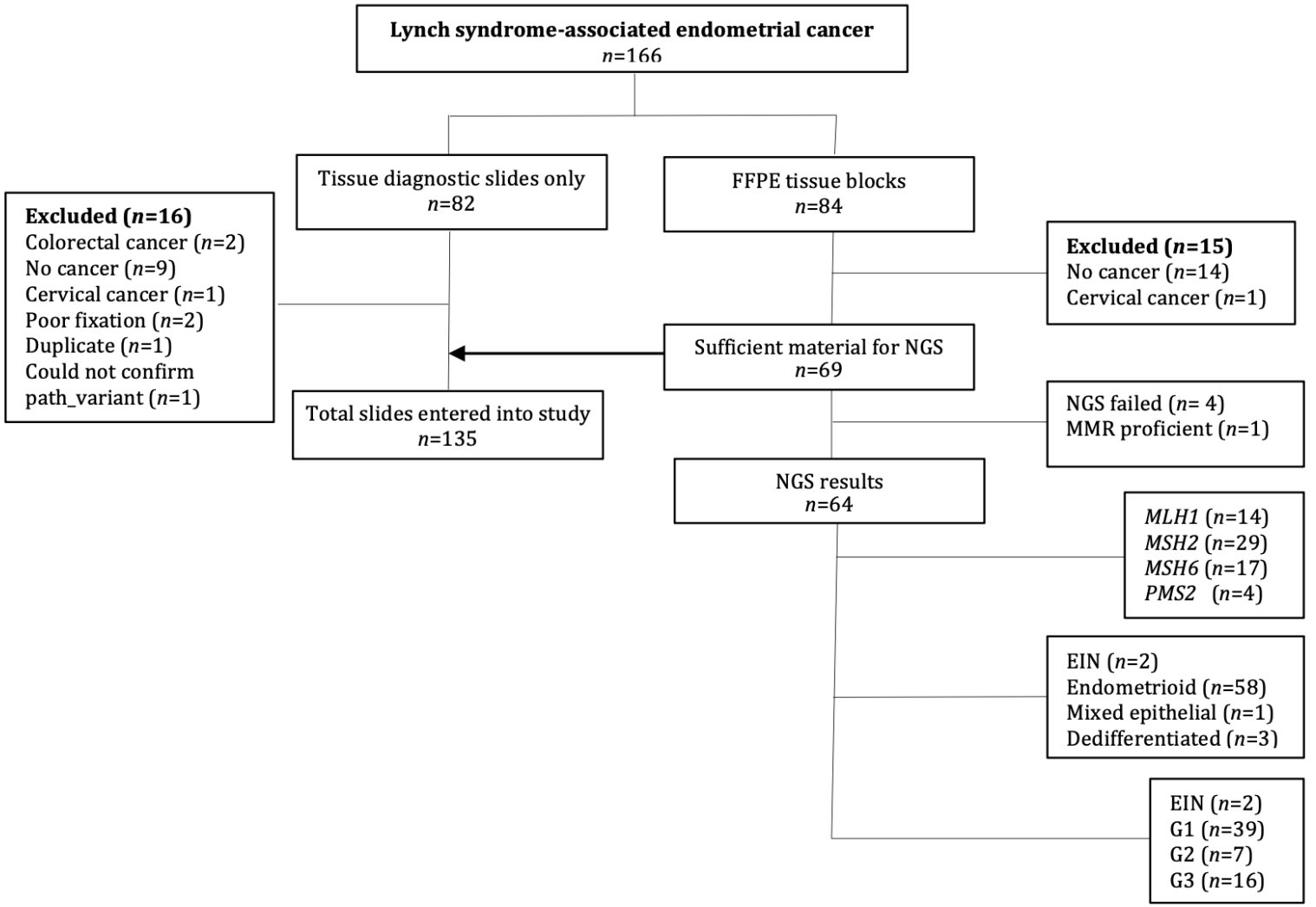
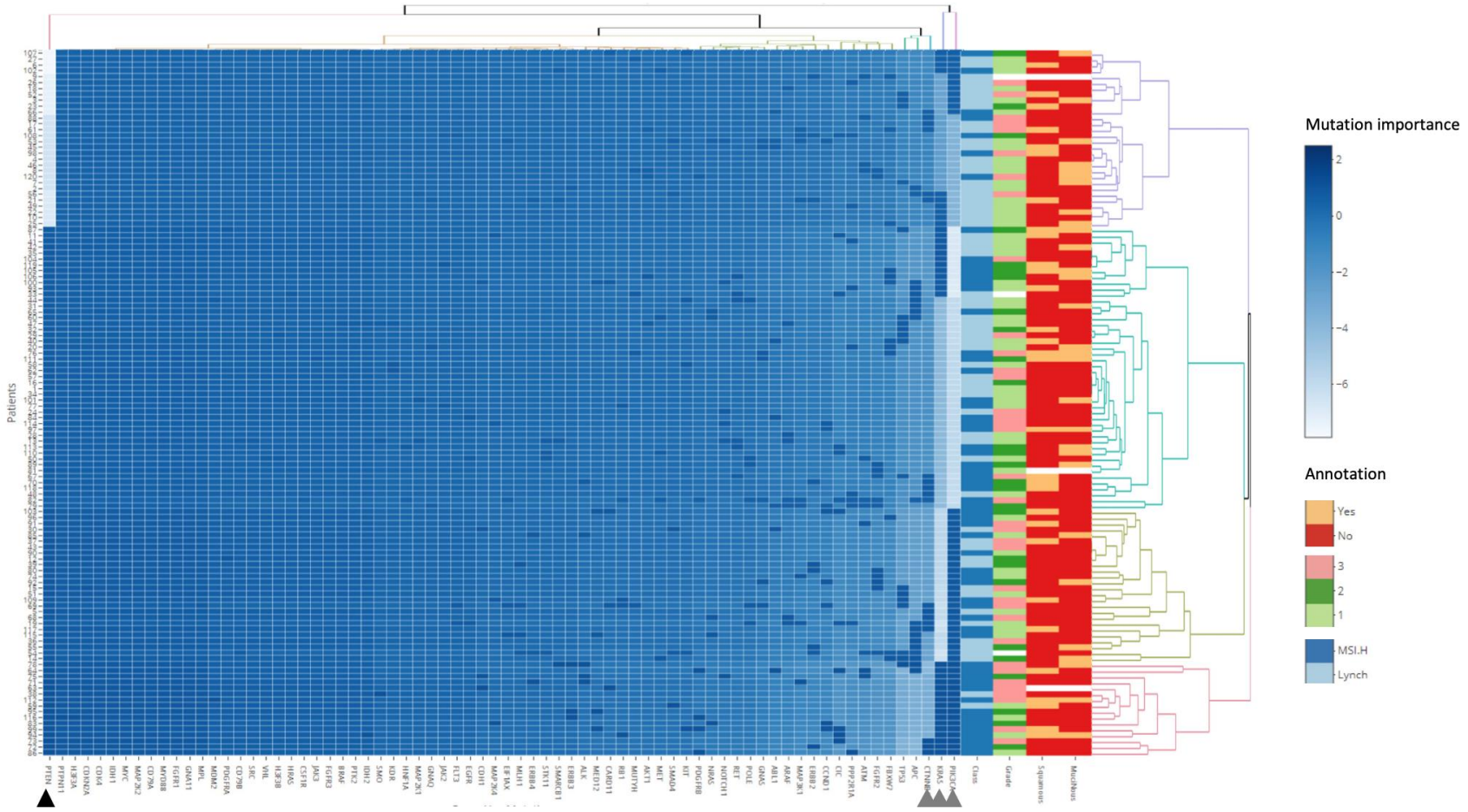
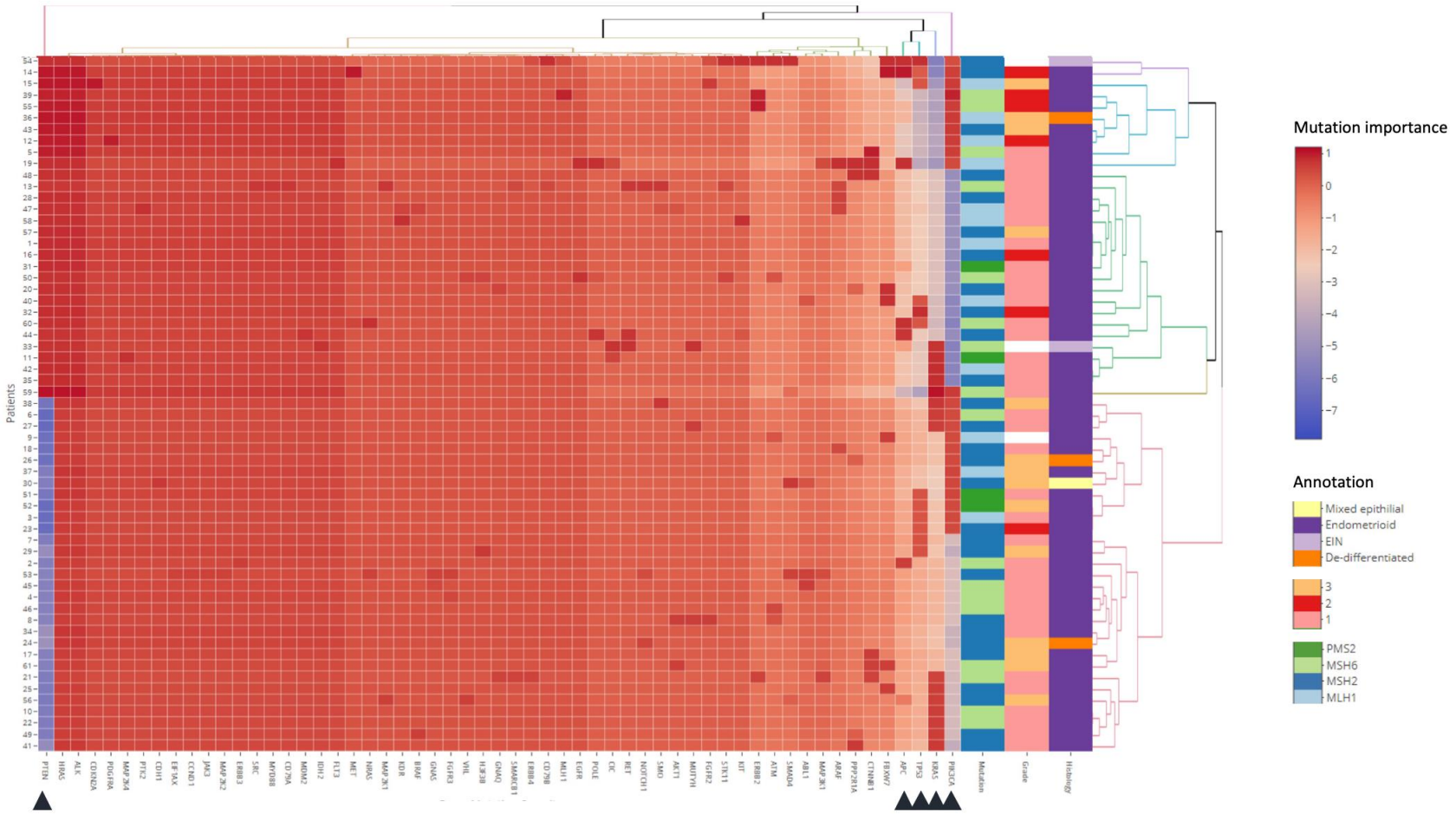


Figure 1. Study flow diagram Abbreviations: EIN: endometrial intraepithelial neoplasia; FFPE: formalin-fixed, paraffin-embedded; G: grade; NGS: next-generation sequencing; NK: not known.


Patients
PTEN
PTPN11
H3F3A
CDKN2A
CDK4
IDH1
MYC
MAP2K2
CD79A
MYD88
GNA11
MPL
MDM2
PDGFRA
CD79B
SRC
VHL
H3F3B
HRAS
CSF1R
JAK3
FGFR3
BRAF
PTK2
IDH2
SMO
KDR
HNF1A
MAP2K1
GNAQ
JAK2
FLT3
EGFR
CDH1
MAP2K4
EP300
MLH1
ERBB4
STK11
SMARCB1
ERBB3
ALK
MED12
CARD11
RB1
MUTYH
AKT1
MET
SMAD4
KIT
PDGFRB
NRAS
NOTCH1
RET
POLE
GNAS
ABL1
ARAF
MAP3K1
ERBB2
CCND1
CIC
PPP2R1A
ATM
FGFR2
FBXW7
TP53
APC
CTNNB1
KRAS
PIK3CA
Class
Grade
Squamous
MacroNuns
Mutation importance
2
0
−2
−4
−6
Annotation
Yes
No
3
2
1
MSI.H
Lynch


Patients
PTEN
HRAS
ALK
CDKN2A
PDGFRA
MAP2K4
PTCH1
CDH1
EIF1AX
CCND1
JAK3
MAP2K2
ERBB3
SRC
MYD88
CD79A
MDM2
IDH2
FLT3
MET
NRAS
MAP2K1
KDR
BRAF
GNAS
FGFR3
VHL
H3F3B
GNAQ
SMARCB1
ERBB4
CD79B
MLH1
EGFR
POLE
CIC
RET
NOTCH1
SMO
AKT1
MUTYH
FGFR2
STK11
KIT
ERBB2
ATM
SMAD4
ABL1
MAP3K1
ARAF
PPP2R1A
CTNNB1
FBXW7
APC
TP53
KRAS
PIK3CA
Mutation
Grade
Histology
Mutation importance
1
0
−1
−2
−3
−4
−5
−6
−7
Annotation
Mixed epithilial
Endometrioid
EIN
De-differentiated
3
2
1
PMS2
MSH6
MSH2
MLH1

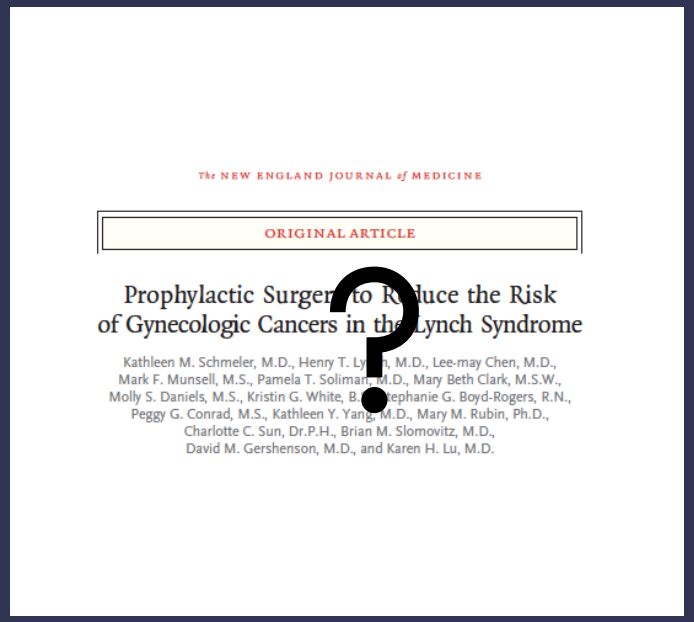
Journal of Pathology
J Pathol July 2022; **257:** 340–351
Published online 1 April 2022 in Wiley Online Library
(wileyonlinelibrary.com) DOI: 10.1002/path.5894

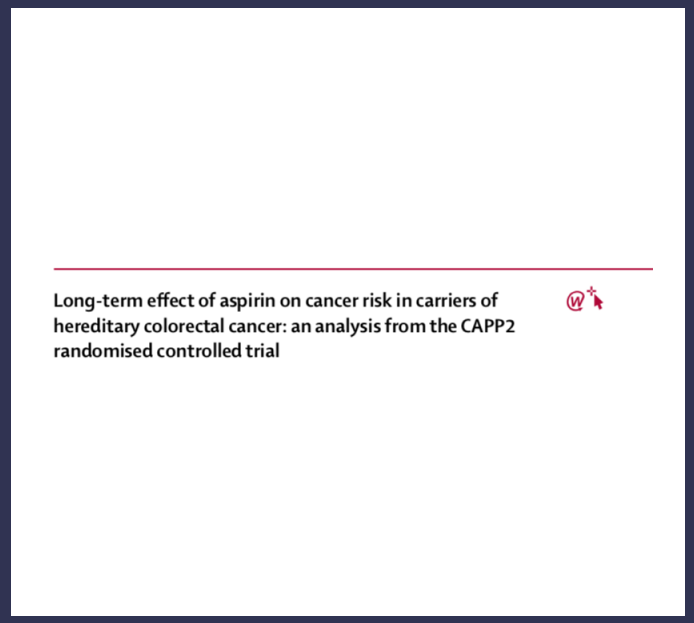
ORIGINAL ARTICLE

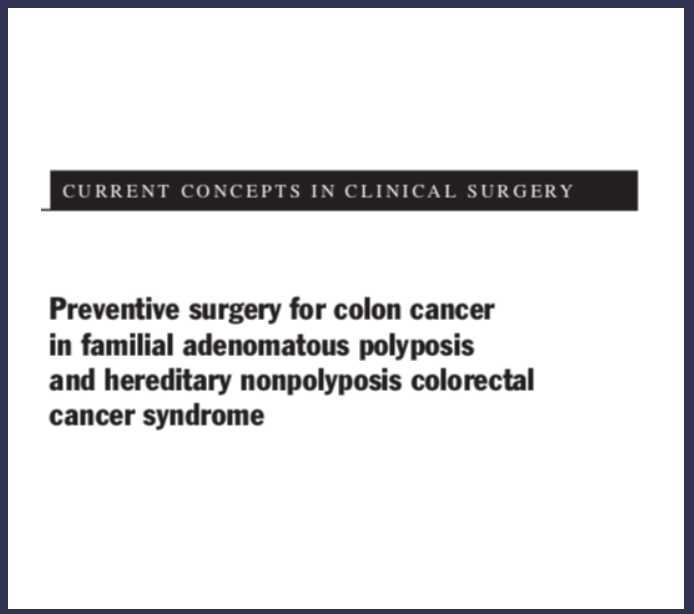
Discordant prognosis of mismatch repair deficiency in colorectal and endometrial cancer reflects variation in antitumour immune response and immune escape

Mark A Glaire[1], Neil AJ Ryan[2,3,4], Marieke E Ijsselsteijn[5], Katarzyna Kedzierska[1], Sofia Obolenski[1], Reem Ali[1], Emma J Crosbie[2,6], Tjalling Bosse[5], Noel FCC de Miranda[5] and David N Church[1,7,8*]

What next







What do we do with all these new women with LS?

Research

JAMA Oncology | Brief Report

Association of Mismatch Repair Mutation With Age at Cancer Onset in Lynch Syndrome

Implications for Stratified Surveillance Strategies

Neil A. J. Ryan, MBChB; Julie Morris, MSc; Kate Green, MPhil; Fiona Lalloo, MD; Emma R. Woodward, PhD; James Hill, MD; Emma J. Crosbie, PhD; D. Gareth Evans, MD

Genetics inMedicine

www.nature.com/gim

ARTICLE

Risk-reducing hysterectomy and bilateral salpingo-oophorectomy in female heterozygotes of pathogenic mismatch repair variants: a Prospective Lynch Syndrome Database report

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	Not
CA125	No	Not stated	No	Not
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).

NIHR | National Institute for Health Research

nature COMMUNICATIONS

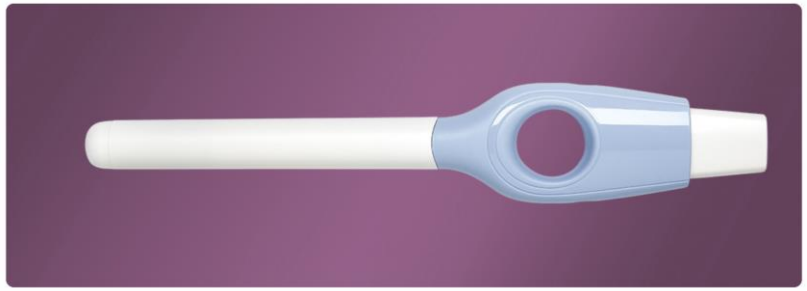
ARTICLE

Check for updates

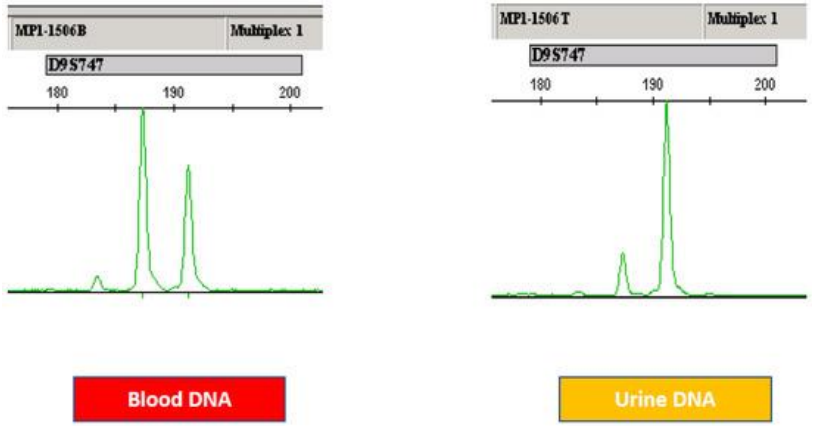
https://doi.org/10.1038/s41467-021-21257-6 OPEN

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]✉



The Academy of Medical Sciences



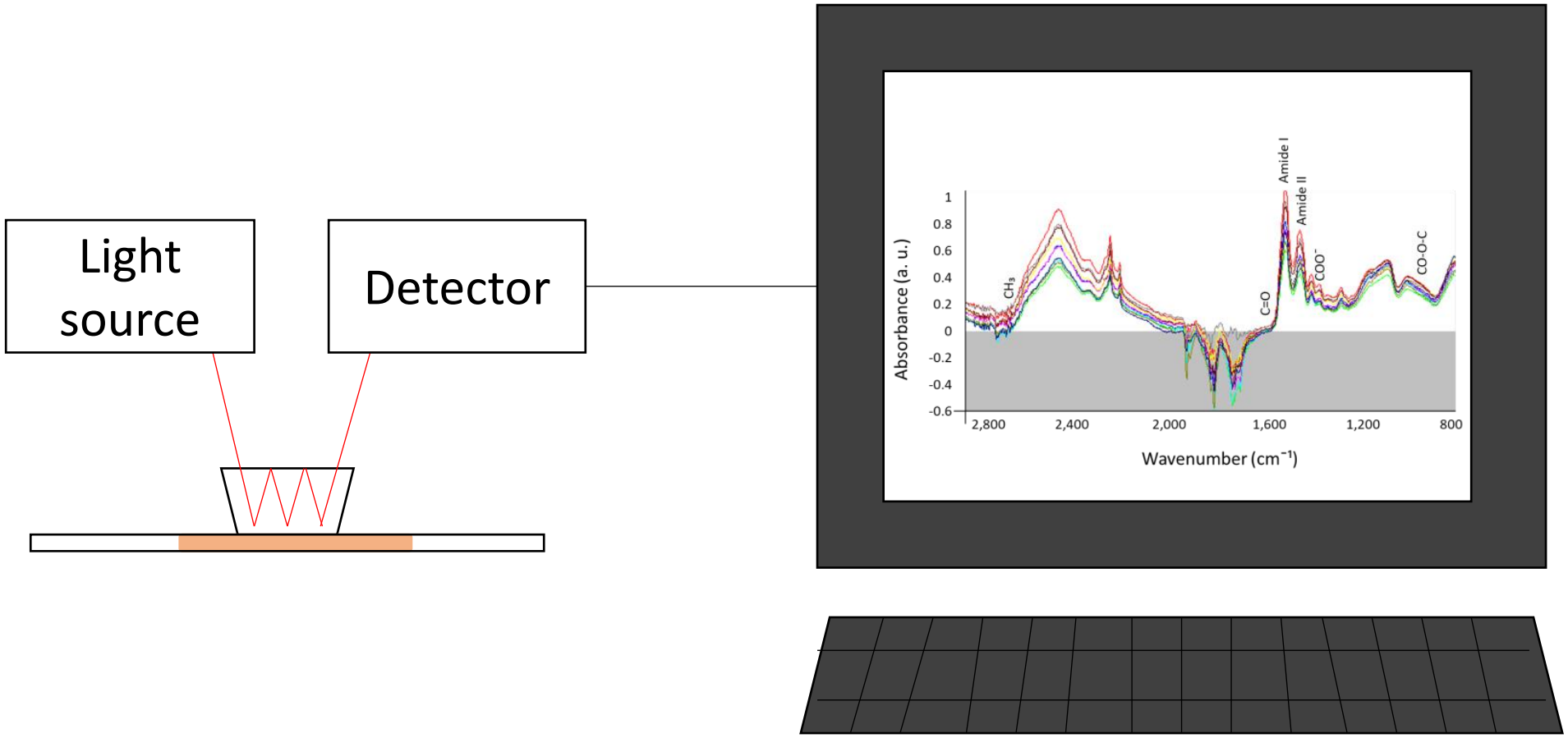
cancers

MDPI

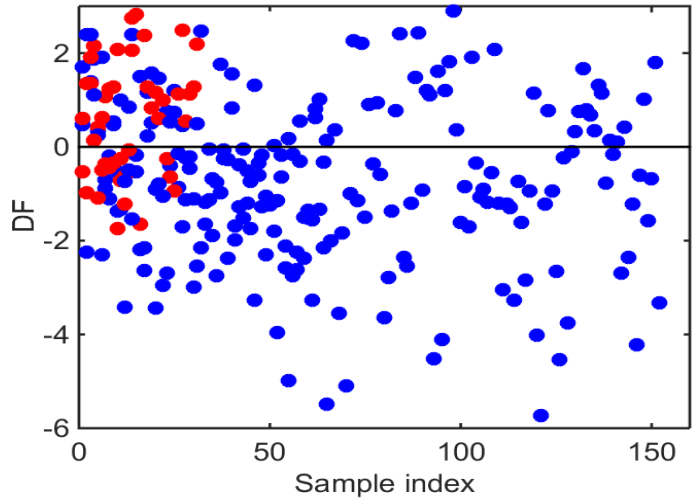
Article

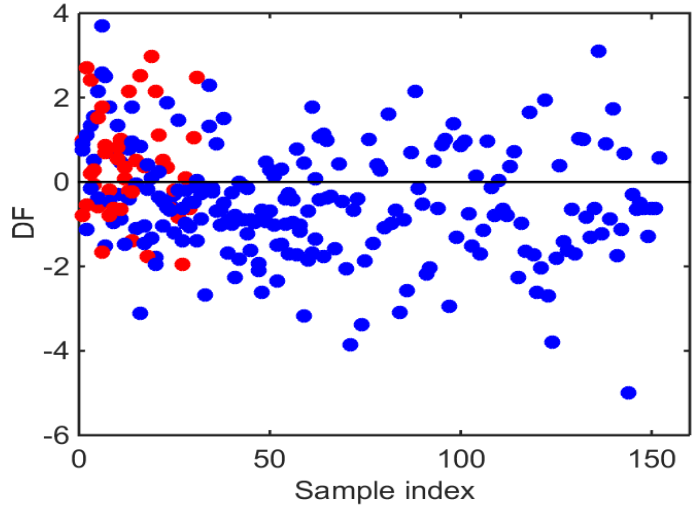
Detecting Endometrial Cancer by Blood Spectroscopy: A Diagnostic Cross-Sectional Study

Maria Paraskevaidi [1,2,*], Camilo L. M. Morais [1], Katherine M. Ashton [3], Helen F. Stringfellow [3], Rhona J. McVey [4], Neil A. J. Ryan [5], Helena O'Flynn [5], Vanitha N. Sivalingam [5], Sarah J. Kitson [5], Michelle L. MacKintosh [6], Abigail E. Derbyshire [6], Cecilia Pow [5], Olivia Raglan [2], Kássio M. G. Lima [7], Maria Kyrgiou [2,8], Pierre L. Martin-Hirsch [9,†], Francis L. Martin [1,†] and Emma J. Crosbie [5,6,†]

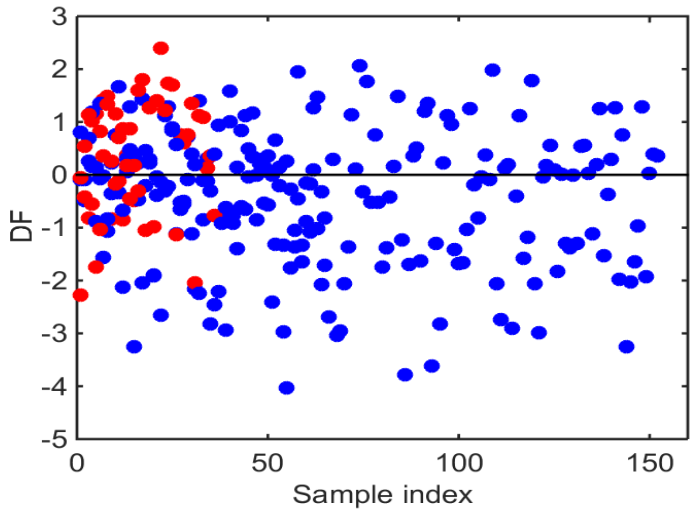

Light source
Detector
Absorbance (a. u.)
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
CH3
C=O
Amide I
Amide II
COO-
CO-O-C
2,800
2,400
2,000
1,600
1,200
800
Wavenumber (cm-1)

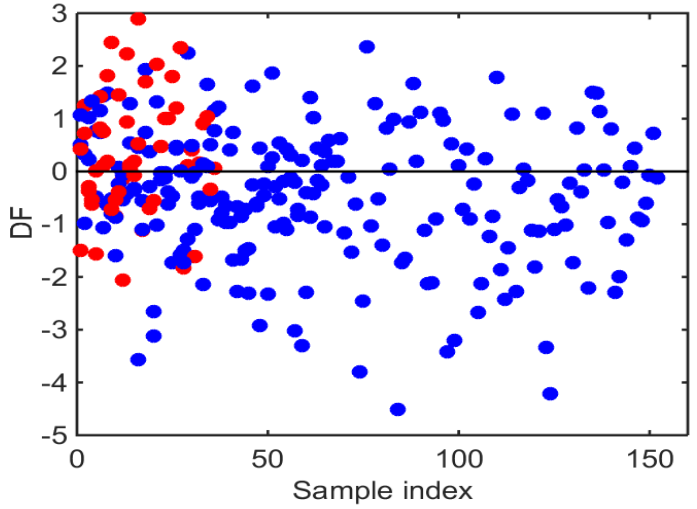
NSMG vs MSI



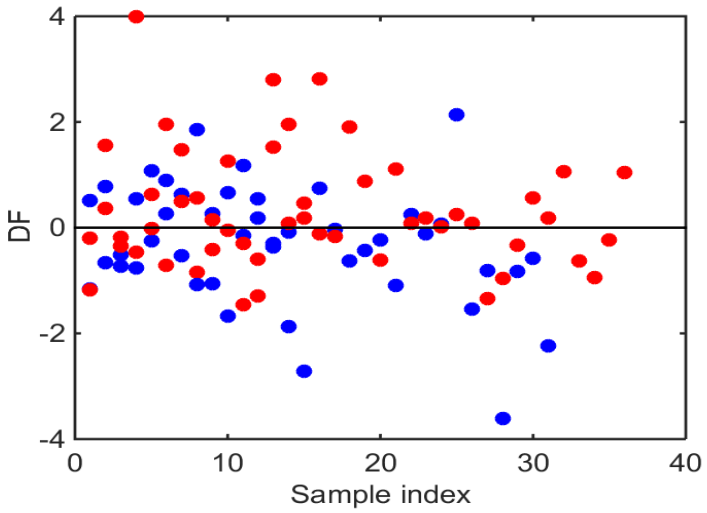


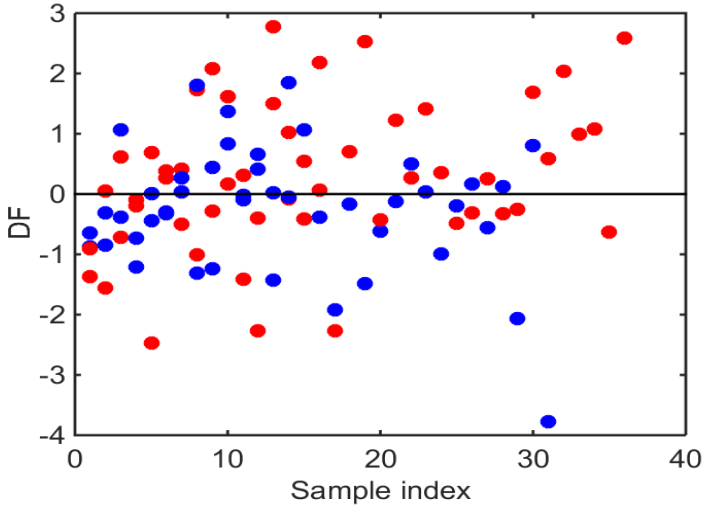
NSMG vs p53





MSI vs p53





OPEN ACCESS

ORIGINAL RESEARCH

Assessment of mismatch repair deficiency in ovarian cancer

Emma J Crosbie ,[1,2] Neil A J Ryan,[1,2,3] Rhona J McVey,[4] Fiona Lalloo,[5] Naomi Bowers,[5] Kate Green,[5] Emma R Woodward ,[3,5] Tara Clancy,[5] James Bolton,[4] Andrew J Wallace,[5] Raymond F McMahon,[4] D Gareth Evans [3,5]

www.nature.com/modpathol

ARTICLE OPEN

Check for updates

Validity of a two-antibody testing algorithm for mismatch repair deficiency testing in cancer; a systematic literature review and meta-analysis

K. T. S. Aiyer[1], T. Doeleman[1], N. A. Ryan[2,3], M. Nielsen[4], E. J. Crosbie[2,5], V. T. H. B. M. Smit[1], H. Morreau[1], J. J. Goeman[6] and T. Bosse[1]✉

Gynecologic Oncology 144 (2017) 491–495

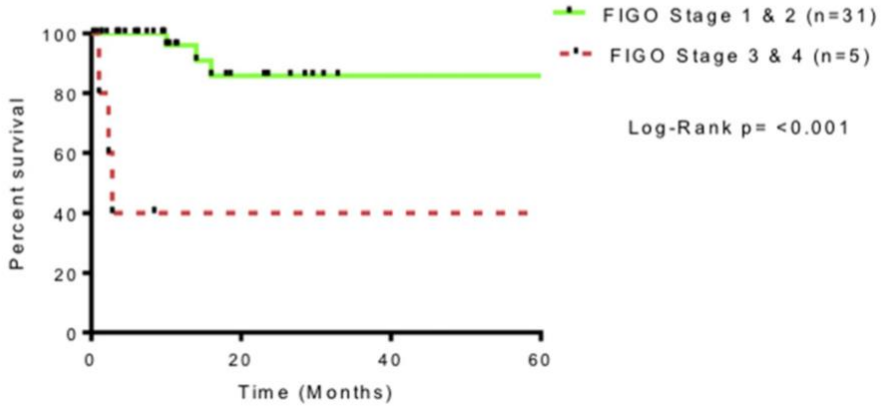
Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Pathological features and clinical behavior of Lynch syndrome-associated ovarian cancer

N.A.J. Ryan [a,b], D.G. Evans [b,c], K. Green [c], E.J. Crosbie [a,d,*]



TUMOR MARKERS AND SIGNATURES

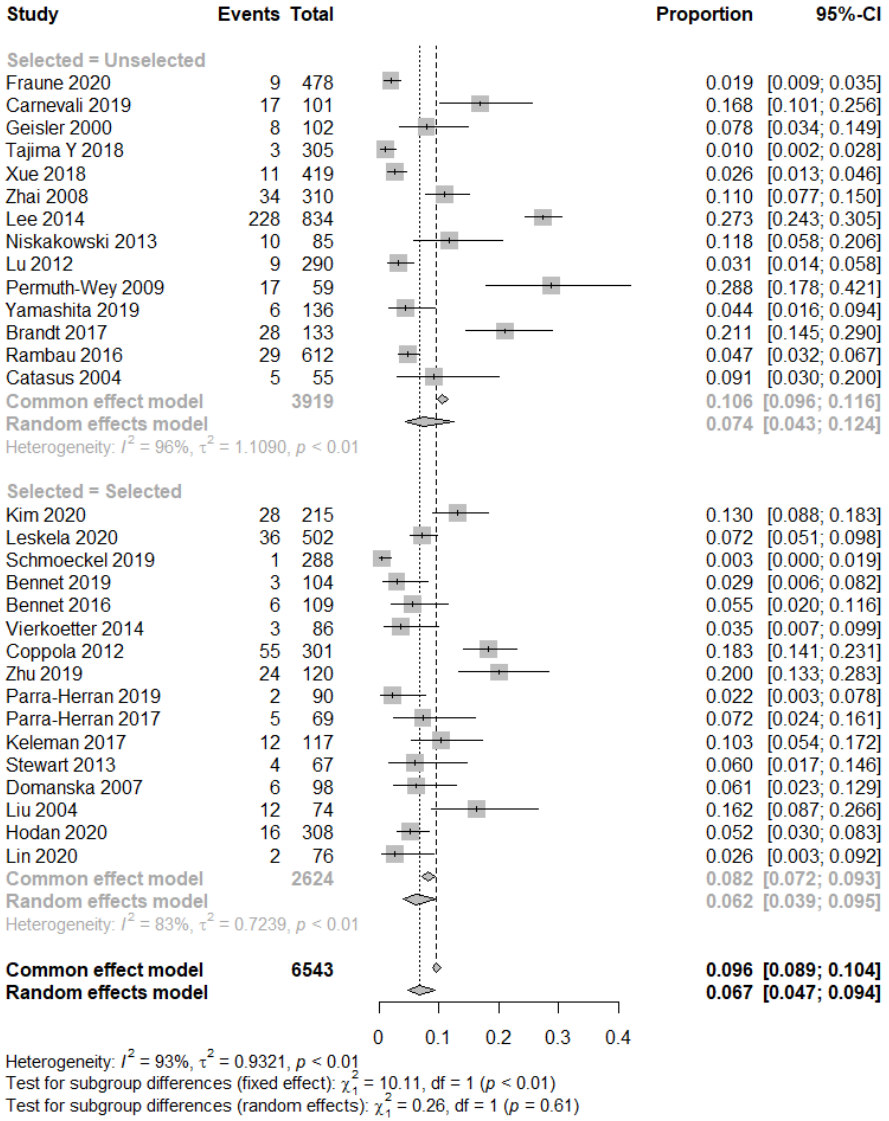
IJC INTERNATIONAL JOURNAL of CANCER

The prevalence of mismatch repair deficiency in ovarian cancer: A systematic review and meta-analysis

Amit Atwal[1] | Tristan Snowsill[2] | Marcus Cabrera Dandy[3] | Thomas Krum[1] | Claire Newton[4] | Dafydd Gareth Evans[5] | Emma J. Crosbie[6] | Neil A. J. Ryan[4,7]

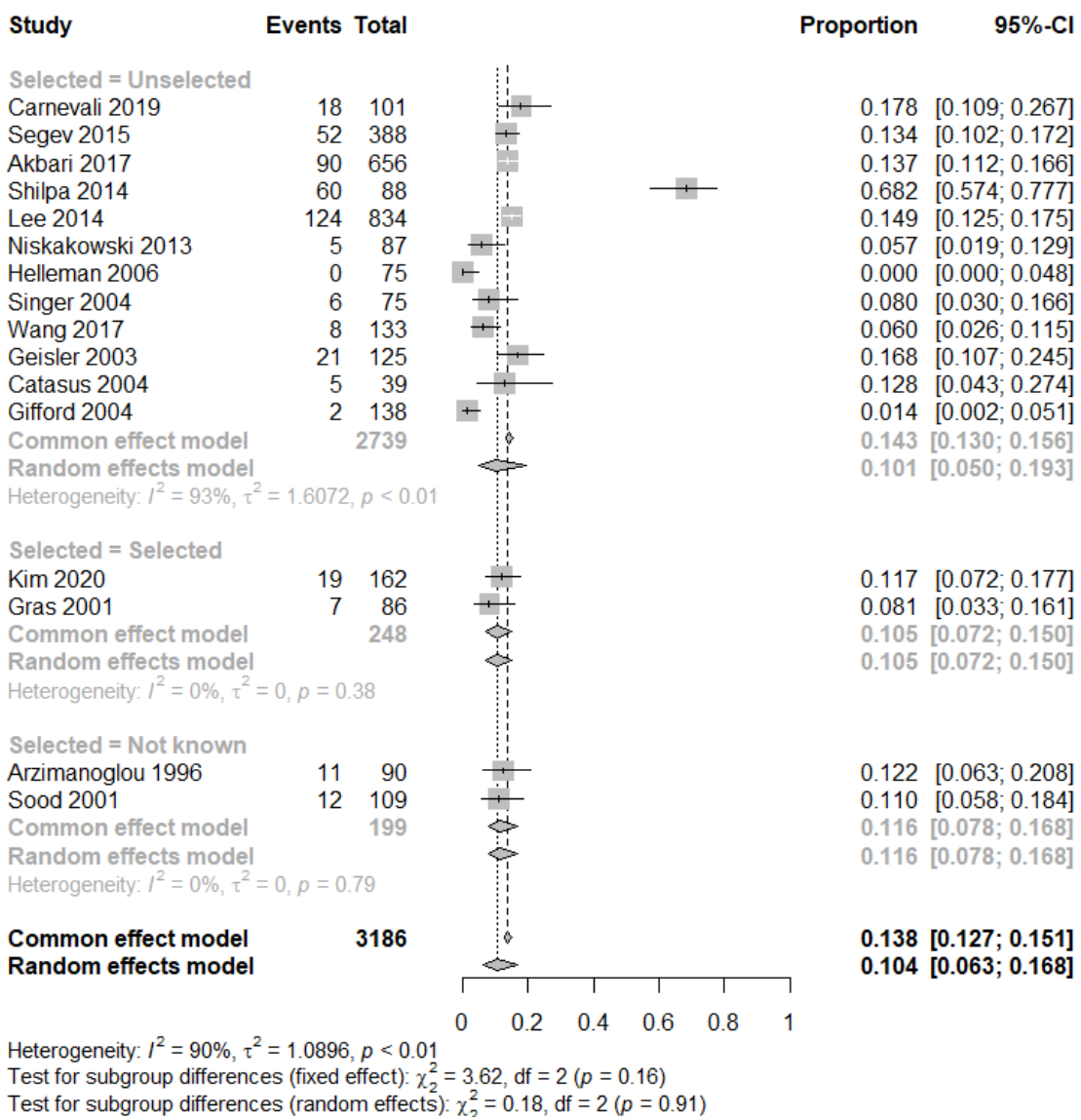
Immunohistochemistry

- 6.7% prevalence of MMRd by IHC



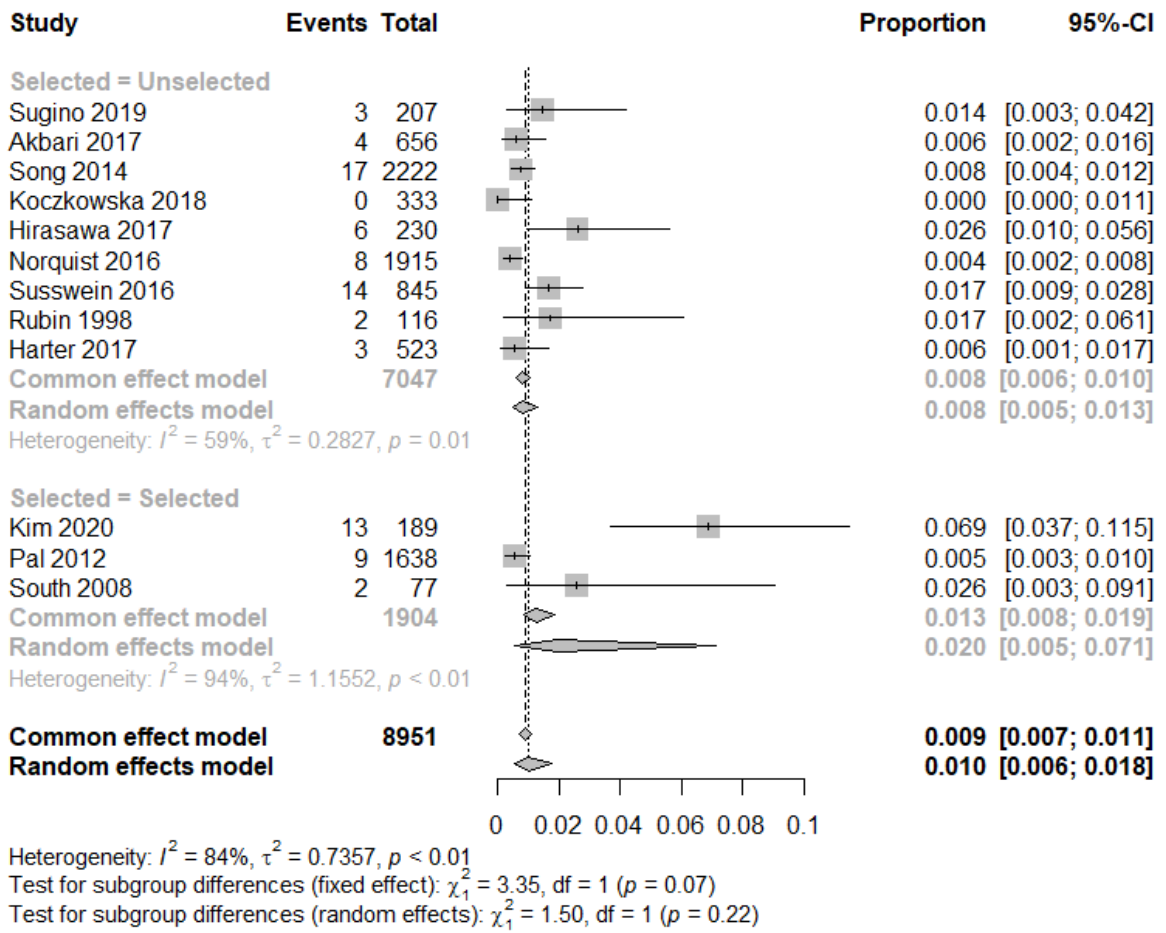
Microsatellite Instability

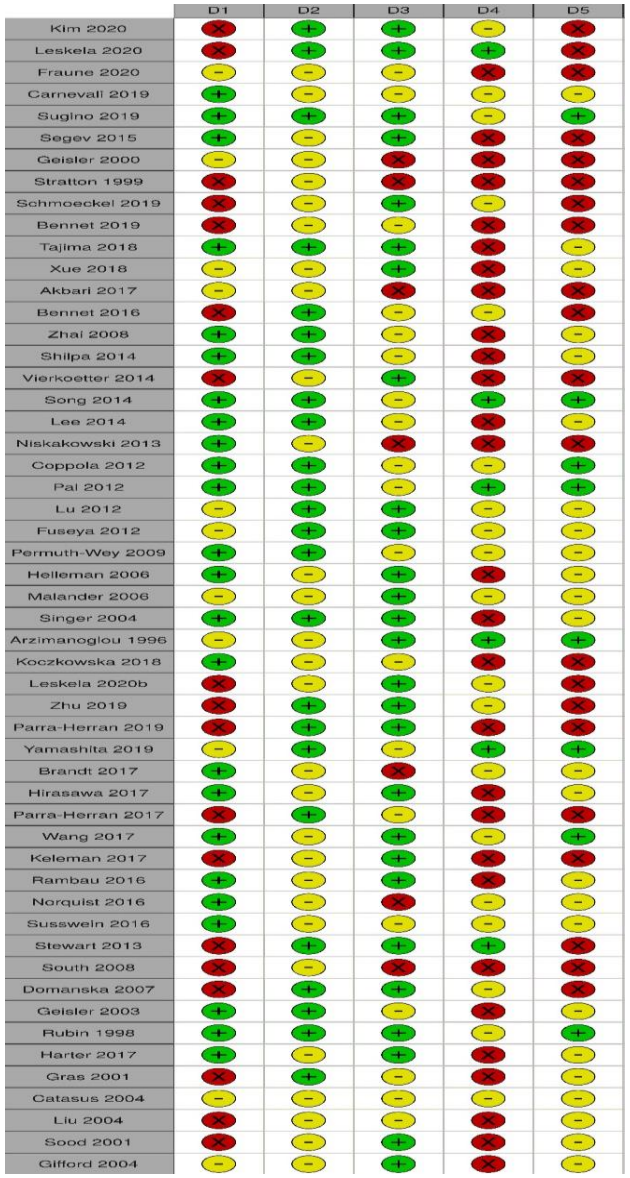
- 10.4% prevalence of MMRd by MSI



Germline

- 0.83% prevalence of Lynch Syndrome





	D1	D2	D3	D4	D5
Kim 2020	High	Low	Low	Some concerns	High
Leskela 2020	High	Low	Low	Low	High
Fraune 2020	Some concerns	Some concerns	Some concerns	High	High
Carnevali 2019	Low	Some concerns	Some concerns	Some concerns	Some concerns
Sugino 2019	Low	Low	Low	Some concerns	Low
Segev 2015	Low	Some concerns	Low	High	High
Geisler 2000	Some concerns	Some concerns	High	High	High
Stratton 1999	High	Some concerns	High	High	High
Schmoeckel 2019	High	Some concerns	Low	Some concerns	High
Bennet 2019	High	Some concerns	Some concerns	High	High
Tajima 2018	Low	Low	Low	High	Some concerns
Xue 2018	Some concerns	Some concerns	Low	High	Some concerns
Akbari 2017	Some concerns	Some concerns	High	High	High
Bennet 2016	High	Low	Some concerns	Some concerns	High
Zhai 2008	Low	Low	Some concerns	High	Some concerns
Shilpa 2014	Low	Low	Some concerns	High	Some concerns
Vierkoetter 2014	High	Some concerns	Low	High	High
Song 2014	Low	Low	Some concerns	Low	Low
Lee 2014	Low	Low	Some concerns	High	Some concerns
Niskakowski 2013	Low	Some concerns	High	High	High
Coppola 2012	Low	Low	Some concerns	Some concerns	Low
Pal 2012	Low	Low	Some concerns	Low	Low
Lu 2012	Some concerns	Low	Low	Some concerns	Some concerns
Fuseya 2012	Some concerns	Low	Low	Some concerns	Some concerns
Permuth-Wey 2009	Low	Low	Some concerns	Some concerns	Some concerns
Helleman 2006	Low	Some concerns	Low	High	Some concerns
Malander 2006	Some concerns	Some concerns	Low	Some concerns	Some concerns
Singer 2004	Low	Low	Low	High	Some concerns
Arzimanoglou 1996	Some concerns	Some concerns	Low	Low	Low
Koczkowska 2018	Low	Some concerns	Some concerns	High	High
Leskela 2020b	High	Some concerns	Low	Some concerns	High
Zhu 2019	High	Low	Low	Some concerns	High
Parra-Herran 2019	High	Low	Low	High	High
Yamashita 2019	Some concerns	Low	Some concerns	Low	Low
Brandt 2017	Low	Some concerns	High	Some concerns	Some concerns
Hirasawa 2017	Low	Some concerns	Low	High	Some concerns
Parra-Herran 2017	High	Low	Some concerns	High	High
Wang 2017	Low	Some concerns	Low	Some concerns	Low
Keleman 2017	High	Some concerns	Low	High	High
Rambau 2016	Low	Some concerns	Low	High	Some concerns
Norquist 2016	Low	Some concerns	High	Some concerns	Some concerns
Susswein 2016	Low	Some concerns	Some concerns	Some concerns	Some concerns
Stewart 2013	High	Low	Low	Low	High
South 2008	High	Some concerns	High	High	High
Domanska 2007	High	Low	Low	Some concerns	High
Geisler 2003	Low	Low	Some concerns	High	Some concerns
Rubin 1998	Low	Low	Low	Some concerns	Low
Harter 2017	Low	Some concerns	Low	High	Some concerns
Gras 2001	High	Low	Some concerns	High	Some concerns
Catasus 2004	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
Liu 2004	High	Some concerns	Some concerns	High	Some concerns
Sood 2001	High	Some concerns	Low	High	Some concerns
Gifford 2004	Some concerns	Some concerns	Low	High	Some concerns

Judgement

- High
- Some concerns
- Low

Domains

D1 = Selection

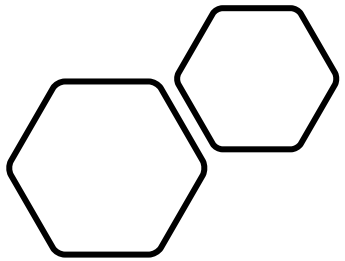
D2 = Comparability

D3 = Exposure

D4 = Outcome

D5 = Overall

POTALS…



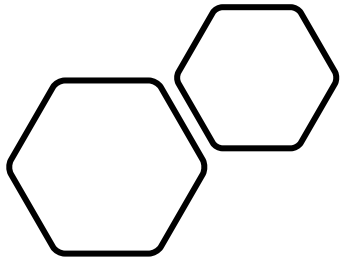
CANCER BIOMARKERS

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

In summary

- Gynecological care for Lynch syndrome and remains behind colorectal
- Our understanding of the science that underpins MMRd gynaecological cancer is still behind colorectal
- The body of work tries to address this
- More is needed to address the inequality seen in Lynch syndrome care
- Collaborations are key in rare disease

mange tak



Email: neilryan@nhs.net Twitter: @neilajryan