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NHS Foundation Trust

The landscape of endometrial cancer research

Professor Emma Crosbie

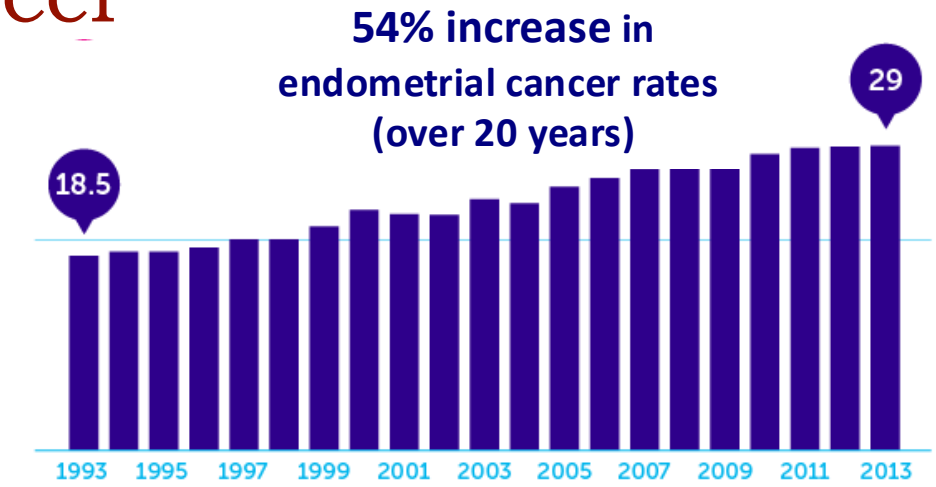
Endometrial = uterine = womb cancer

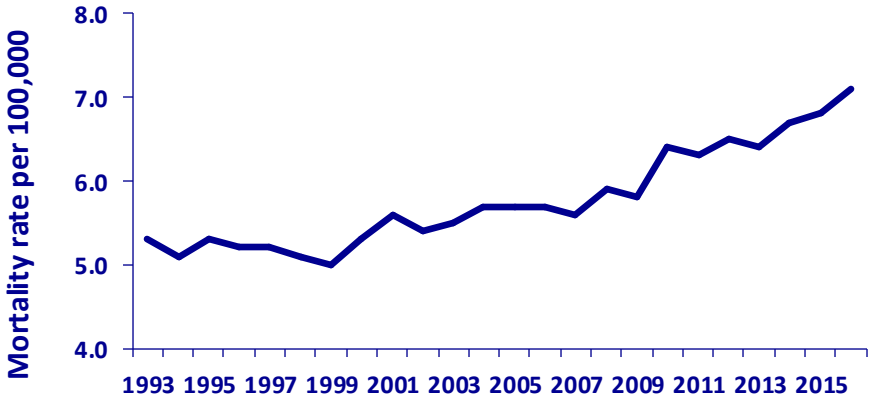
theguardian

Womb cancer: the most common diagnosis you've never heard of

Womb cancer is the fourth most common cancer in women, yet there is very little awareness about it. One woman who was diagnosed with the disease last year explains the symptoms and treatment options

The Guardian, Sunday 21 September 2014 18.30 BST

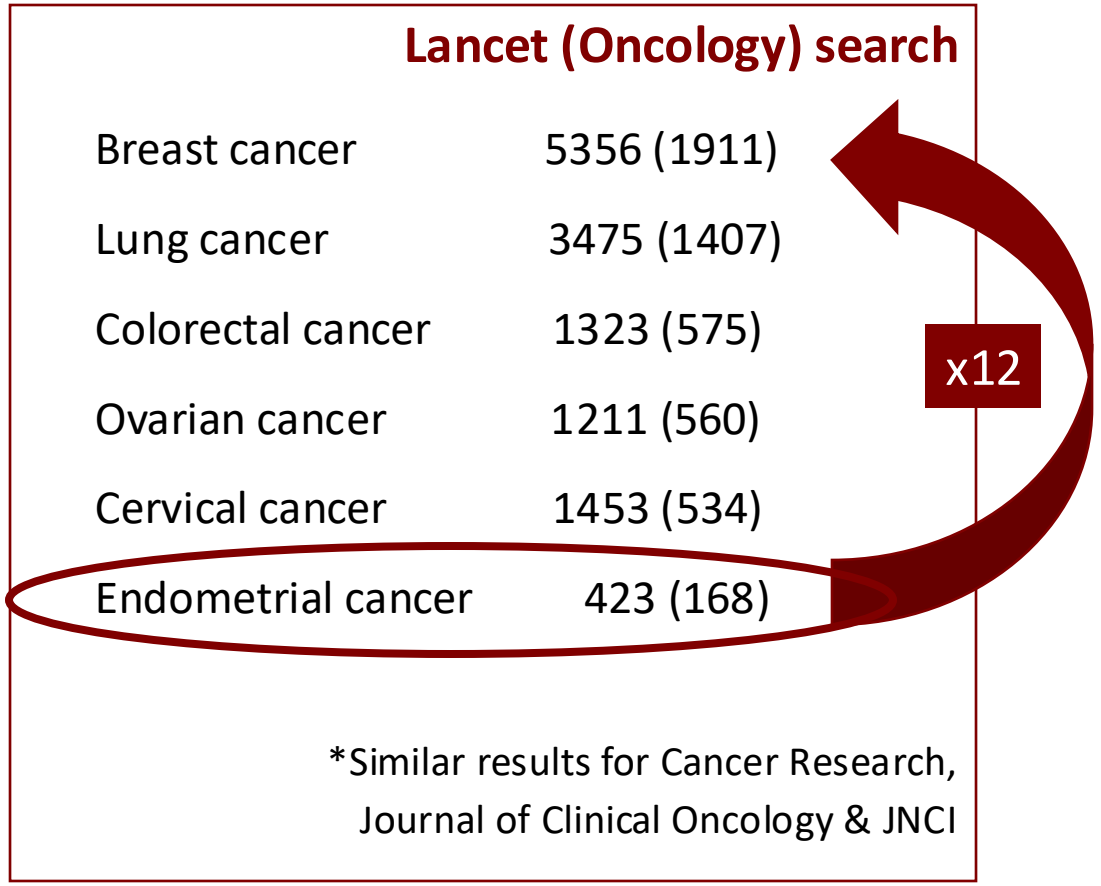




CANCER RESEARCH UK

Endometrial cancer is under-researched

- Few systematic reviews guiding patient care
- Few trials registered on national trial databases (UK and US)
- Funding streams do not prioritise endometrial cancer research
- 0.7% (£3.3million) of the UK's total cancer research budget spent on endometrial cancer in 2012



James Lind Alliance
Priority Setting Partnerships

Gynecologic Oncology 143 (2016) 287–293

Contents lists available at ScienceDirect

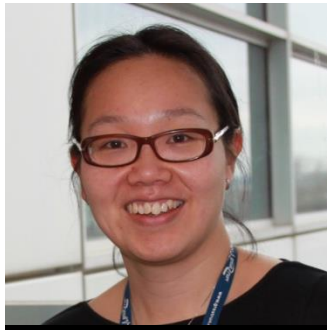
Gynecologic Oncology

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

Working together to shape the endometrial cancer research agenda: The top ten unanswered research questions

Y. Louise Wan [a,b], Rachel Beverley-Stevenson [b], Daloni Carlisle [b], Sinead Clarke [b], Richard J. Edmondson [a,b], Steve Glover [b,c], Julie Holland [b], Carol Hughes [b], Henry C. Kitchener [a,b], Sarah Kitson [a,b], Tracie Miles [b], Richard Morley [b,d], Jo Morrison [b], Linsey Nelson [a,b], Melanie Powell [b], Laura Sadler [b], Anne Tomlinson [b], Katharine Tylko-Hill [b], Jo Whitcombe [b,c], Emma J. Crosbie [a,b,*]

Womb Cancer Alliance



Louise Wan

1

Is it possible to develop a personalised score that reflects a woman's epidemiological risk of developing endometrial cancer?

2

Which women with abnormal vaginal bleeding should be referred for specialist care?

3

What are the most effective treatments available for metastatic endometrial cancer and what key molecular pathways should be targeted when developing new treatments?

4

Can we predict which women will benefit from adjuvant chemotherapy or radiotherapy after surgery and avoid ineffective treatment?

5

Are blood tests, including markers like CA125, useful in predicting duration of survivorship and/or whether cancer has recurred?

6

What ways of raising public awareness about endometrial cancer are most effective and cost effective?

7

What are the psychological issues surrounding diagnosis and treatment of endometrial cancer and what interventions might be helpful?

8

What are the underlying causes of different types of endometrial cancer and how do they develop?

9

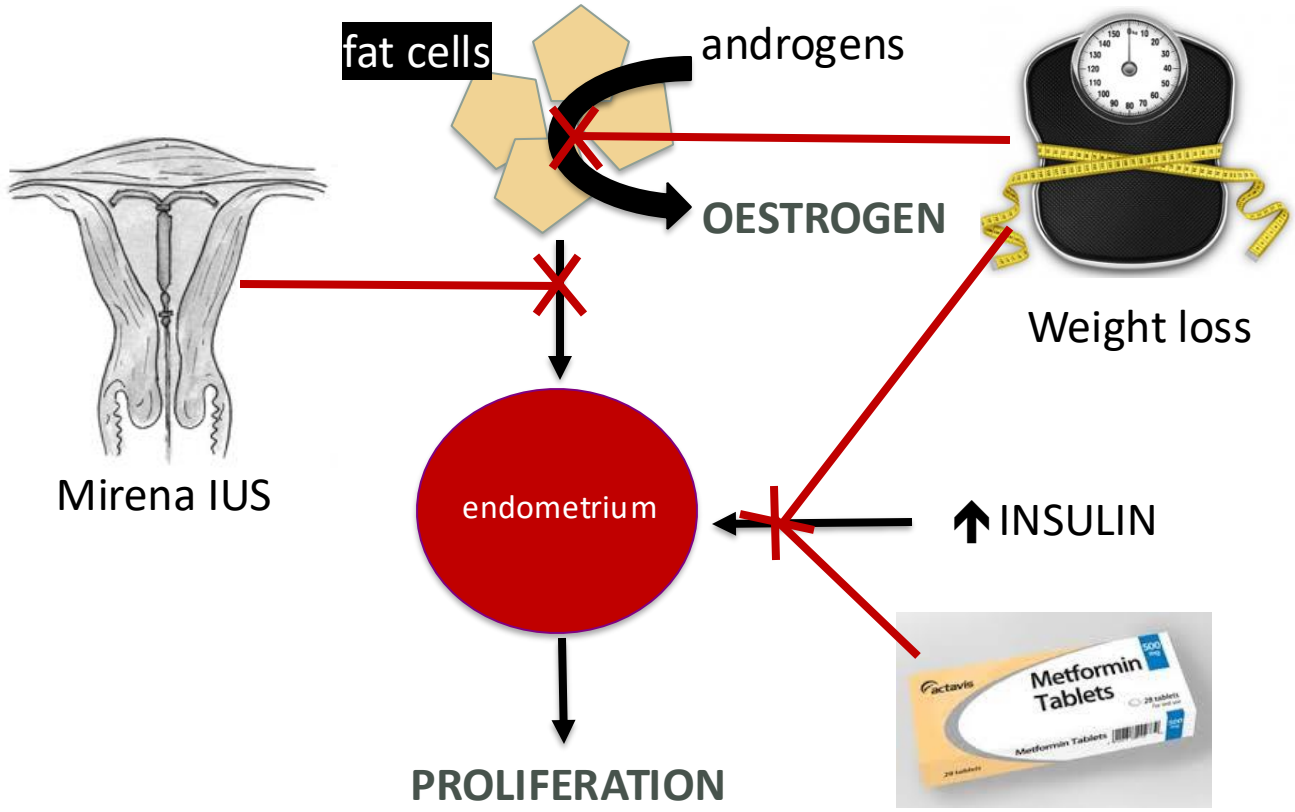
Can we predict at the time of diagnosis which endometrial cancers and pre-cancerous lesions will respond to hormonal treatments?

10

Do changes in lifestyle, including weight loss, reduce the risk of recurrence and improve survival in women who have been treated for endometrial cancer?

Preventing obesity-driven endometrial cancer

- Obesity-driven endometrial cancer
- 3 interventions: weight loss, metformin, intrauterine progestin
- Opportunities for prevention



Prevention studies are challenging

- In treatment trials, recurrence or death are the only meaningful clinical endpoints
- Prevention trials would require thousands of women over many years of follow up if prevention of endometrial cancer was endpoint
- This is wasteful, expensive, inefficient and even unethical if there are no robust data to support its use

Who should we target for prevention?

Sarah Kitson

Cemsel Bafligil

Review

Cancer Prevention Research

Identifying High-Risk Women for Endometrial Cancer Prevention Strategies: Proposal of an Endometrial Cancer Risk Prediction Model

Sarah J. Kitson[1,2], D. Gareth Evans[3], and Emma J. Crosbie[1,2]

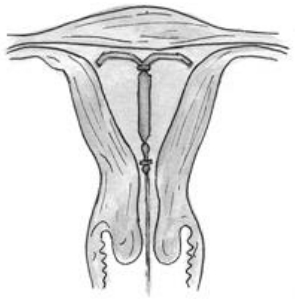
EC risk prediction model		
Obesity score Reproductive score Insulin resistance score Genetic score	Low risk	Reassess 5 years
	Intermediate risk	Diet, exercise + Mirena OR metformin
	High risk	Diet, exercise + Mirena + metformin +/- bariatric surgery

Cancer genetics

ORIGINAL RESEARCH

Association between genetic polymorphisms and endometrial cancer risk: a systematic review

Cemsel Bafligil [1], Deborah J Thompson,[2] Artitaya Lophatananon,[3] Miriam J Smith [4], Neil AJ Ryan,[1] Anie Naqvi,[5] D Gareth Evans [4], Emma J Crosbie [1,6]



UICC global cancer control

IJC International Journal of Cancer

The impact of obesity and bariatric surgery on circulating and tissue biomarkers of endometrial cancer risk

Michelle L. MacKintosh[1], Abigail E. Derbyshire[1], Rhona J. McVey[2], James Bolton[2], Mahshid Nickkho-Amiry[1], Catherine L. Higgins[2], Martyna Kamieniorz[2], Philip W. Pemberton[3], Bilal H. Kirmani[4], Babur Ahmed[5], Akheel A. Syed[5,6], Basil J. Ammori[5,6], Andrew G. Renehan[7], Henry C. Kitchener[8] and Emma J. Crosbie[1,8]

International Journal of Obesity www.nature.com/ijo

ARTICLE OPEN

Check for updates

Molecular Biology

The impact of obesity and bariatric surgery on the immune microenvironment of the endometrium

Anie Naqvi[1], Michelle L. MacKintosh[2], Abigail E. Derbyshire[2], Anna-Maria Tsakiroglou[3], Thomas D. J. Walker[4], Rhona J. McVey[5], James Bolton[5], Martin Fergie[6], Steven Bagley[7], Garry Ashton[7], Philip W. Pemberton[8], Akheel A. Syed[9,10], Basil J. Ammori[10,11], Richard Byers[3,5] and Emma J. Crosbie[2,4]

British Journal of Cancer (2016) 114, 281–289

Measuring the biological effect of presurgical metformin treatment in endometrial cancer

V N Sivalingam[1], S Kitson[1], R McVey[2], C Roberts[3], P Pemberton[4], K Gilmour[5], S Ali[6], A G Renehan[7], H C Kitchener[1] and E J Crosbie[*,1]

Translational Cancer Mechanisms and Therapy

Clinical Cancer Research

Check for updates

PRE-surgical Metformin In Uterine Malignancy (PREMIUM): a Multi-Center, Randomized Double-Blind, Placebo-Controlled Phase III Trial

Sarah J. Kitson[1], Zoe Maskell[1], Vanitha N. Sivalingam[1], Jennifer L. Allen[1], Saad Ali[2,3], Sean Burns[4], Kyle Gilmour[5], Rahamatulla Latheef[4], Richard J. Slade[6], Phil Pemberton[7], Joseph Shaw[8], W. David Ryder[9], Henry C. Kitchener[1,3], and Emma J. Crosbie[1,2]

CANCER PREVENTION RESEARCH | RESEARCH ARTICLE

PROgesterone Therapy for Endometrial Cancer Prevention in Obese Women (PROTEC) Trial: A Feasibility Study

Abigail E. Derbyshire[1], Jennifer L. Allen[2], Matthew Gittins[3], Bhavna Lakhiani[2], James Bolton[4], Joseph Shaw[4], Philip W. Pemberton[5], Michelle Needham[6], Michelle L. MacKintosh[1], Richard J. Edmondson[1,2], Henry C. Kitchener[2], and Emma J. Crosbie[1,2]

CANCER PREVENTION RESEARCH | RESEARCH ARTICLE

Weight Loss During Intrauterine Progestin Treatment for Obesity-associated Atypical Hyperplasia and Early-Stage Cancer of The Endometrium

Chloe E. Barr[1,2], Neil A.J. Ryan[1], A.E. Derbyshire[2], Y. Louise Wan[1], Michelle L. MacKintosh[2], Rhona J. McVey[3], James Bolton[3], Cheryl Fitzgerald[2], Dina Awad[4], Richard J. Slade[5], Akheel A. Syed[6,7], Basil J. Ammori[6,7], and Emma J. Crosbie[1,2]


Michelle MacKintosh


Vanitha Sivalingam


Abi Derbyshire


Sarah Kitson

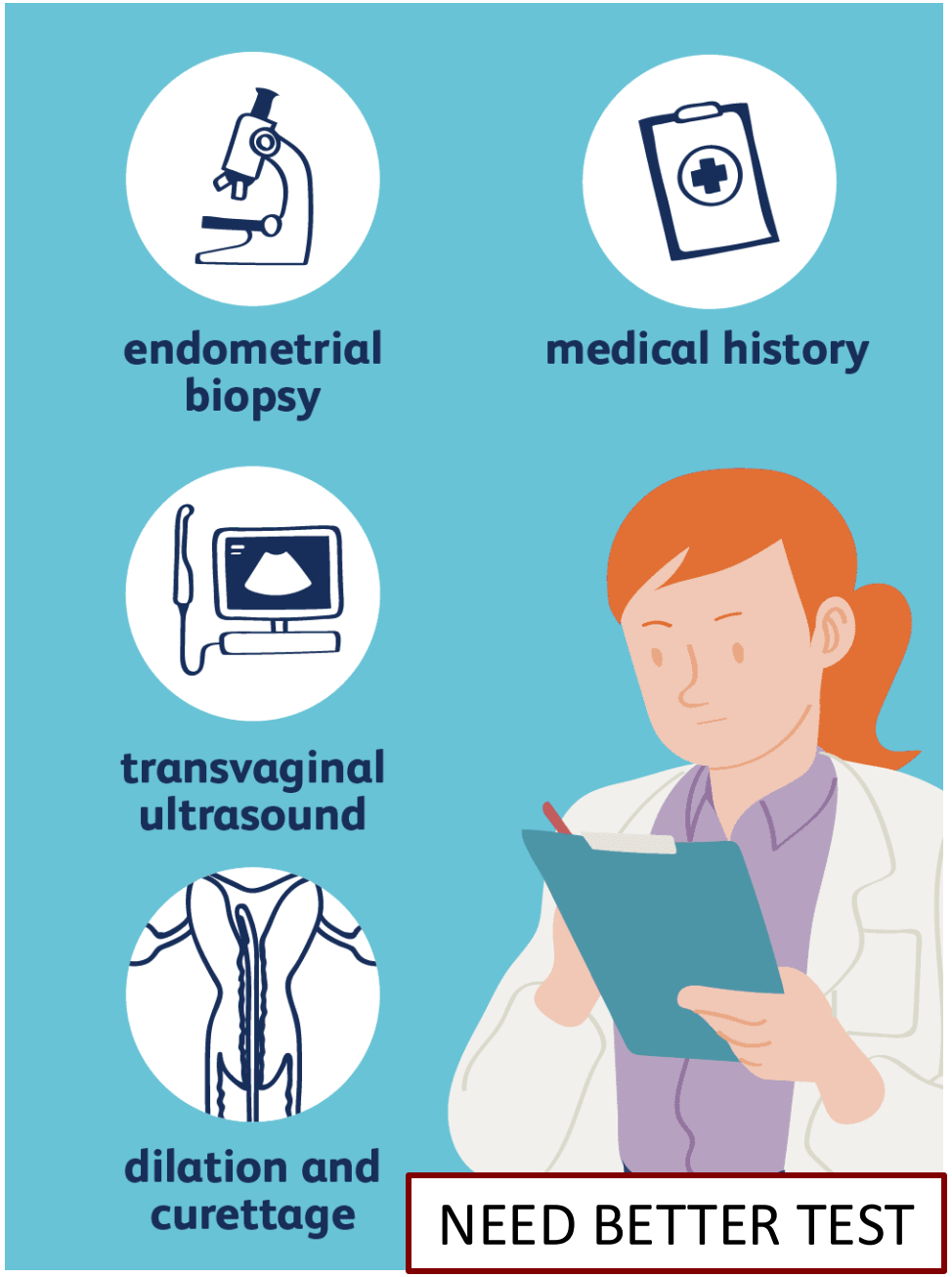

Chloe Barr


Helen Clarke


Holly Baker-Rand

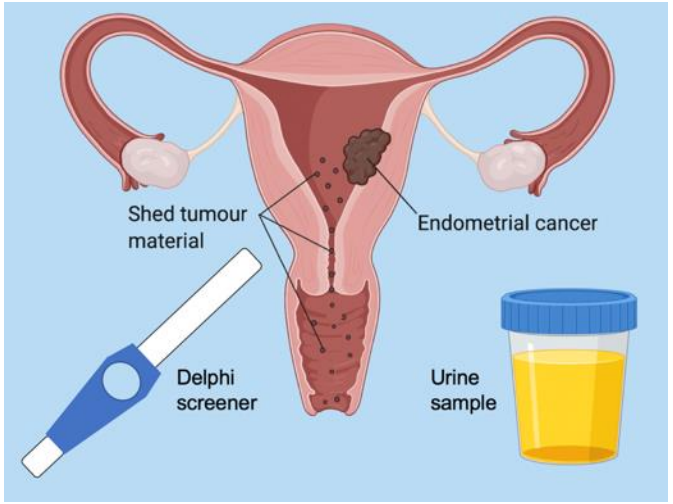
Diagnosing endometrial cancer

- Nearly 10,000 cases per year and rates are rising
- Red flag symptom is postmenopausal bleeding
- PMB is very common and only 5% have underlying endometrial cancer
- Current tests include transvaginal ultrasound, hysteroscopy & biopsy
- Tests are invasive, anxiety-provoking & painful
- Around 180,000 women are investigated for PMB every year
- Costs NHS around £750 per patient



detect

DEveloping Tests for Endometrial Cancer deTection



nature COMMUNICATIONS

ARTICLE

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]✉

Detection of endometrial cancer in cervico-vaginal fluid and blood plasma: leveraging proteomics and machine learning for biomarker discovery

Kelechi Njoku, Andrew Pierce, Davide Chiasserini, Bethany Geary, Amy E. Campbell, Janet Kefsall, Rachel Reed, Nophar Geifman, Anthony D. Whetton, and Emma J. Crosbie

You've basically improved… the lives of half the people on this planet!

Jane, 62

Leah, 54

We'd all prefer a urine test, wouldn't we ladies?

The hysteroscopy…. was torture…

Katherine, 58

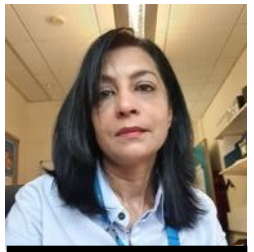

Suzanne Carter


Helena O'Flynn


Neil Ryan


Eleanor Jones

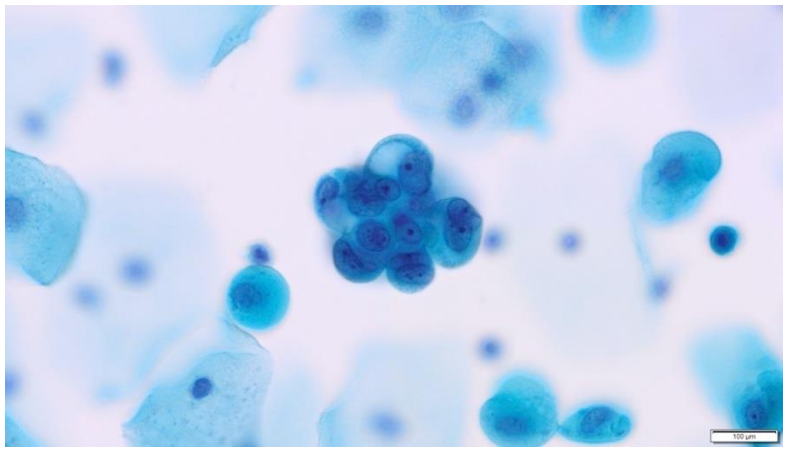

Chloe Barr


Nadira Narine


David Shelton


Durgesh Rana


Kelechi Njoku



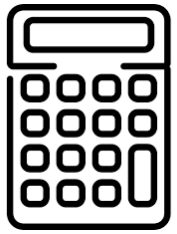

Jean Johnson

THE TIMES

Simple urine test may take pain out of womb cancer check

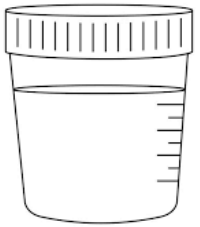
NIHR Research Professorship

PREDICT-EC: A risk prediction tool to streamline diagnostic pathways for suspected endometrial cancer



online risk calculator

WID-Easy vaginal swab test



spectroscopy urine test

Endometrial cancer in Lynch syndrome

- Lynch syndrome is most common inherited cancer predisposition syndrome
- Affects 1in 300 people, most of whom are unaware
- Familial defect in DNA mismatch repair (MMR)
- Increases risk of colorectal, endometrial & other cancers
- Endometrial cancer is often the first cancer in women with Lynch syndrome
- Identifying Lynch syndrome enables
  - bowel cancer screening
  - aspirin chemoprevention
  - cascade testing of at risk family members
- *interventions known to save lives*

BJOG An International Journal of Obstetrics and Gynaecology

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]

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]

MRC Medical Research Council

NIHR | National Institute for Health and Care Research

petals

Proportion of Endometrial Tumours Associated with Lynch Syndrome

Neil Ryan

Ray McMahon

Gareth Evans

Emma Crosbie

- First UK prospective study
- Unselected endometrial cancer population (n=500)
- Selecting women based on age and family history misses cases of LS, so better to test everyone
- Tumour testing by MMR IHC with reflex *MLH1* methylation testing is 100% sensitive, 97% specific
- Women want to be tested for LS - 99% uptake
- Testing everyone is cost effective for the NHS

PLOS MEDICINE

RESEARCH ARTICLE

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

Neil A. J. Ryan[1,2], Raymond McMahon[3], Simon Tobi[4], Tristan Snowsill[5], Shona Esquibel[3], Andrew J. Wallace[4], Sancha Bunstone[4], Naomi Bowers[4], Ioana E. Mosneag[1], Sarah J. Kitson[1], Helena O'Flynn[1], Neal C. Ramchander[1], Vanitha N. Sivalingam[1], Ian M. Frayling[6], James Bolton[3], Rhona J. McVey[3], D. Gareth Evans[2,4*], Emma J. Crosbie[1,7*]

Journal of Clinical Medicine

MDPI

Article

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

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,*]

frontiers in Oncology

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

RESEARCH ARTICLE

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

Tristan M. Snowsill[1*], Neil A. J. Ryan[2,3], Emma J. Crosbie[2,4], Ian M. Frayling[5], D. Gareth Evans[3,6], Chris J. Hyde[7]

Testing strategies for Lynch syndrome in people with endometrial cancer

NICE National Institute for Health and Care Excellence

Diagnostics guidance

Published: TBC

www.nice.org.uk/guidance/dg42

”All endometrial cancer patients should be offered testing for Lynch syndrome”

NICE, October 2020

MANCHESTER CANCER RESEARCH CENTRE

MANCHESTER 1824
The University of Manchester

PEACHES
WOMB CANCER TRUST

"I'm so thankful that testing after my womb cancer revealed I have Lynch syndrome. I can now take steps to reduce my chance of getting other cancers and, crucially, my family have all been tested too."

Helen

MANCHESTER 1824
The University of Manchester

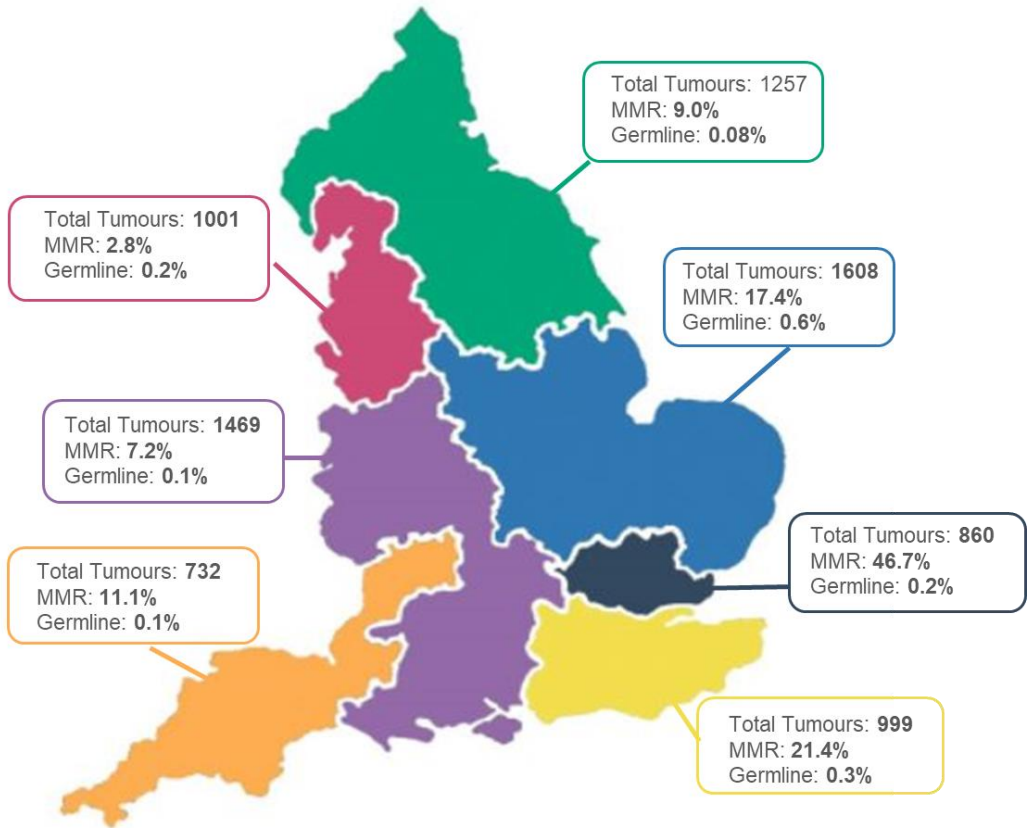
the eve appeal

Bowel Cancer UK
Beating bowel cancer together

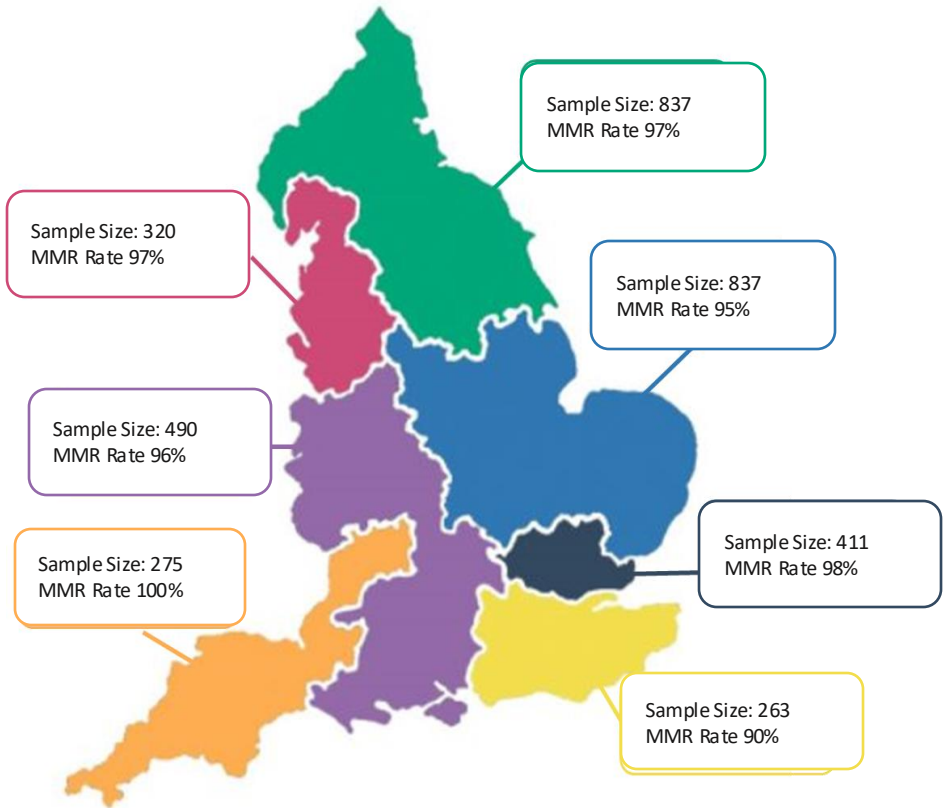
“This excellent decision will undoubtedly save lives from bowel and other cancers by identifying more people at risk through Lynch syndrome."

Genevieve Edwards
Chief Executive, Bowel Cancer UK

2019 MMR & germline testing rates for all endometrial tumours



2023 MMR testing rates for all endometrial tumours



Impact of NICE guideline

- New care model that improves patient experience & outcomes
- NHS Cancer Programme funding for NHS implementation
- Upskilling of workforce, capacity building, national resources
- Reflex MMR IHC & *MLH1* methylation testing
- Gynaecology-led germline testing (mainstreaming)
- Improved Lynch syndrome case finding
- Reduced time to diagnosis
- Reduced healthcare disparities related to age, status, postcode & socioeconomic status

Greater Manchester Cancer Awards 2022

MANCHESTER 1824
The University of Manchester

Making a Difference Award for Social Responsibility 2021

WINNER

AACR American Association for Cancer Research®

thebmjawards
Highly commended in Cancer Care Team of the Year 2021

AACR TEAM SCIENCE AWARD 2024

NCRI Cancer Research Excellence in Surgical Trials (CREST) Award 2019

Endometrial cancer is classified by molecular group

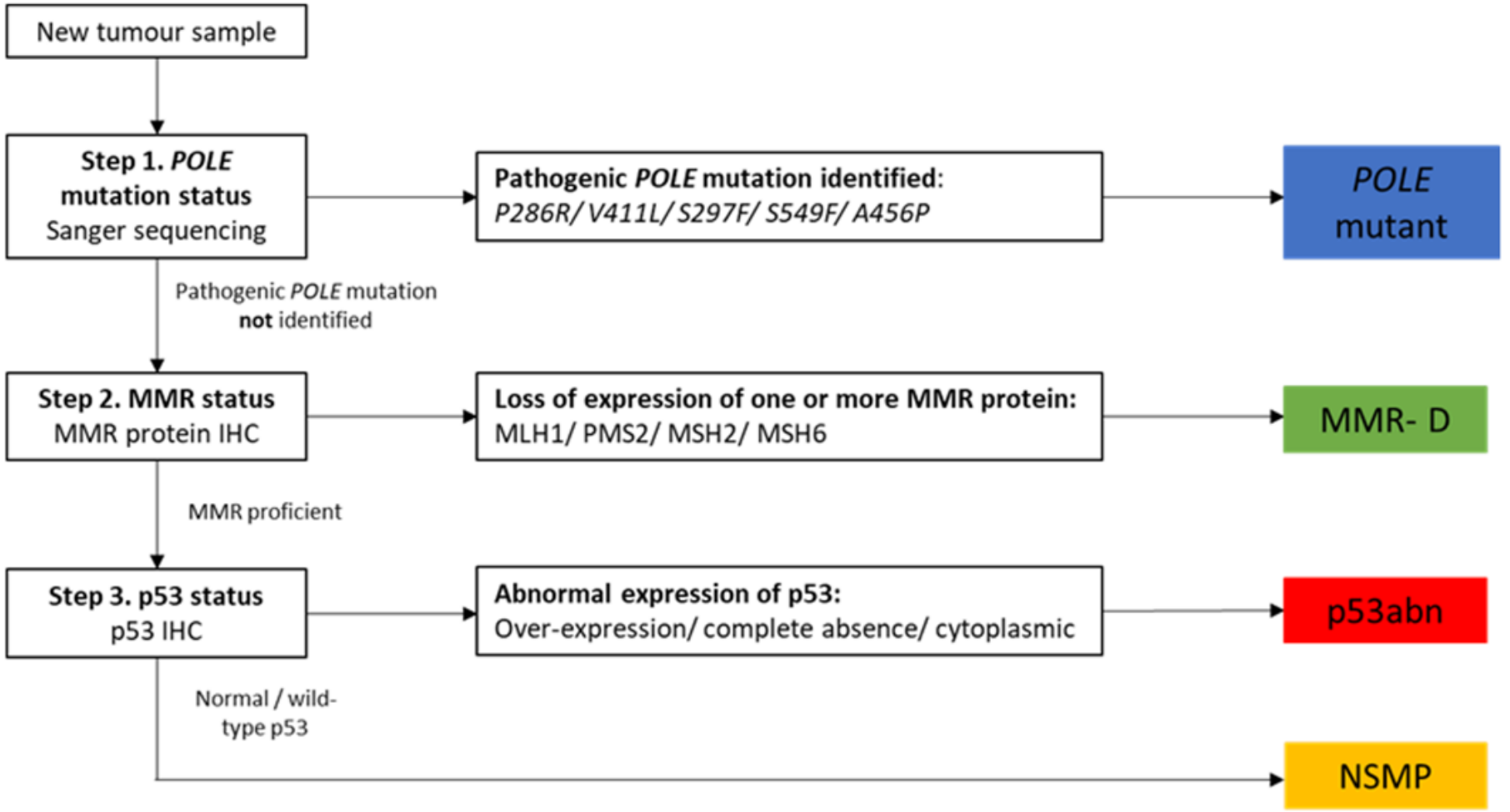


Figure by Dr Chloe Barr (2023)

Molecular group is strongly prognostic in endometrial cancer

- PORTEC 3 trial
- RCT adjuvant radiotherapy vs carboplatin/ paclitaxel chemoradiotherapy in endometrial cancer
- 410 tumours molecularly classified:
  - p53-abn (23%)
  - MMR-deficient (33%)
  - NSMP (32%)
  - *POLE*-mutant (12%)
- Molecular group predicted recurrence risk and overall survival

original reports

Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy

Alicia León-Castillo, MD[1]; Stephanie M. de Boer, MD[2]; Melanie E. Powell, MD[3]; Linda R. Mileshkin, MBBS[4]; Helen J. Mackay, MD[5]; Alexandra Leary, MD, PhD[6]; Hans W. Nijman, MD, PhD[6,7]; Naveena Singh, MD, MBBS[8]; Pamela M. Pollock, PhD[9]; Paul Bessette, MD[10]; Anthony Fyles, MD[11]; Christine Haie-Meder, MD[12]; Vincent T. H. B. M. Smit, MD, PhD[1]; Richard J. Edmondson, MD[13]; Hein Putter, MD[14]; Henry C. Kitchener, MD[13]; Emma J. Crosbie, MD, PhD[13]; Marco de Bruyn, PhD[7]; Remi A. Nout, MD[2]; Nanda Horeweg, MD, PhD[2]; Carien L. Creutzberg, MD, PhD[2]; and Tjalling Bosse, MD, PhD[1] on behalf of the TransPORTEC consortium

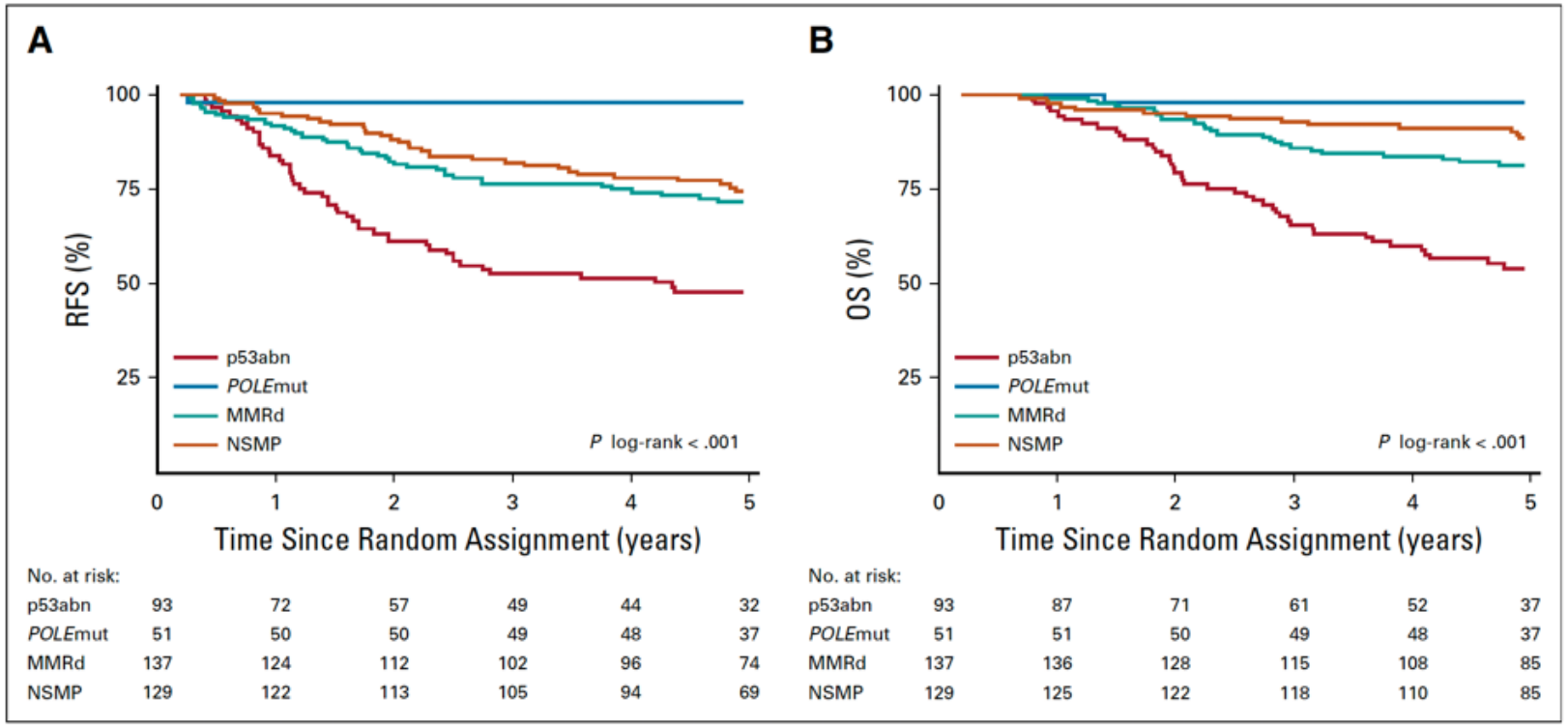


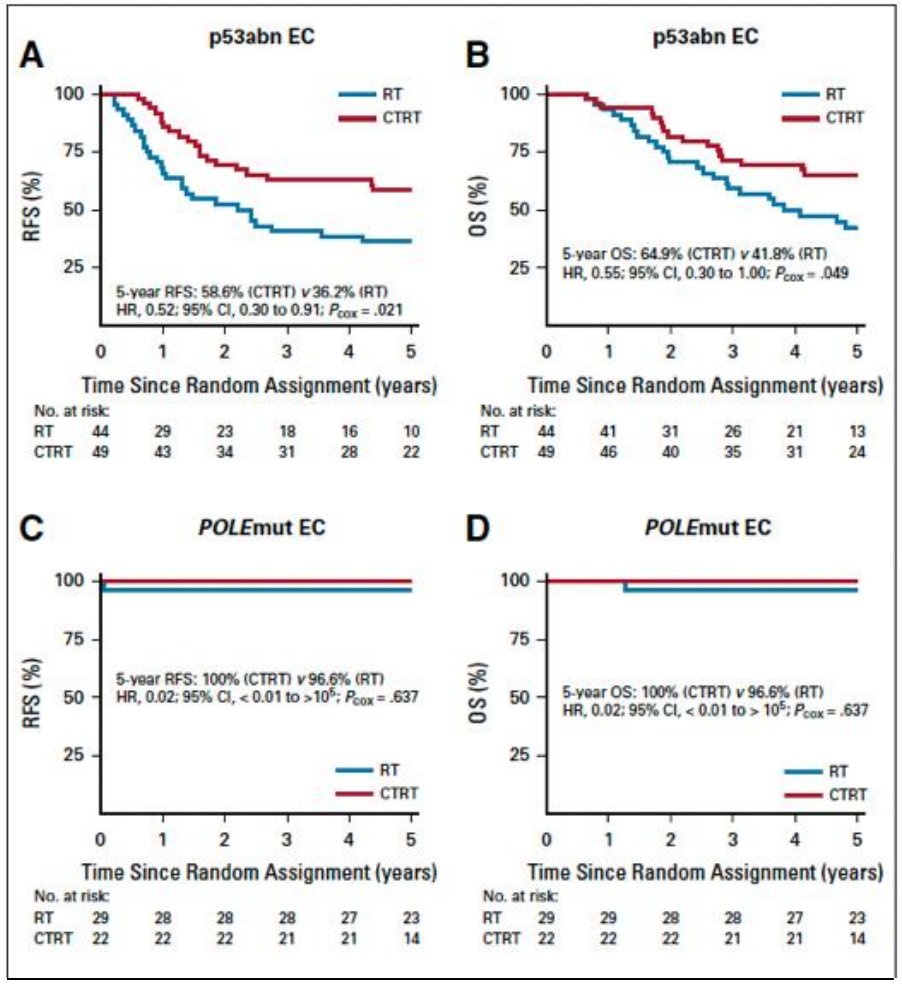
FIG 2. Kaplan-Meier survival curves for 5-year (A) recurrence-free survival (RFS) for patients with p53abn endometrial cancer (EC; 48.0%), *POLE*mut EC (98.0%), MMRd (71.7%), or NSMP EC (74.4%), and (B) overall survival (OS) in patients with p53abn EC (54.0%), *POLE*mut EC (98.0%), MMRd (81.3%), or NSMP EC (88.5%). MMRd, MMR-deficient; NSMP, no specific molecular profile; p53abn, p53-abnormal; POLEmut, POLE-ultramutated.

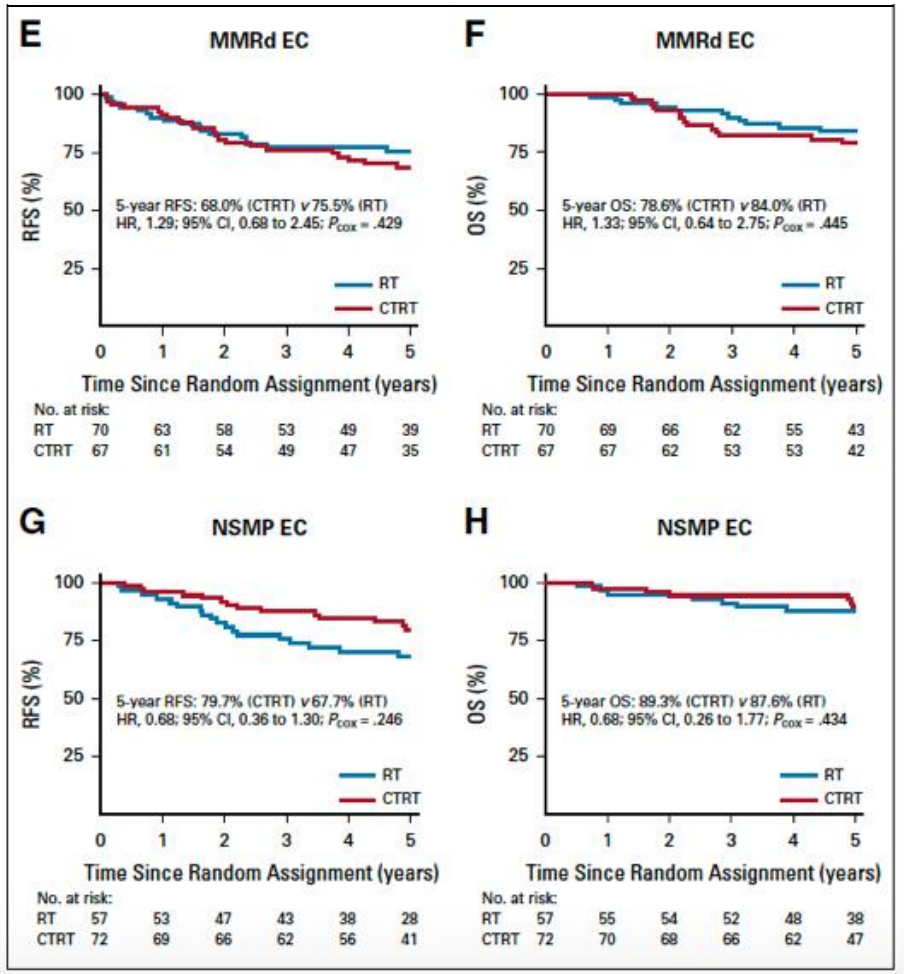
Molecular group predicts outcome from chemotherapy in endometrial cancer

original reports

Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy

Alicia León-Castillo, MD[1]; Stephanie M. de Boer, MD[2]; Melanie E. Powell, MD[3]; Linda R. Mileshkin, MBBS[4]; Helen J. Mackay, MD[5]; Alexandra Leary, MD, PhD[6]; Hans W. Nijman, MD, PhD[6,7]; Naveena Singh, MD, MBBS[8]; Pamela M. Pollock, PhD[9]; Paul Bessette, MD[10]; Anthony Fyles, MD[11]; Christine Haie-Meder, MD[12]; Vincent T. H. B. M. Smit, MD, PhD[1]; Richard J. Edmondson, MD[13]; Hein Putter, MD[14]; Henry C. Kitchener, MD[13]; Emma J. Crosbie, MD, PhD[13]; Marco de Bruyn, PhD[7]; Remi A. Nout, MD[2]; Nanda Horeweg, MD, PhD[2]; Carien L. Creutzberg, MD, PhD[2]; and Tjalling Bosse, MD, PhD[1] on behalf of the TransPORTEC consortium





Molecular classification stratifies patients for adjuvant therapy

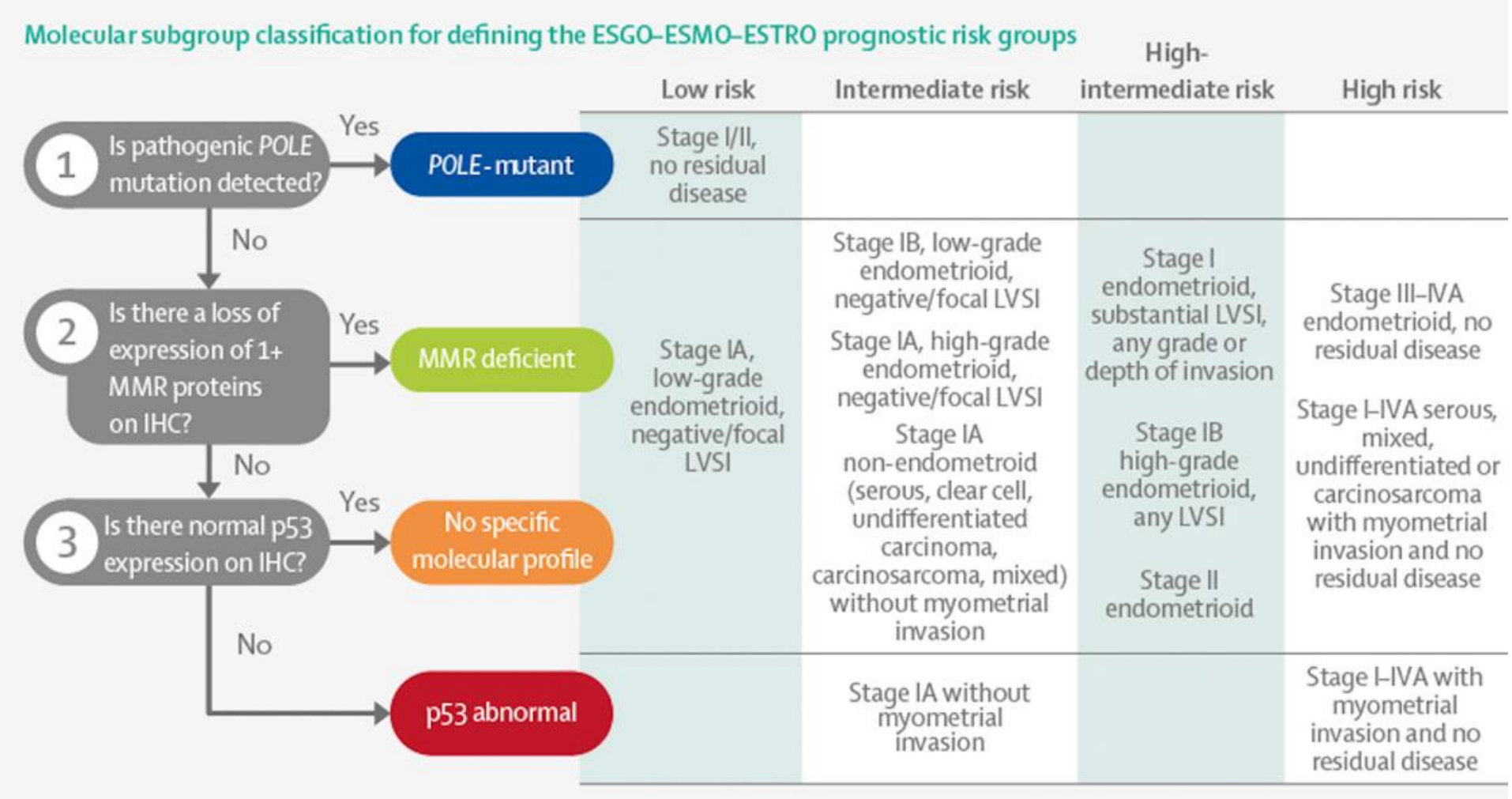
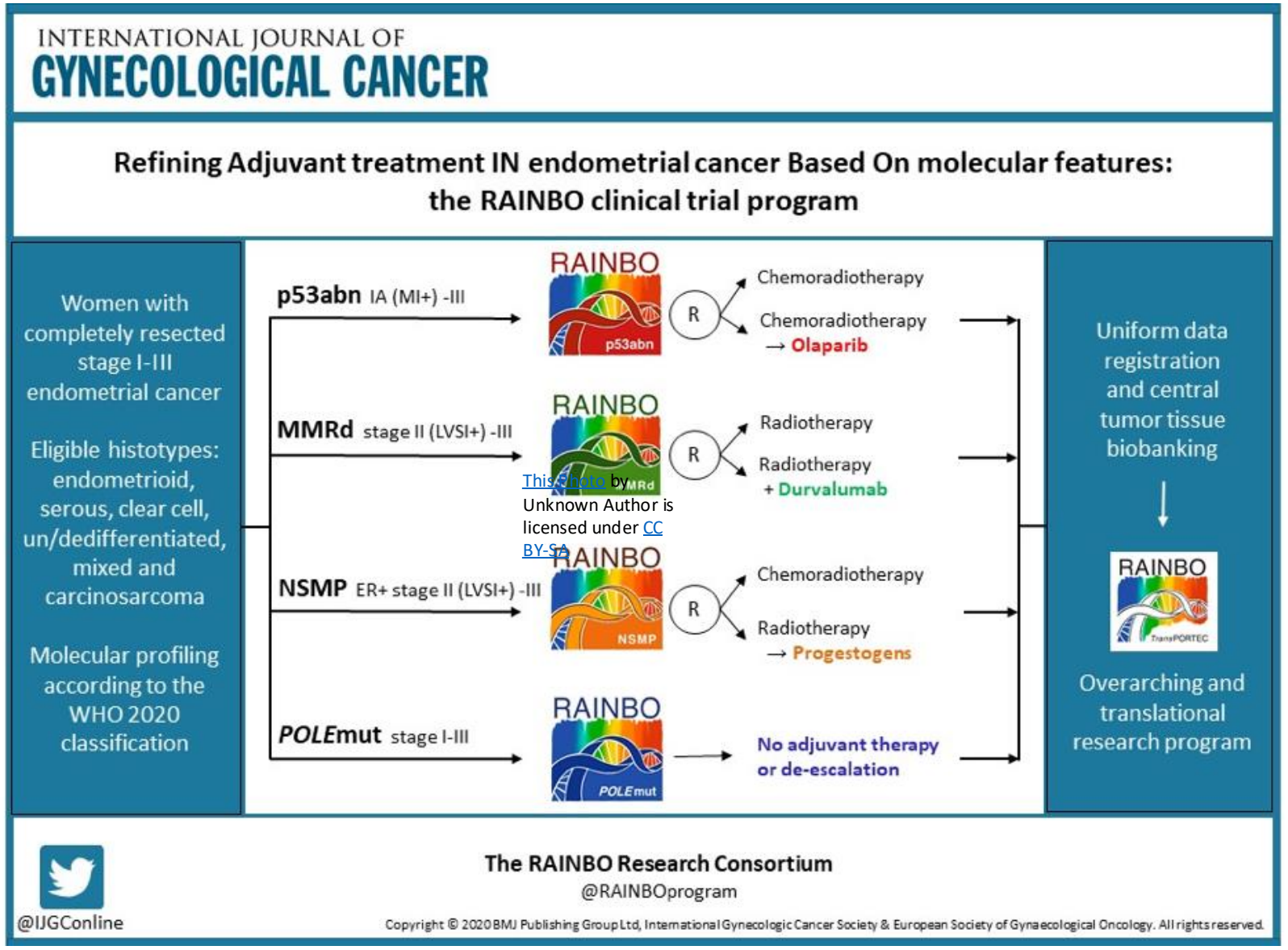


Figure from Crosbie et al, Lancet 2022

Novel adjuvant treatment strategies targeted to molecular group




Heather Agnew


Sarah Kitson

OPTIMUS

ENDO-Care

Could supported weight loss reduce endometrial cancer surgery complications?

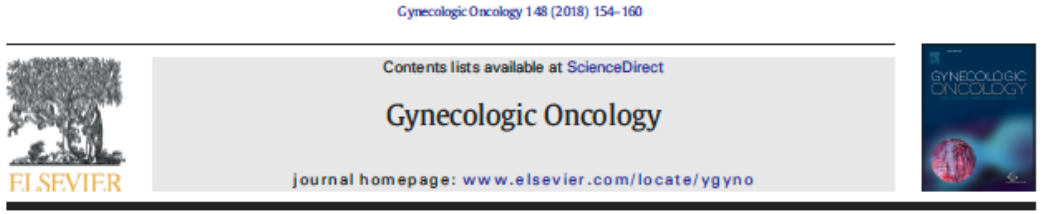
A multicentre pre-surgical window feasibility study

PI Dimitris Koutoukidis
Co-PI Emma Crosbie


Dimitrios Koutoukidis


Holly Baker-Rand

OPtimising cardiovascular healTh In endoMetrial cancer sUrvivorS



The unrecognized burden of cardiovascular risk factors in women newly diagnosed with endometrial cancer: A prospective case control study

Sarah J. Kitson [a], Jennifer Lindsay [a], Vanitha N. Sivalingam [a], Mark Lunt [b], Neil A.J. Ryan [a], Richard J. Edmondson [a,c], Martin K. Rutter [d,e], Emma J. Crosbie [a,c,*]

PEACHES

WOMB CANCER TRUST

Improving the lives of those affected by womb cancer

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