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Perspectives on Early Detection Strategies

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Centre for Reproductive Health
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Disclosures

CMO for Ellele Health

No Breast Cancer

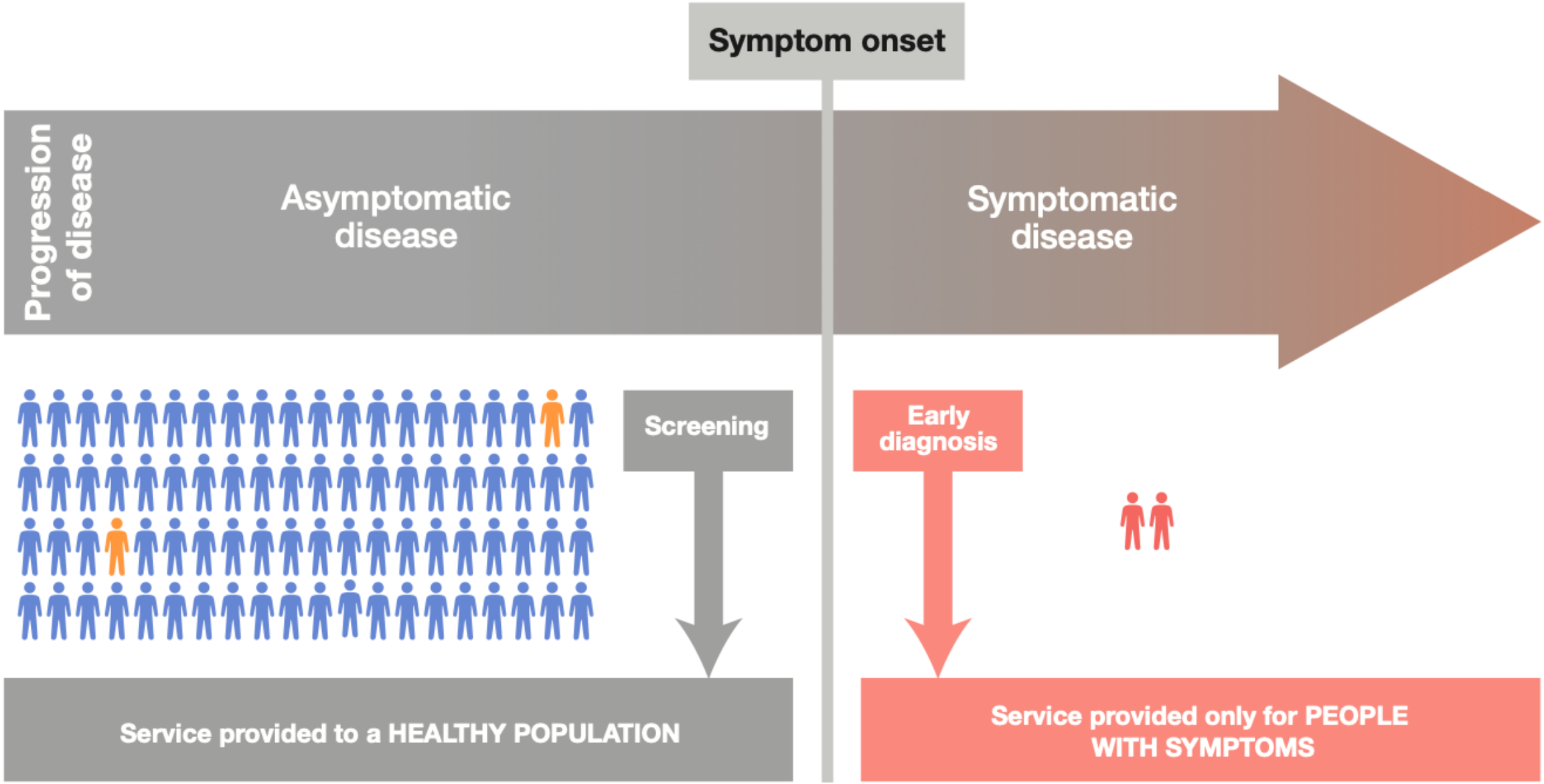
The early detection problem

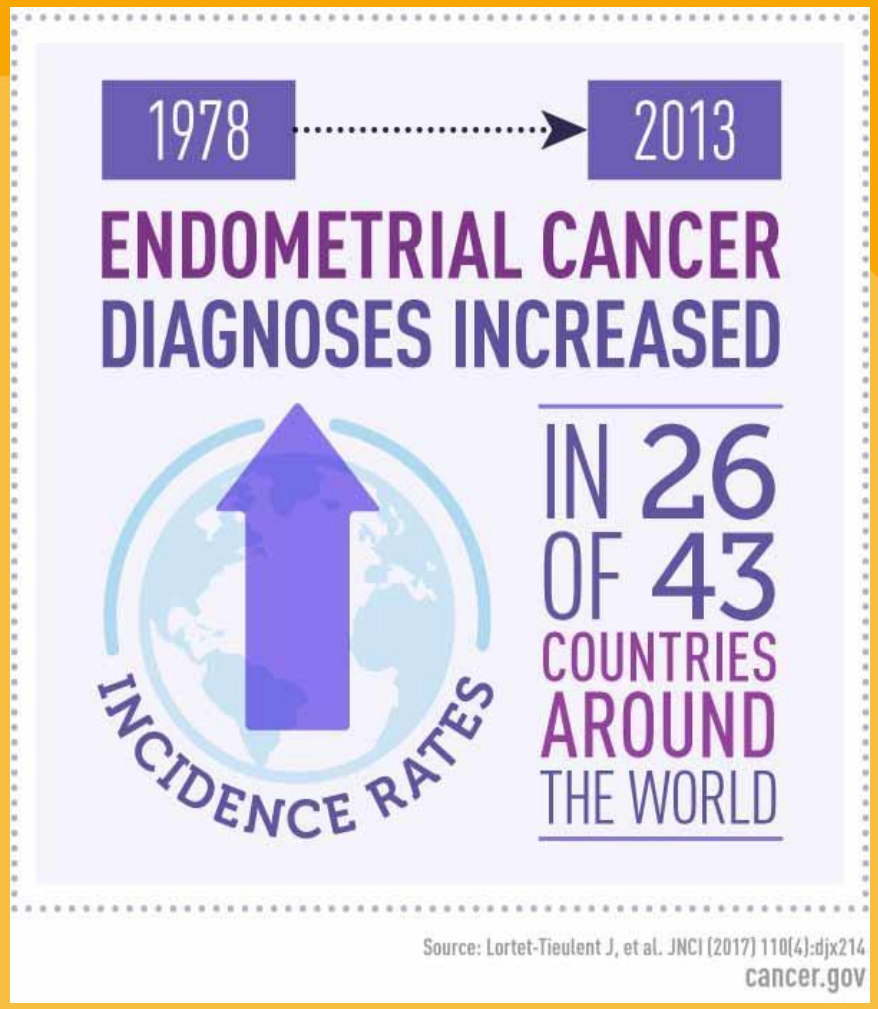
Non-specific symptoms; most ovarian cancers still present late

Historically limited screening performance (general population)

Opportunity: **targeted** approaches in defined high-risk groups (Lynch/BRCA)

Emerging **multi-omic** and **minimally invasive** tests


Symptom onset
Progression of disease
Asymptomatic disease
Symptomatic disease
Screening
Early diagnosis
Service provided to a HEALTHY POPULATION
Service provided only for PEOPLE WITH SYMPTOMS



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Cochrane Database of Systematic Reviews | Editorial

The emerging epidemic of endometrial cancer: time to take action

Emma Crosbie, Jo Morrison Authors' declarations of interest

Version published: 22 December 2014

https://doi.org/10.1002/14651858.ED000095

Endometrial cancer is the fifth most common cancer in women, affecting 318,000 women per year globally.[1] Incidence is higher than for ovarian cancer and is increased in developed nations, reflecting differences in lifestyle risk factors.[1] In the UK, endometrial cancer is the fourth most common cancer in women, but there is little public awareness about the disease,[2] and there is no endometrial cancer charity in the UK. There is also very little research effort on international level: a simple PubMed search using the term 'endometrial cancer' revealed 28,218 references, compared

High risk poulations

Ovarian Cancer – High-Risk Populations

- **Genetic / inherited syndromes**
- **BRCA1 and BRCA2 pathogenic variant carriers**
- **Lynch syndrome** (increased risk, though lower than for endometrial cancer)
- **Other rare syndromes**: Peutz–Jeghers (STK11), RAD51C/D, BRIP1, PALB2

Medical / reproductive / treatment-related groups

- Women with **endometriosis** (especially clear cell and endometrioid ovarian cancer risk)
- Women with **primary infertility** or **low lifetime parity**
- Long-term **hormone replacement therapy** (some subtypes)
- Strong **family history** of ovarian or breast cancer

Endometrial Cancer – High-Risk Populations

•**Lynch syndrome** (MMR gene pathogenic variants: MLH1, MSH2, MSH6, PMS2, EPCAM)
•**Cowden syndrome / PTEN Hamartoma Tumour Syndrome**
•**Polymerase proofreading–associated polyposis** (POLE, POLD1 mutations)

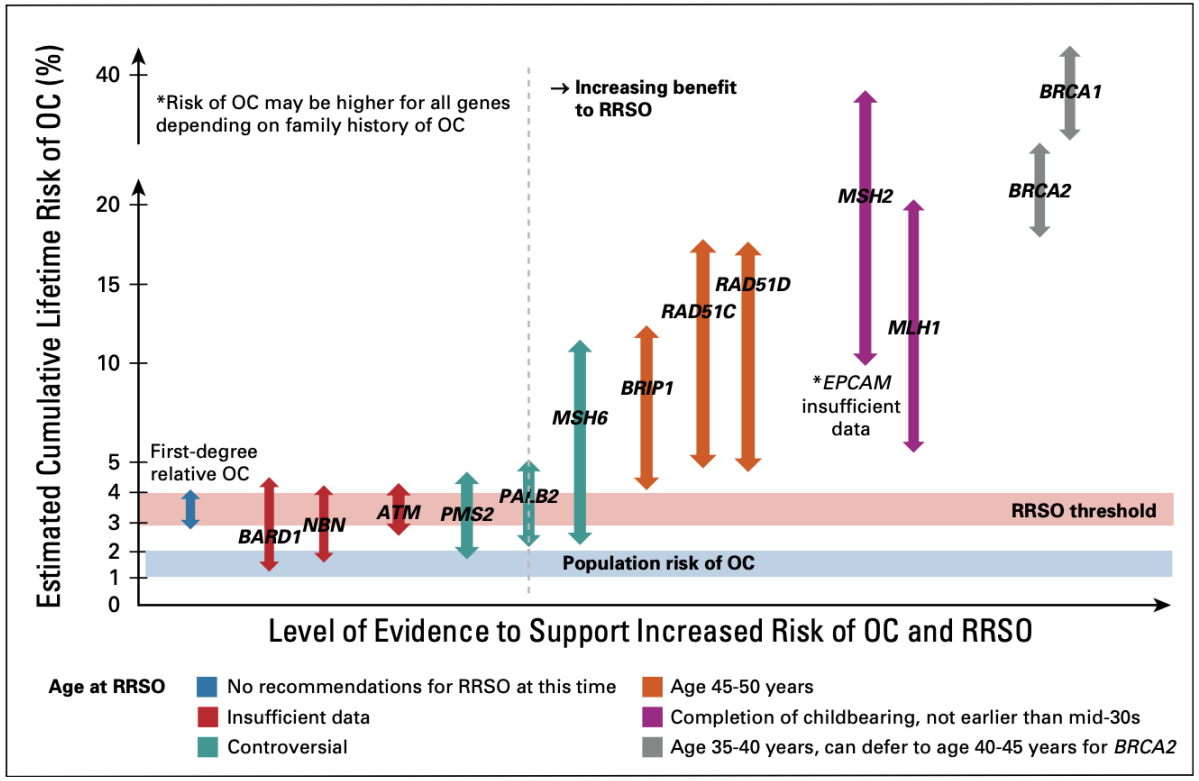
Medical / hormonal risk groups

•Women with **long-standing unopposed oestrogen exposure** (e.g. obesity, chronic anovulation/PCOS, oestrogen-only HRT)
•Women with **early menarche, late menopause, nulliparity**
•**Tamoxifen users** (breast cancer survivors)
•Patients with **diabetes mellitus** and **metabolic syndrome**
•Strong **family history** of endometrial or related cancers

23% OF OVARIAN CANCERS ARE RELATED TO HEREDITARY CONDITIONS

Toss A, Tomasello C, Razzaboni E, et al. Hereditary ovarian cancer: not OnlyBRCA1 and 2 genes. Biomed Res Int. 2015;2015:1–11. doi:10.1155/2015/341723

Risk reduction

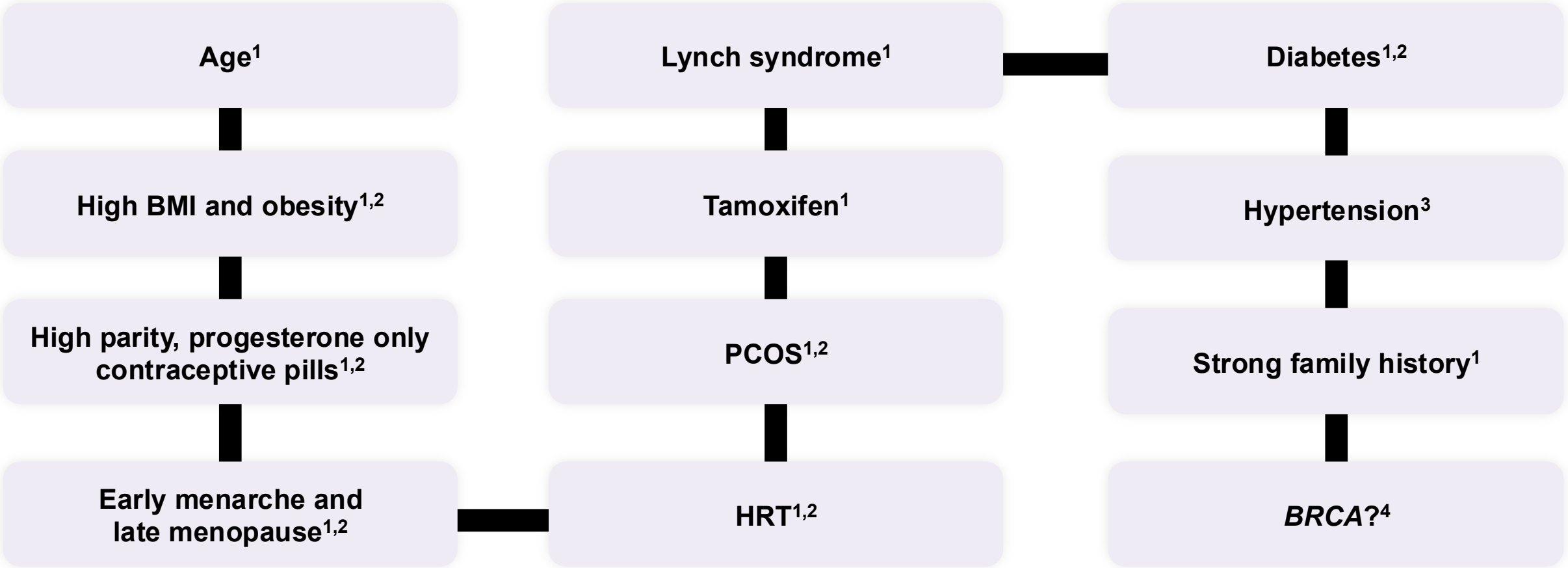


TUBectomy With Delayed Oophorectomy in High-Risk Women to Assess the Safety of Prevention (TUBA-WISP-II)

PROTECTOR: Preventing ovarian cancer through early excision of tubes and late ovarian removal (PROTECTOR) study

https://doi.org/10.1200/OP.21.00382

Risk factors in endometrial cancer



BMI, body mass index; BRCA, BReast CAncer gene; HRT, hormone replacement therapy; PCOS, polycystic ovary syndrome.
Image provided courtesy of the speaker.

1. https://www.cancer.org/cancer/types/endometrial-cancer/causes-risks-prevention/risk-factors.html (accessed Aug 2023). 2. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer/risk-factors#heading-Zero (accessed Aug 2023). 3. Zhao J, *et al. BMC Womens Health*. 2021; **21**:312. 4. de Jonge MM, *et al. J Natl Cancer Inst*. 2021; **113**:1203–1211

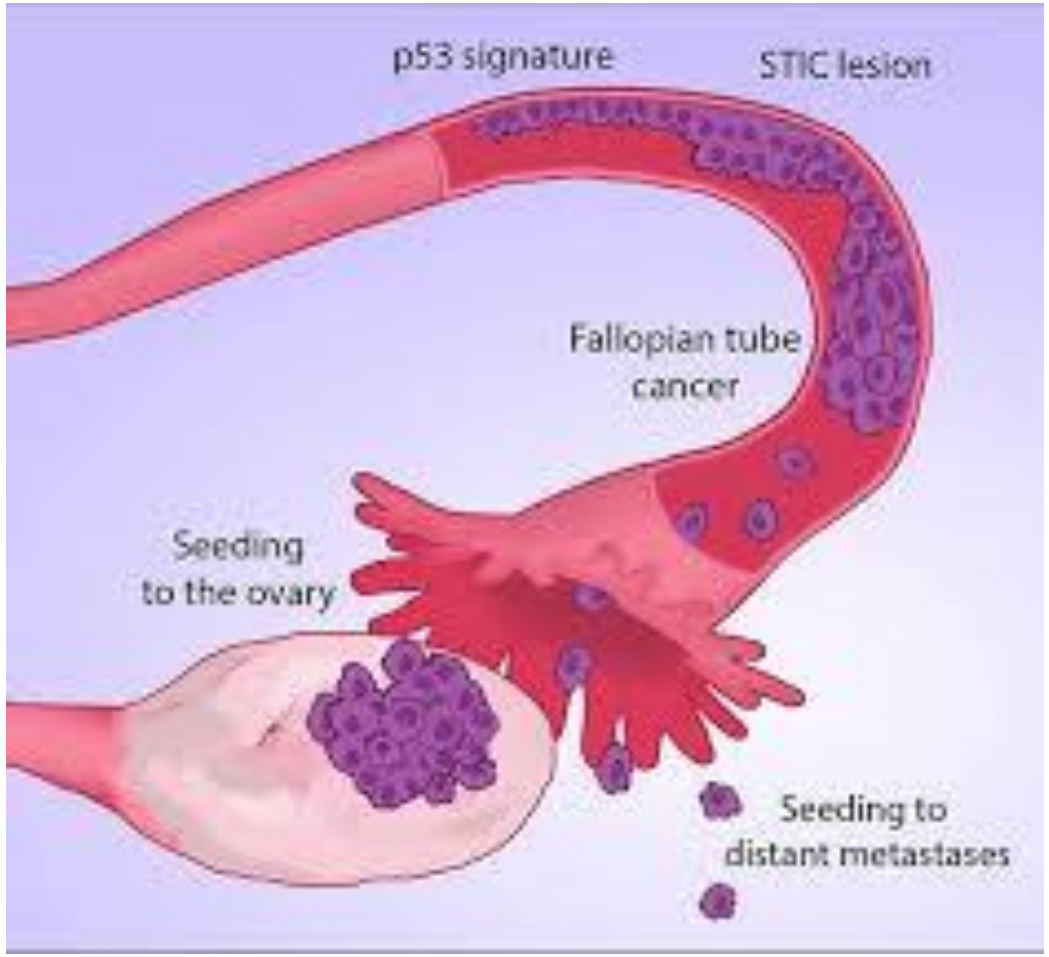
ORIGINAL ARTICLE

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.

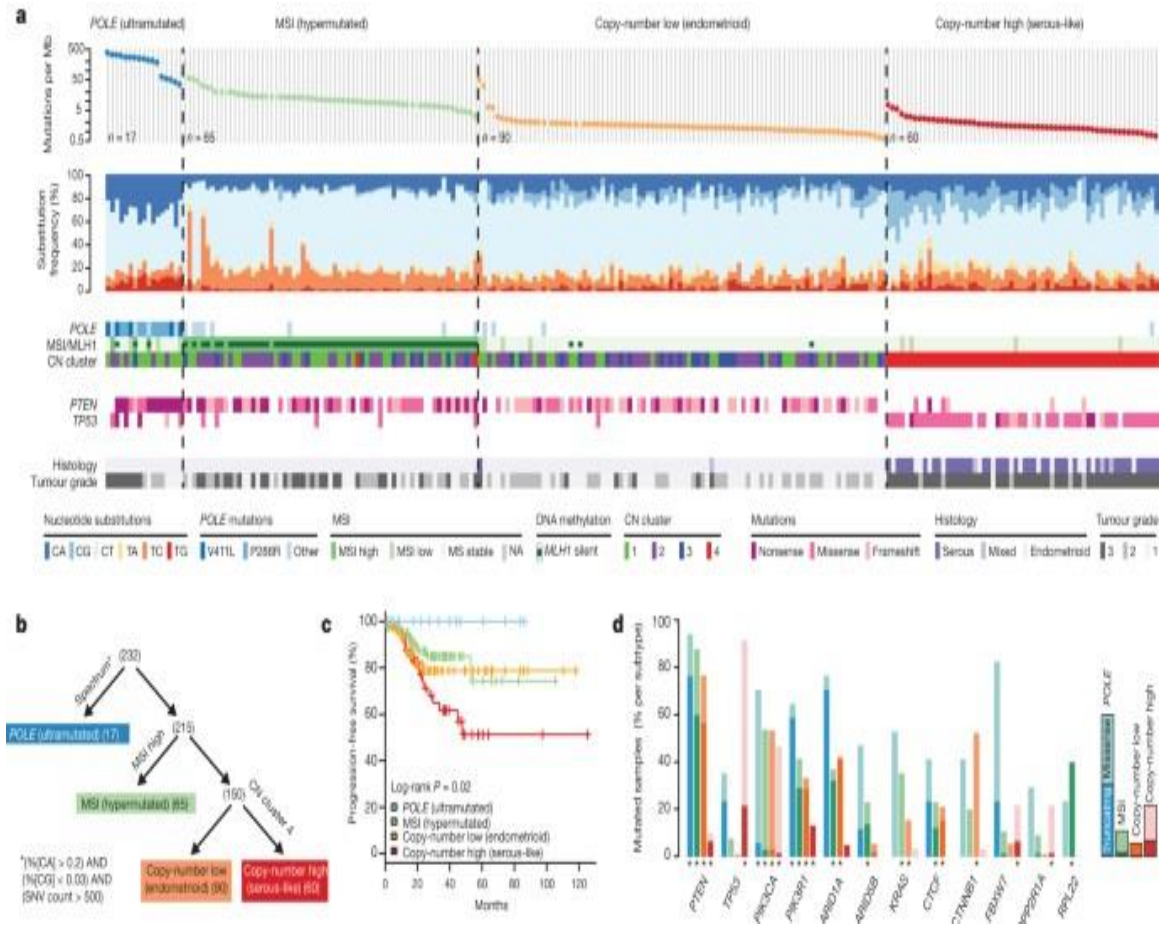
ABSTRACT

Biology that informs strategy



- Fallopian tube origin of many HGSOCs; STIC as a precursor
- Window for interception may be **tubal** rather than ovarian
- Circulating and local (vaginal/uterine) signals precede diagnosis
- Implication: sample the **right compartment** at the **right time**

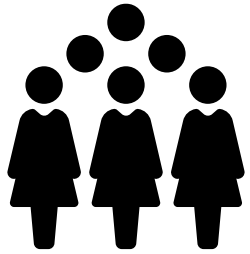
Biology that informs strategy



- Endometrial cancers have 4 distinctive molecular signatures
- Most are slow growing
- Pathognomonic symptom or post menopausal
- Implication: sample the **right compartment** at the **right time – molecular targets**

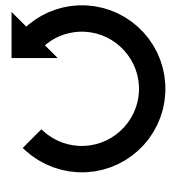
Survival rates remain low for patients with advanced* or recurrent EC

EC in the 2020s

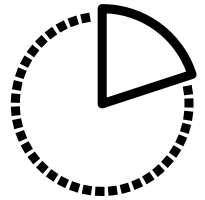


>400,000 new cases
globally in 2020[1]

63 years
is the median age at diagnosis[2]



~13%
of EC patients have recurrent disease[3]



≤20% survival at 5 years
for patients with advanced* or recurrent EC[3,4]

*Stage IV. EC, endometrial cancer.

1. World Health Organization International Agency for Research on Cancer (IARC). GLOBOCAN 2020: Corpus Uteri Factsheet. Accessed 17.8.2022 from: https://gco.iarc.fr/today/data/factsheets/cancers/24-Corpus-uteri-fact-sheet.pdf; 2. Colombo N et al. Ann Oncol. 2016;27;16-41; 3. Huijgens AN, Mertens HJ. Facts Views Vis ObGyn. 2013;5:179-186; 4. Cancer Research UK. Uterine cancer survival statistics. Accessed 18.8.2022 from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer/survival#heading-Three.

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Test	Characteristics	Use in Current Pathway	Advantages	Disadvantages
Transvaginal ultrasound (TVUSS)	Ultrasound probe inserted into vagina to measure endometrial thickness (ET).	Initial diagnostic test in symptomatic women; ET ≥4 mm → referral. Potential for screening.	Minimally invasive; safe; real-time; useful if lining uniform.	Non-definitive; thick ET ≠ cancer; may miss with distortion; operator-dependent.
Cervical cytology (smear test)	Sample from cervix; atypical endometrial cells may prompt investigation.	Screening for cervical cancer; incidental EC findings; potential EC screening.	Widely acceptable; simple; inexpensive.	Speculum discomfort; contact bleeding; may miss EC; dependent on cytologist.
Endometrial cytology	Direct sampling of endometrium (brush/lavage/suction).	Used in Japan for women ≥50 yrs or with bleeding; rarely used in West.	Direct sampling; can combine with hysteroscopy; histology possible.	Invasive; pain/discomfort; may miss focal lesions; infection/bleeding risk.
Imaging (CT/MRI)	Cross-sectional imaging of womb/pelvis.	Not diagnostic; used for staging/planning when spread suspected.	Painless, non-invasive; MRI avoids radiation.	CT radiation; MRI expensive; contraindicated with metal.
Hysteroscopy (camera test)	Endoscopic visualisation of uterine cavity.	Used in high-risk symptomatic women; biopsy of suspicious lesions.	Direct visualisation; targeted biopsy; therapeutic removal possible.	Invasive; pain; technical issues; may be abandoned if poor access.
Potential minimally invasive tests	Blood, urine, vaginal tampon, swabs for biomarkers (DNA, proteins, metabolites).	Investigational; possible screening/triage role.	Non/minimally invasive; self-collection possible (urine/tampon).	Blood tests may lack sensitivity in early disease; tampons less acceptable in older women.

Would you want yearly hysteroscopy?

Features Nadine Dorries Craig Brown Richard Eden **Good Health** TV Cainer & Cartoons Letters City & Finance Sport

HEALTH

Daily Mail, Tuesday, March 4, 2025 Page 31

Picture: GETTY

Agonising procedure: Patient and GP Maria Waters

He was horrified and asked what had happened. We made it back home before I vomited.'

Like many other women who've undergone a hysteroscopy, Alix assumed she was at fault for being unable to tolerate the pain, as she was led to believe most women get through the procedure without a fuss.

'I now tell anyone I meet who needs a hysteroscopy not to be gaslighted into believing that you are just making a fuss by requesting pain relief,' says Alix.

'I truly believe that if the procedure involved a tube and camera going up a man's penis, a general anaesthetic would be standard.'

Months on, she still feels traumatised by the experience.

'I would describe the procedure as barbaric and there was a complete failure to warn me about what was about to happen.'

The Campaign Against Painful Hysteroscopy's objective is not to scare women off from having the procedure – because it's important, says Jocelyn – 'We want all women to be offered a real choice'.

'These horror stories – and I don't think there's an alternative way of describing them – are true and they have to be believed, but it is important to recognise they are not the majority,' says Mary Connor, a gynaecologist from Sheffield.

'The practice wouldn't have continued for 30 years if it was unacceptable for most women.'

She has trained thousands of doctors to perform the procedure and points to an audit in 2019 of more than 5,000 British women that found pain 'for the majority was manageable'.

'But I suppose the thing that we forget is how vulnerable and disempowered people may feel when they are undergoing procedures. That's why it's so important with hysteroscopies to have a patient advocate, whose main job is to alert the hysteroscopist if the patient is in severe pain or distress and can't, or is unable to, speak up.'

Last September, reports of women's experiences prompted the RCOG to update its clinical guidance again. For instance, the advice includes using the narrowest possible hysteroscope and the lowest possible pressure of the fluid.

'It is disturbing to hear about some women's negative experiences,' says gynaecologist Geeta Kumar, vice president for clinical quality at the RCOG.

'If a procedure is traumatic, it can impact a woman's life for ever. But the procedure is vital for many patients in order to diagnose and treat them.

'That is why the RCOG encourages all those carrying out hysteroscopies to read and follow our guidance.

'If we stopped doing outpatient hysteroscopies, it would be a massive disadvantage, not just because general anaesthesia carries additional risks, but because it takes away the choice of setting for many women and can lead to potential delay due to the current length of waiting lists for women waiting for procedures to be done in theatre. Right now, the NHS just doesn't have the resources to increase that capacity.'

A consultant gynaecologist at the Betsi Cadwaladr University Health Board in north Wales, Dr Kumar has been carrying out hysteroscopies for 20 years.

'The difficult thing is you can't predict who will experience the most pain,' she says. 'There are certain features that can potentially predict a more painful procedure – if somebody gets very severe period pain or finds smears or speculum examinations painful, then those can be predictors.

'But it doesn't always mean that they will not tolerate outpatient hysteroscopy – and it's important to pre-warn all women and make sure that you discuss the options for pain relief beforehand.'

Maria Waters agrees that choice is key – and with the vantage point of a patient, she says: 'I always used to tell women that the procedure may be painful, but is usually well-tolerated. I now add that it can be extremely painful for some, especially those who have not delivered a child vaginally.

'I'm also extra careful to advise them to consider all their options and pain management ahead of their appointments as, during the consultation, there will be little time to discuss and weigh up options and alternatives.'

An NHS spokesperson said: 'While patients may feel some discomfort during intimate procedures like hysteroscopies, no one should have to experience pain, and all NHS trusts should be following the latest clinical guidance from the RCOG to deliver the best clinical and psychological care for women.

'Different pain relief options should be discussed with a clinician before any procedure as part of NHS England's standardised consent forms for hysteroscopy.'

'When you hear people screaming, you start to worry'

'UNTIL you've had a hysteroscopy, you do not know what pain is,' says Kathleen Ryan, 63, a retired nurse from Birmingham. 'It's like somebody's ripping your insides out. It's torture.

'And I've got a high pain threshold – I breezed my way through spiral fracture to my ankle, and it was a really bad break. I didn't need any painkillers in the ambulance or after the operation.'

When she later had a hysterectomy, even then she didn't need strong painkillers – 'It is standard to take strong analgesia, but I just had a couple of paracetamol pills for a few days.'

Kathleen says she will never forget her first hysteroscopy in 2019 for post-menopausal bleeding, at Birmingham Women's Hospital, where she had worked as a pain nurse until her recent retirement.

'It's amazing to think now that I went along to the clinic never imagining what they would do,' she says. 'It's only when you're sat waiting when you can hear people screaming, that you start to worry.

'I assumed there would be some sort of pain relief but there was absolutely none. I hadn't been told to take any before either.

'There were two nurses either side of me who tried to distract me. When I gasped and said it was very painful, they said it'll only last a minute or so. They made me feel like I was the only one who had found it painful; I thought I must be a real wuss.

'When the gynaecologist removed the instruments, I felt like I was going to pass out. Then I sat up and saw the bucket under my legs full of blood. I staggered to the day room, was given a cup of tea and a ginger biscuit, and then told I was ready to go. I was in such a state of shock, I was in the car park for an hour before I could even drive.'

Kathleen's biopsies showed she had a pre-cancerous condition called complex atypical hyperplasia, and so would need regular hysteroscopies to monitor it. At her next

Ordeal: Kathleen Ryan

appointment three months later, she says she pleaded for pain relief. 'I was in agony and said: "You've got to stop!"'

'I was then given gas and air but it really didn't help. As I was leaving, one of the nurses took my hand, and said: "Next time have a couple of gins before you come. It'll help you relax." I was stunned.'

After that, the thought of having another procedure made Kathleen 'a nervous wreck'. She was meant to have the procedures every three months but they were so horrendous she negotiated for them to be twice yearly.

'During one it was so painful, I flinched and said: "You have got to stop." And the nurses got their elbows on my knee and pinned me down. It sounds medieval and it absolutely is.'

On another occasion she took codeine and diazepam beforehand, as prescribed by her GP, but this made little difference. So the next time she requested a general anaesthetic but was told neither this nor sedation was possible as an outpatient.

'With my next appointment looming in November 2021, I decided I wasn't going back. I told a friend I didn't care if I died – it seemed a better option.' She saw a consultant privately and the following year had a full hysterectomy on the NHS.

'I thank God every day that I don't need more hysteroscopies. But I can't understand how in this day and age, something so brutalising is allowed. I would go as far as to say it's a violent assault.'

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Test	Characteristics	Use in Current Pathway	Advantages	Disadvantages
CA125	Glycoprotein elevated in many ovarian cancers.	Diagnosis and monitoring; included in RMI and ROCA.	Simple blood test; widely available; good for monitoring.	Poor specificity; low sensitivity for early disease.
HE4	Protein overexpressed in epithelial ovarian cancer.	Used with CA125 in ROMA algorithm.	Improved specificity; useful adjunct.	Misses early disease; less available.
Ultrasound (TVUS/abdominal)	Imaging of ovaries/adnexa.	First-line for symptomatic women or adnexal masses.	Non-invasive; readily available; real-time.	Operator-dependent; limited sensitivity for stage I.
CT/MRI/PET imaging	Cross-sectional imaging.	Used for staging/planning; not for screening.	Good anatomical detail (MRI); whole-body staging (CT/PET).	Expensive; CT/PET radiation; not sensitive for microscopic disease.
Multimodal algorithms (ROCA)	Serial CA125 with statistical modelling.	Trialled in UKCTOCS for population screening.	More sensitive than single CA125; dynamic assessment.	Stage shift but no mortality reduction; not adopted.
Genetic testing (BRCA, RAD51C/D, BRIP1, Lynch)	Identifies inherited risk genes.	Routine in epithelial OC; informs family prevention; PARP eligibility.	Precision prevention; therapeutic implications.	Not a detection tool; identifies risk not disease.
Emerging minimally invasive tests	cfDNA methylation, exosomal RNA/proteins, proteomics, vaginal sampling.	Research use; potential triage or screening.	Minimally invasive; may capture earlier disease.	Not validated; limited sensitivity in early disease.

Population Level

Ovarian cancer population screening and mortality after long-term follow-up in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial

Usha Menon, Aleksandra Gentry-Maharaj, Matthew Burnell, Naveena Singh, Andy Ryan, Chloe Karpinskyj, Giulia Carlino, Julie Taylor, Susan K Massingham, Maria Raikou, Jatinderpal K Kalsi, Robert Woolas, Ranjit Manchanda, Rupali Arora, Laura Casey, Anne Dawnay, Stephen Dobbs, Simon Leeson, Tim Mould, Mourad W Seif, Aarti Sharma, Karin Williamson, Yiling Liu, Lesley Fallowfield, Alistair J McGuire, Stuart Campbell, Steven J Skates, Ian J Jacobs, Mahesh Parmar

PLCO (U.S.) Trial
Design: Randomised controlled trial, ~78,000 women (55–74 years).
Screening arm: Annual **CA125** (fixed cutoff of 35 U/mL) + **transvaginal ultrasound**.
Control arm: Usual care (no organised screening).
Follow-up: Median ~12 years.
Findings:
- No reduction in ovarian cancer mortality.
- High false-positive rate → unnecessary surgery and complications.

Conclusion: CA125 threshold + TVUS is **not effective** for population screening.

UKCTOCS (UK)
Design: >200,000 women, postmenopausal.
Screening arm (MMS): CA125 interpreted by **ROCA algorithm** (longitudinal changes), with second-line TVUS.
Control arms: TVUS alone, or no screening.
Findings: Stage shift (more early-stage disease detected) but **no mortality reduction**.
👉 **Key distinction:**
PLCO used **fixed CA125 cut-off** → poor sensitivity.
UKCTOCS used **ROCA (risk algorithm)** → better stage shift, but still no mortality benefit.

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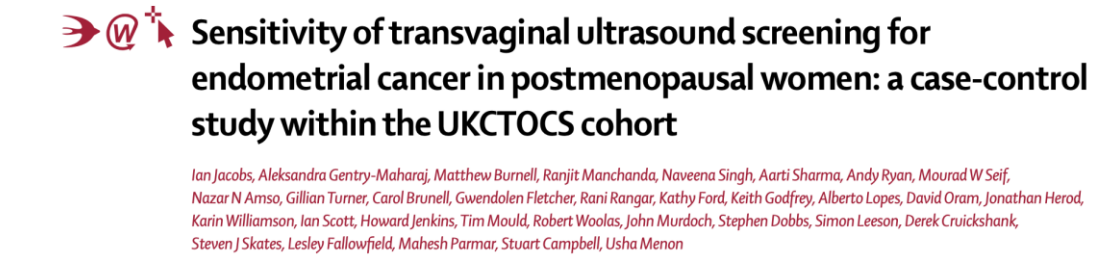
Population Level

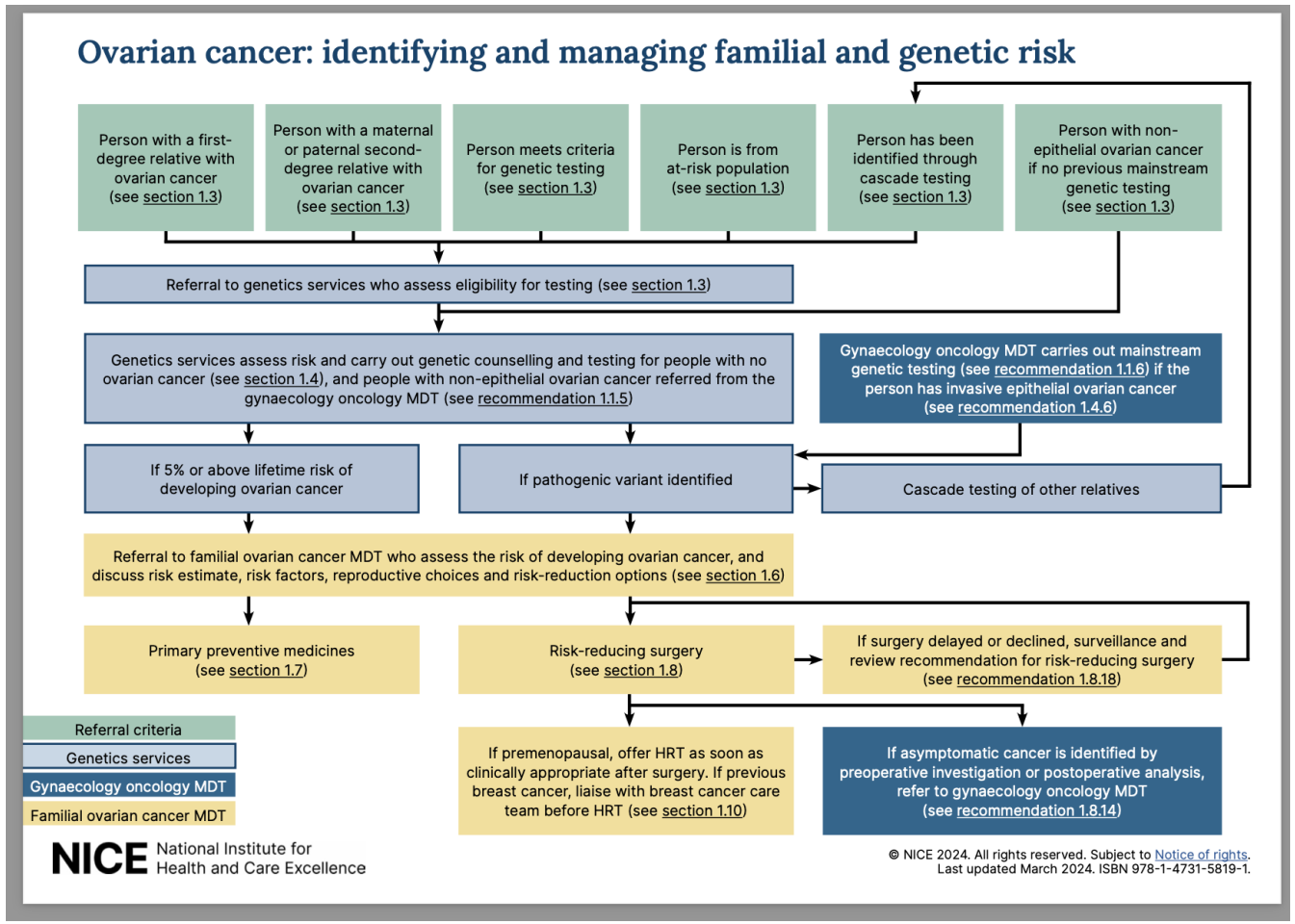


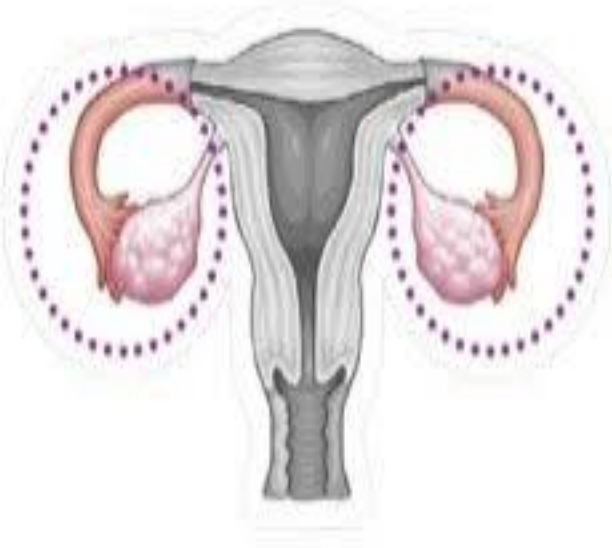
Sensitivity of transvaginal ultrasound screening for endometrial cancer in postmenopausal women: a case-control study within the UKCTOCS cohort

Ian Jacobs, Aleksandra Gentry-Maharaj, Matthew Burnell, Ranjit Manchanda, Naveena Singh, Aarti Sharma, Andy Ryan, Mourad W Seif, Nazar N Amso, Gillian Turner, Carol Brunell, Gwendolen Fletcher, Rani Rangar, Kathy Ford, Keith Godfrey, Alberto Lopes, David Oram, Jonathan Herod, Karin Williamson, Ian Scott, Howard Jenkins, Tim Mould, Robert Woolas, John Murdoch, Stephen Dobbs, Simon Leeson, Derek Cruickshank, Steven J Skates, Lesley Fallowfield, Mahesh Parmar, Stuart Campbell, Usha Menon

- **Sensitivity of TVUS for Endometrial Cancer (UKCTOCS)**
- **Design:** Nested case–control study within UKCTOCS cohort (>200,000 postmenopausal women).
- **Participants:** 136 women with endometrial cancer vs 136 matched controls.
- **Test:** Transvaginal ultrasound screening, endometrial thickness (ET) cut-off.
- **Key Findings:**
- At ET ≥5 mm, sensitivity **80.5%** and specificity **85.7%**.
- At ET ≥3 mm, sensitivity rose to **93.5%**, but specificity fell to **77.1%**.
- **Conclusion:** TVUS can detect most endometrial cancers in postmenopausal women, but the trade-off between sensitivity and specificity limits its value as a screening tool.
- **Implication:** Useful in symptomatic women as triage, but not suitable for population-level screening without additional biomarkers.

High Risk Level





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High Risk Level

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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

5 Department of Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

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Published: 2 September 2021

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 uncertain if this improves survival, and the optimal testing strategy is not established
- Inform women with Lynch syndrome about their risk of developing cancer and initiate a discussion about their preference for risk reducing surgery which is definitive, or options for annual review and gynaecological surveillance, explaining their risks and benefits

Guidelines published in 2020 by the National Institute for Health and Care Excellence (NICE) recommend testing for Lynch syndrome in women with 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]

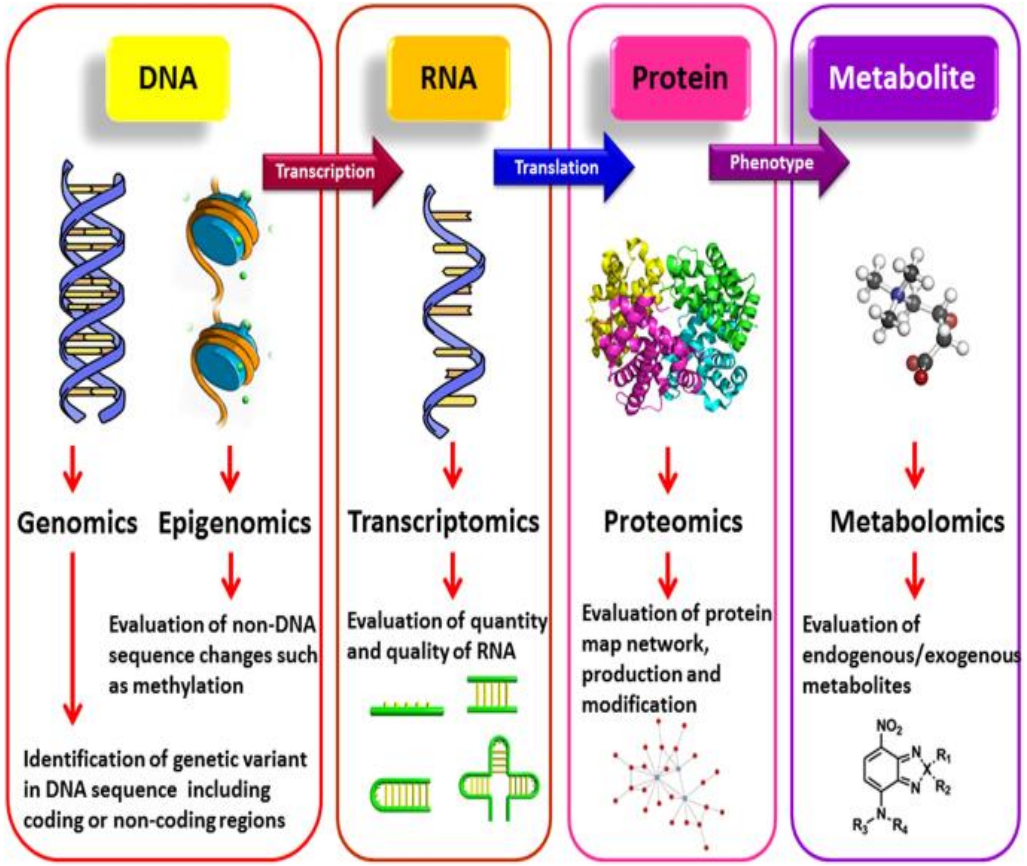
Data sources and selection strategy

We searched CENTRAL, Medline, Embase, and the Cochrane Database of Systematic Reviews for articles in English from the database inception to February 2021. Our search yielded 974 records. After removal of duplicates, 719 were available to screen. Screening was done by two independent reviewers using the Rayyan platform (https://www.rayyan.ai). Of these, 49 underwent full title review. Full manuscripts (not conference abstracts) are summarised in the supplementary table. All the studies identified were observational in nature. Our systematic review also identified four guidelines that addressed gynaecological surveillance in Lynch syndrome carriers; these are detailed in table 1.

Targets for diagnosis

What are “omics”?

- **From Structure to Biology**
  - Shifting from anatomical to biological decisions
  - Genomic risk now informs staging and treatment (e.g., endometrial cancer)
- **Actionable Biology**
  - Omics reveals new treatment targets and resistance mechanisms
  - Enables smart escalation **(when aggressive disease is detected)**
  - Supports safe de-escalation **(e.g. POLEmut EC, responders to IO)**
- **The Rise of the Liquid Biopsy**
  - cfDNA, proteomics, microbiome = accessible, repeatable, real-time sampling
  - Increases power to detect cancer earlier and monitor response non-invasively
- **Redefining the Clinician**
  - From knife to navigator: surgeons, gynae and generalists guiding molecular care
  - Omics as a universal tool — not just for trials, but for everyday decisions



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Biofluids for endometrial cancer detection

Biofluid	Source of biomarkers	Pros	Cons
Venous blood 	Haematogenous spread	- Good patient acceptability	- Tumour biomarkers at low concentration in early-stage disease
Uterine lavage 	Lavage fluid in direct contact with tumour	- Can be collected routinely during hysteroscopy	- Invasive sampling - Few advantages over current diagnostics
Cervical smear 	Natural tumour shed through cervix into lower genital tract	- Minimally-invasive sampling - Suitable for community care - Could be used to triage women for further diagnostic tests	- Requires healthcare professional to collect sample
Vaginal fluid 			- Vaginal tampons may be unacceptable method of biomarker collection for some women
Urine 	Contamination of urinary flow by natural tumour shed via lower genital tract	- Excellent patient acceptability - Suitable for community or home-based sampling - Could be useful as screening tool in high risk women	- Success depends on natural tumour shed, which may be unreliable - Proof of principle data only - More research is needed

cancers

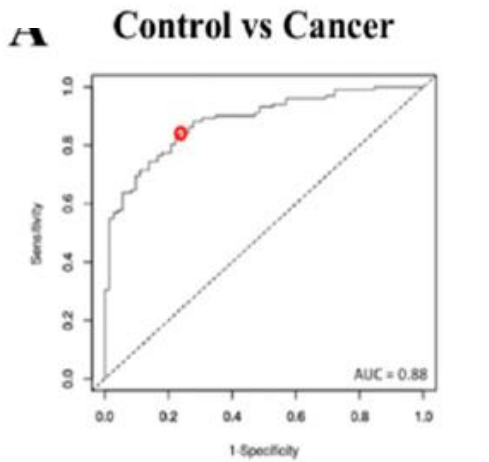
MDPI

Article

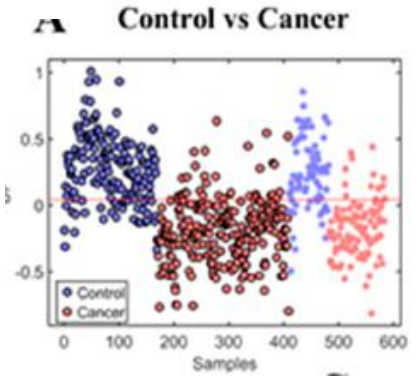
Detecting Endometrial Cancer by Blood Spectroscopy: A Diagnostic Cross-Sectional Study

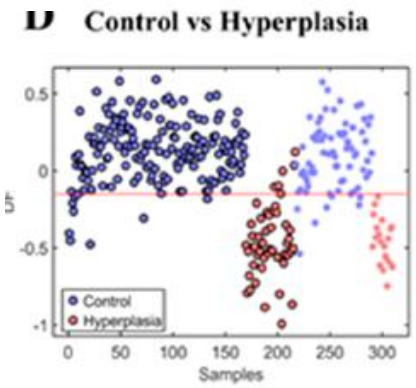
Maria Paraskevaidi [1,2,*], Camilo L. M. Morais [1], Katherine M. Ashton [3], Helen F. Stringfellow [3], Rhona J. McVey [4], Neil A. J. Ryan [5], Helena O'Flynn [5], Vanitha N. Sivalingam [5], Sarah J. Kitson [5], Michelle L. MacKintosh [6], Abigail E. Derbyshire [6], Cecilia Pow [5], Olivia Raglan [2],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

- Plasma samples from patients with
  - Endometrial cancer n=342
  - Atypical hyperplasia n=68
  - Healthy controls n=242
- ATR-FTIR spectroscopy & machine learning algorithms



Accuracy	Sensitivity	Specificity
83%	87%	78%





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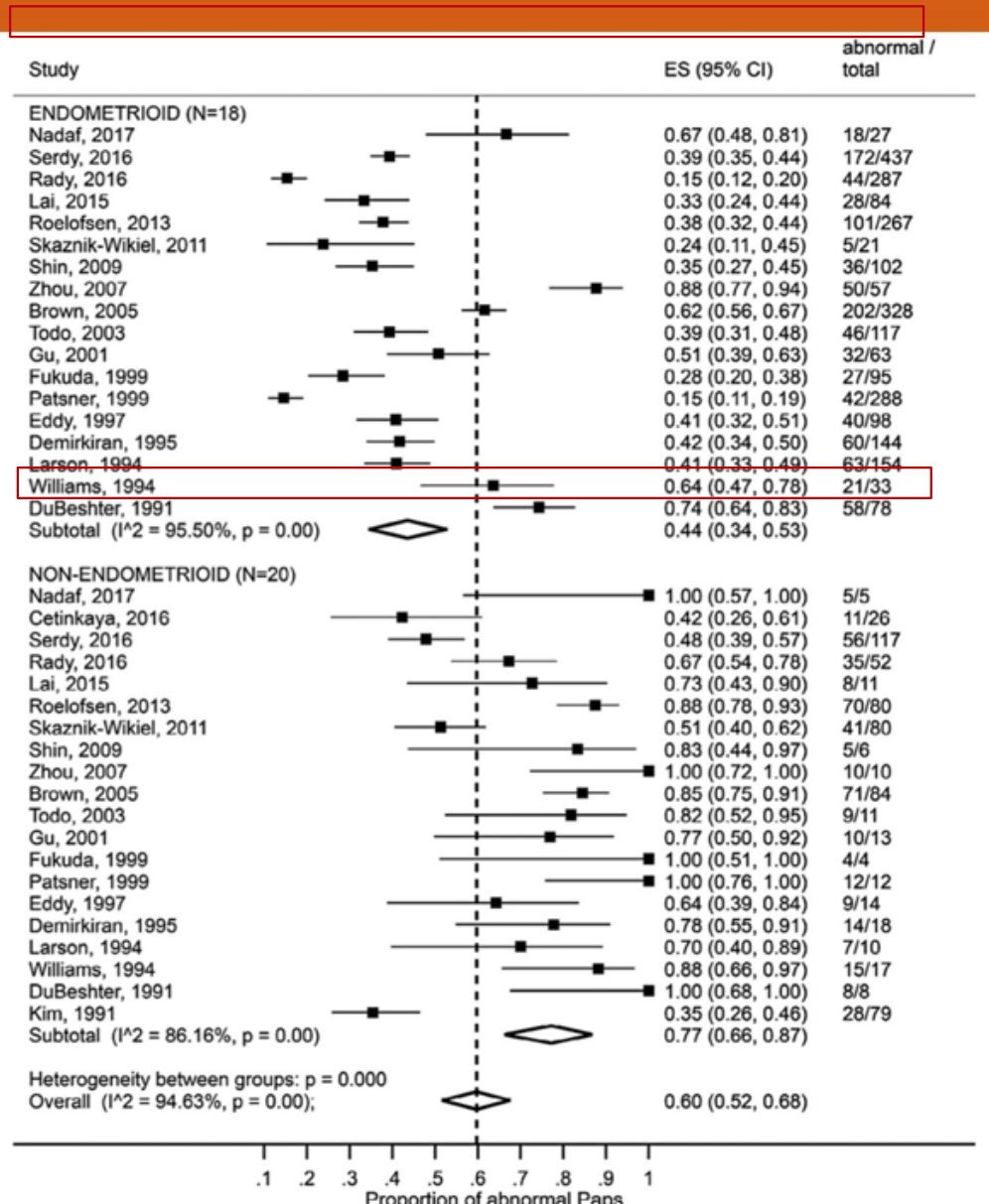
Sensitivity of Cervico-vaginal Cytology in Endometrial Carcinoma: A Systematic Review and Meta-analysis

Frias-Gomez *et al* Cancer Cytopathol 2020

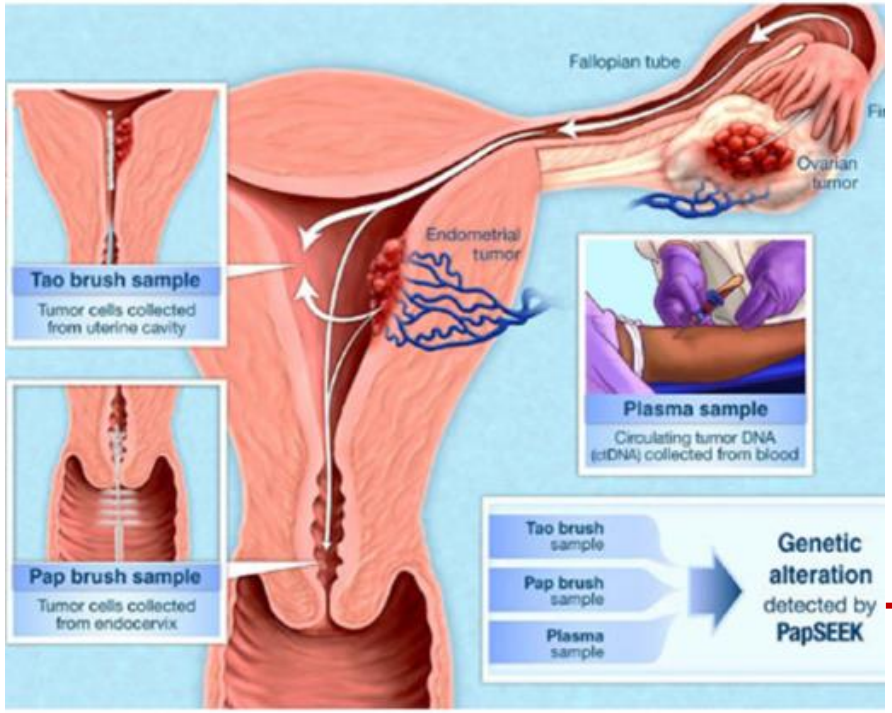
- Systematic review with meta-analysis
- 45 studies, 6599 women with endometrial cancer
- **Abnormal cervical cytology in 45%** (95%CI 40%-50%) women prior to diagnosis / surgery for endometrial cancer
- Significantly higher detection rate of non-endometrioid vs endometrioid cancers
  - 77% (95% CI, 66%-87%) non-endometrioid
  - 44% (95% CI, 34%-53%) endometrioid



Evaluation of liquid from the Papanicolaou test and other liquid biopsies for the detection of endometrial and ovarian cancers

Wang *et al* Sci Transl Med 2018

- papSEEK – incorporates assays for mutations in 18 genes & test for aneuploidy
- Pap brush samples from n=382 endometrial cancer patients, **81% positive** (95% CI 77%-85%), incl 78% patients with early stage disease
- Only 1 of 714 women without disease had positive pap brush samples
- Intrauterine sampling with Tao brush **increased sensitivity to 93%** of 123 patients (95% CI 87%-97%)

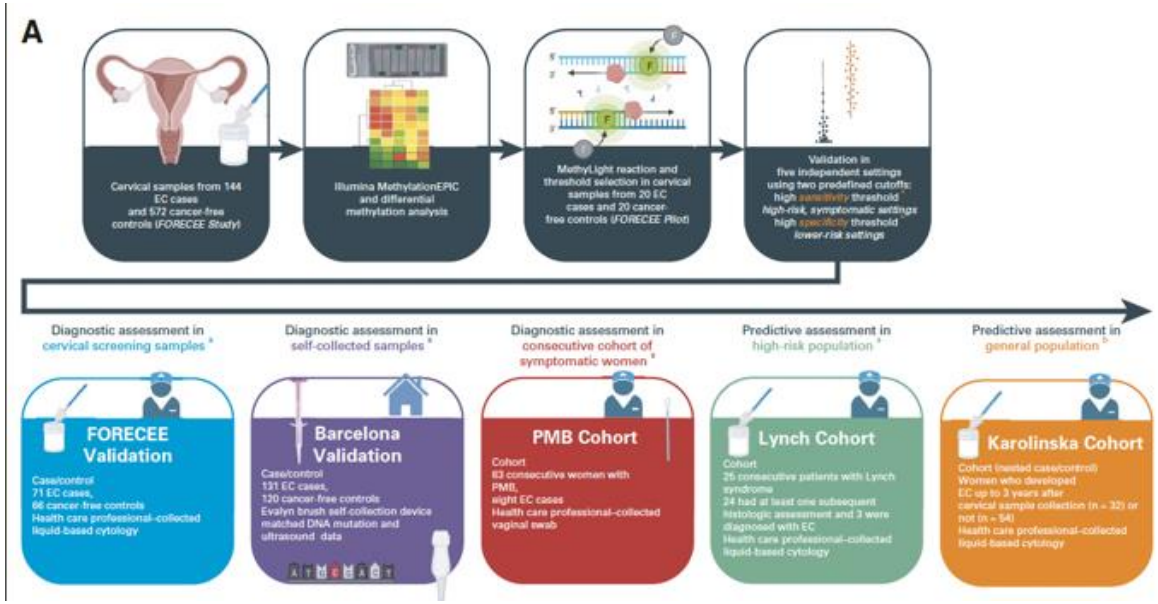


Mutations in: *AKT1, APC, BRAF, CDKN2A, CTNNB1, EGFR, FBXW7, FGFR2, KRAS, MAPK1, NRAS, PIK3CA, PIK3R1, POLE, PPP2R1A, PTEN, RNF43*, and *TP53*
+/- aneuploidy

original reports

A Simple Cervicovaginal Epigenetic Test for Screening and Rapid Triage of Women With Suspected Endometrial Cancer: Validation in Several Cohort and Case/Control Sets

Chiara Herzog, PhD[1,2]; Fátima Marín, PhD[3,4]; Allison Jones, BSc[5]; Iona Evans, PhD[5]; Daniel Reisel, PhD[5]; Elisa Redl, MSc[1,2]; Lena Schreiberhuber, MSc[1,2]; Sonia Paytubi, PhD[6]; Beatriz Pelegrina, MSc[6]; Álvaro Carmona, PhD[6]; Paula Peremiquel-Trillas, MD[6]; Jon Frias-Gomez, MSc[6]; Marta Pineda, PhD[3,4]; Joan Brunet, MD, PhD[3,4,7]; Jordi Ponce, PhD[4,8]; Xavier Matias-Guiu, PhD[4,9]; Silvia de Sanjosé, PhD[10]; Laia Alemany, PhD[6,11]; Adeola Olaitan, MD[12]; Michael Wong, PhD[12]; Davor Jurkovic, PhD[12]; Emma J. Crosbie, MD[13,14]; Adam N. Rosenthal, PhD[5]; Line Bjørge, PhD[15,16]; Michal Zikan, PhD[17]; Lukas Dostalek, MD, PhD[18]; David Cibula, PhD[18]; Karin Sundström, PhD[19]; Joakim Dillner, PhD[19]; Laura Costas PhD[6,11]; and Martin Widschwendter, MD[1,5,2,20]



WID-qEC test

Developed n=726; Tested n=562 samples

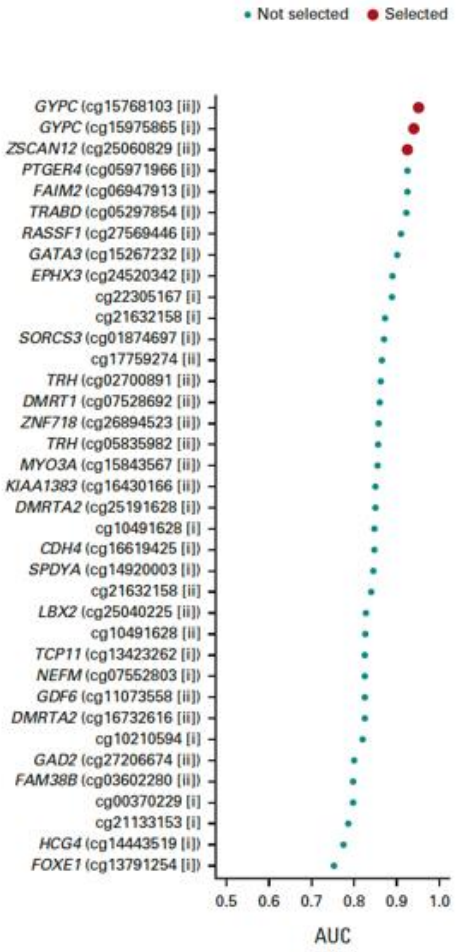
- Cervical smear
- Vaginal swab

4 settings:

- Case/ control
- PMB
- Lynch
- Screening cohort

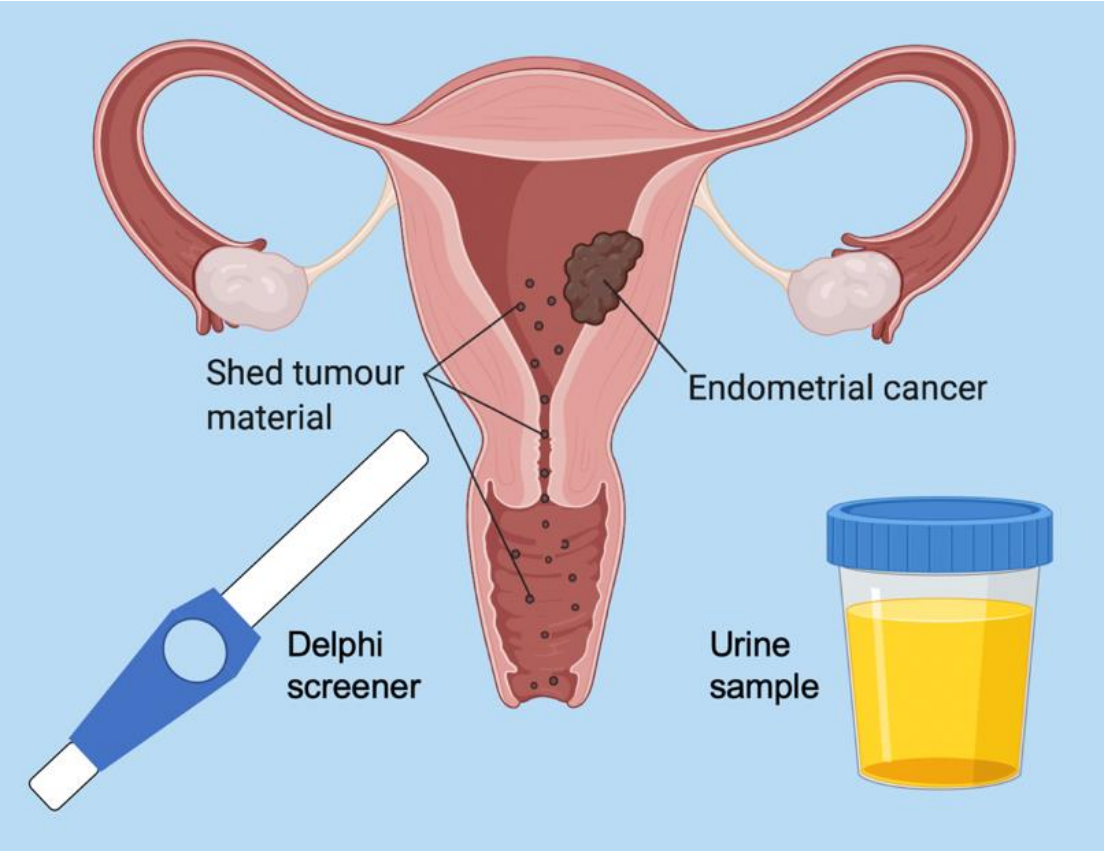
3 methylation biomarkers

- 90.1-100% sensitivity in symptomatic patients
- 90.9% sensitivity in asymptomatic patients



Hypothesis

- PMB offers liquid biopsy to enable endometrial cancer detection
- Shed malignant endometrial cells can be collected from vaginal fluid or urine and identified by cytology



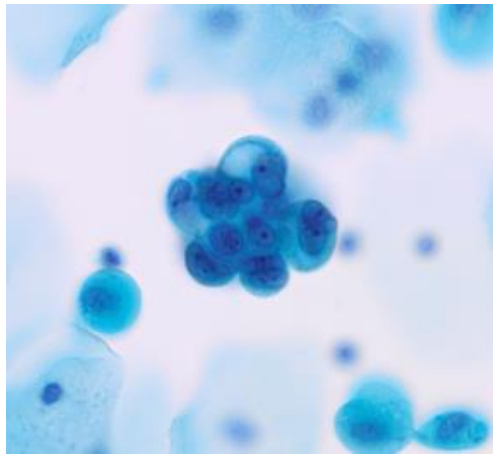
Proof of concept study

- Women attending with
  - Known endometrial cancer (EC)
  - Unexplained PMB
- Vaginal and urine samples were collected prior to any clinical procedures
- Cytologists blinded to cancer outcomes
- Two independent cytologists

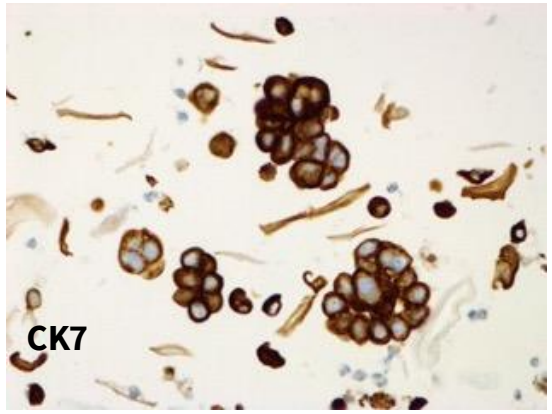
Matched samples Women with EC	Cytology +	Cytology -
Urine n=96	67 (70%)	29 (30%)
Vaginal fluid n=102	92 (90%)	10 (10%)

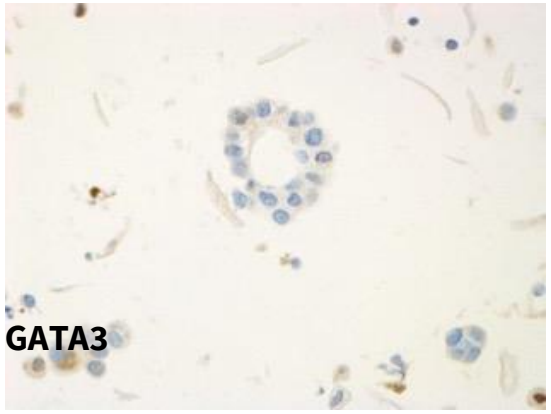
Matched samples Women with PMB		Cytology +	Cytology -
Urine n=99	EC	4 (100%)	0
	no EC	2*	92
Vaginal fluid n=100	EC	4 (100%)	0
	no EC	11**	84

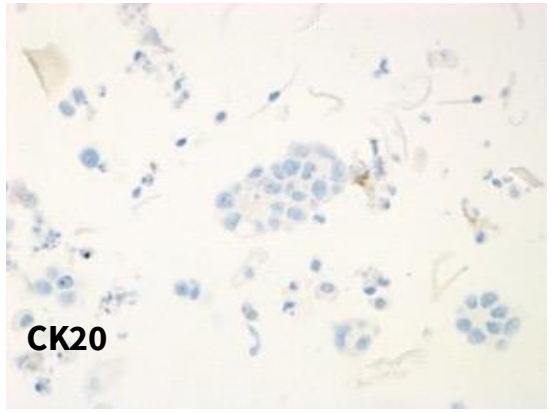
*bladder & ovarian cancer;
**cervix cancer & 11 false positives

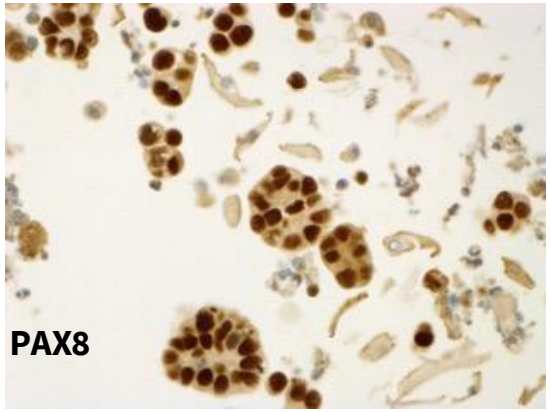


IHC profile consistent with female genital tract









nature COMMUNICATIONS

ARTICLE

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

Check for updates

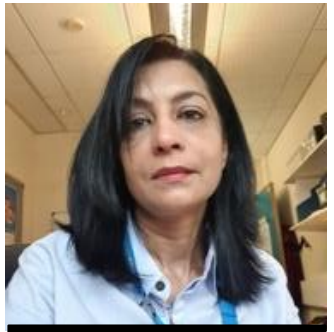
Diagnostic accuracy of cytology for the detection of endometrial cancer in urine and vaginal samples

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


Helena O'Flynn


Neil Ryan

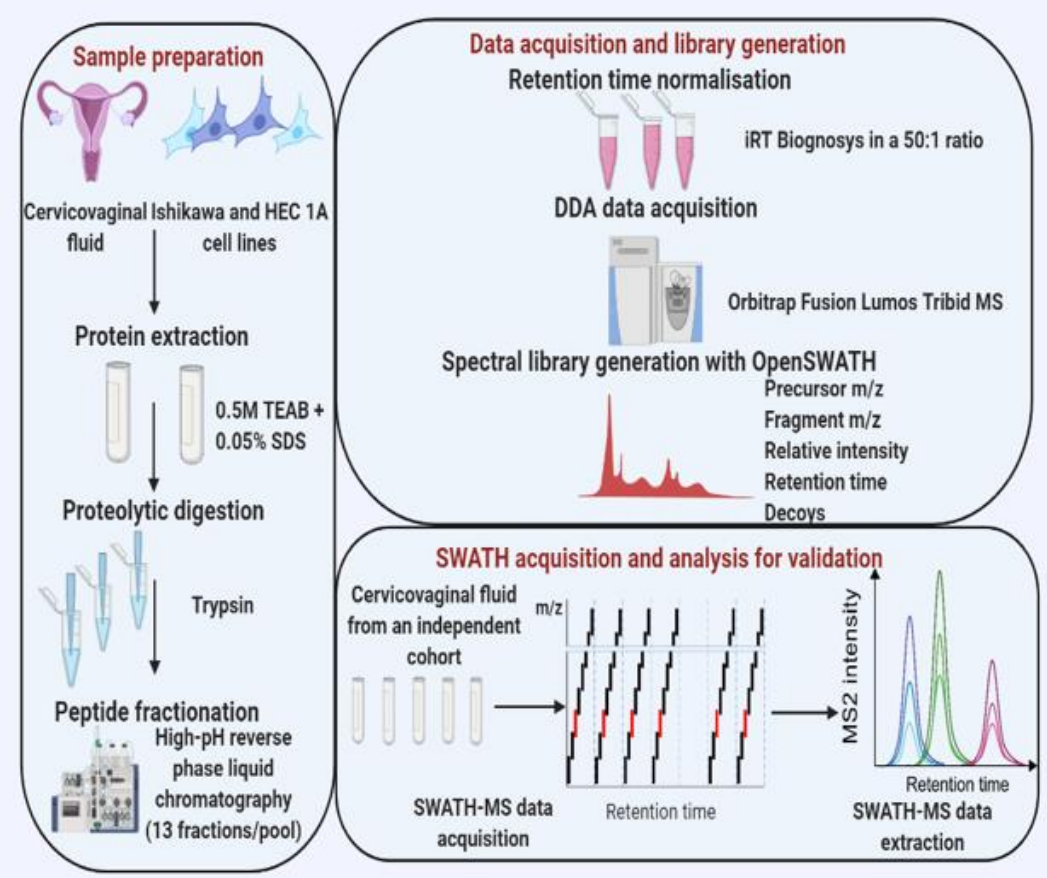

Emma Crosbie


Nadira Narine


David Shelton


Durgesh Rana

Protein-based biomarker panel



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

Kelechi Njoku,[a,b,c,**] Andrew Pierce,[d] Davide Chiasserini,[e] Bethany Geary,[f] Amy E. Campbell,[b] Janet Kelsall,[b] Rachel Reed,[b] Naphar Geifman,[g] Anthony D. Whetton,[h,i] and Emma J. Crosbie[a,i,*]

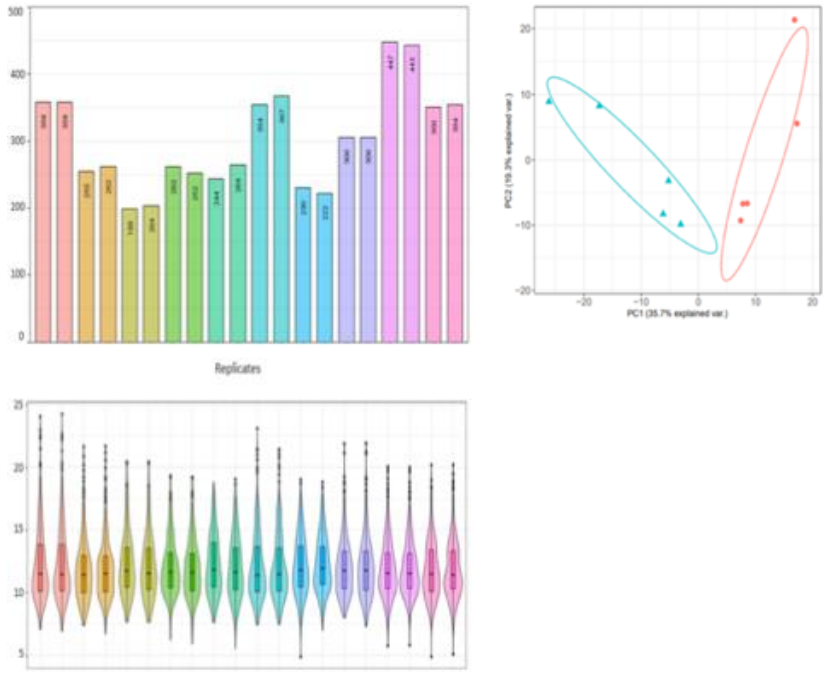
eBioMedicine
2024;102: 105064
Published Online 20 March 2024

cancers
MDPI

Article

Comprehensive Library Generation for Identification and Quantification of Endometrial Cancer Protein Biomarkers in Cervico-Vaginal Fluid

Kelechi Njoku [1,2,3,4], Davide Chiasserini [3,5], Bethany Geary [3,4], Andrew Pierce [4], Eleanor R. Jones [1,2], Anthony D. Whetton [3,4,*] and Emma J. Crosbie [1,2,*]



Kelechi Njoku

Tony Whetton

PREDI—Lynch

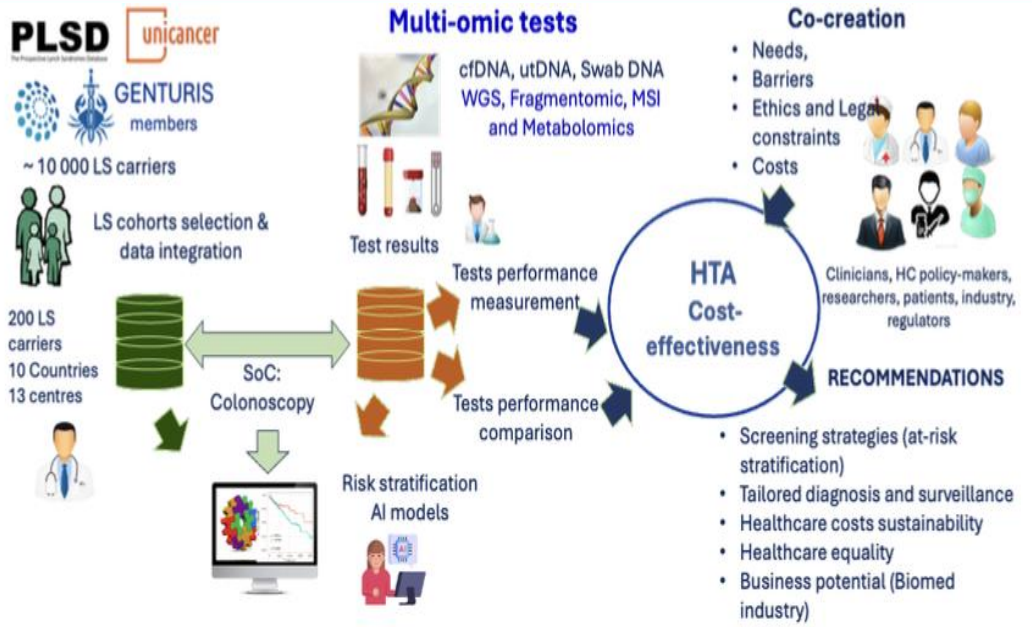
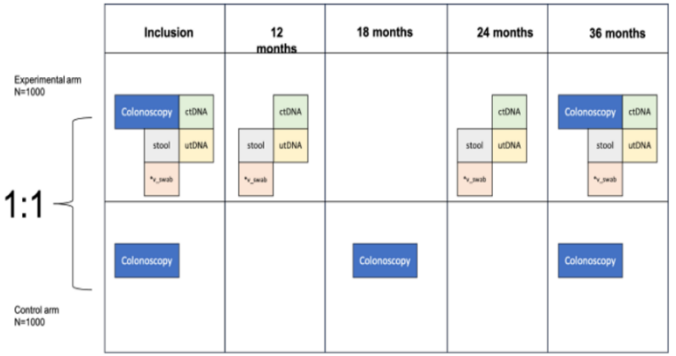
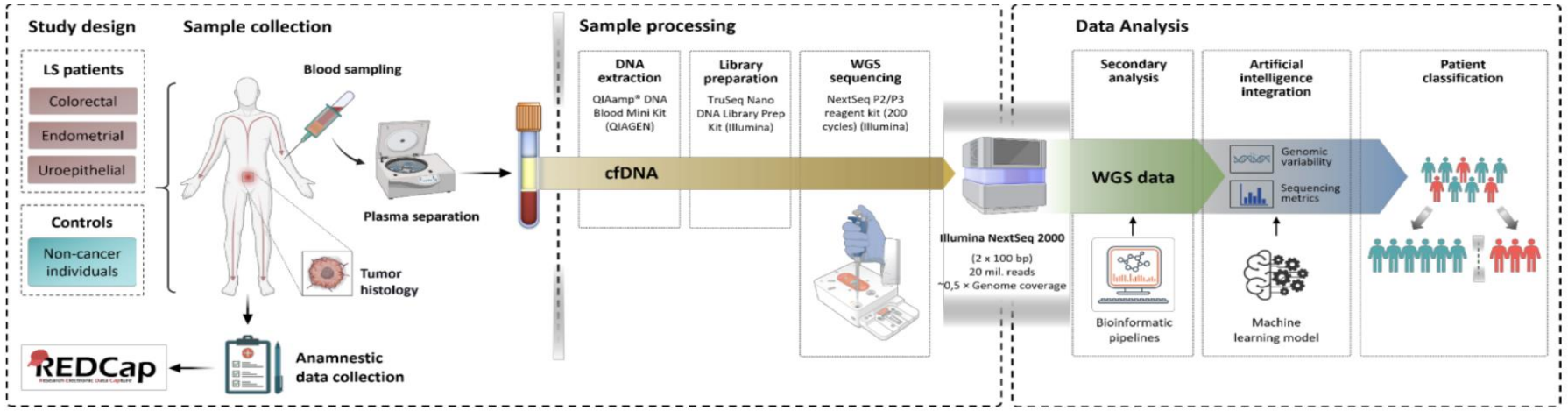


Figure 1. PREDI-LYNCH concept.





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€13.6 million funding for early detection of Lynch syndrome cancers

The PREDI-LYNCH project, co-led by IRR's Dr Neil Ryan, has been funded by the European Union's Horizon Missions programme and will involve 28 organisations from across Europe.

"By using novel liquid biopsy approaches—testing blood or other body fluids instead of relying on surgical procedures—we aim to create a non-invasive, accessible, and cost-effective way to monitor cancer risk. If we get this right, we can reach more people, detect cancers earlier, and prevent many from ever developing." - Neil Ryan

Read our article: https://edin.ac/45wblux

€13.6 million funding for early detection of Lynch...
regeneration-repair.ed.ac.uk

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Ellele Device

- The Ellele device is an innovative vaginal sampling device that captures cellular material from the vaginal wall for downstream laboratory analysis.

Easy

The 5-minute procedure can be administered by any HCP. No patient preparation, and minimal exclusion criteria.

Low cost

The device is single-use, has a low unit cost, facilitating large-scale deployment with outstanding health economics.

Acceptable

In our feasibility study, all women preferred the device to a standard speculum examination.

1

The device is inserted into the opening of the vagina up to 4cm max.

2

A small membrane is inflated to collect a sample from the wall of the vagina on its external surface.

3

The membrane is retracted and inverted, protecting the specimen within the device.

4

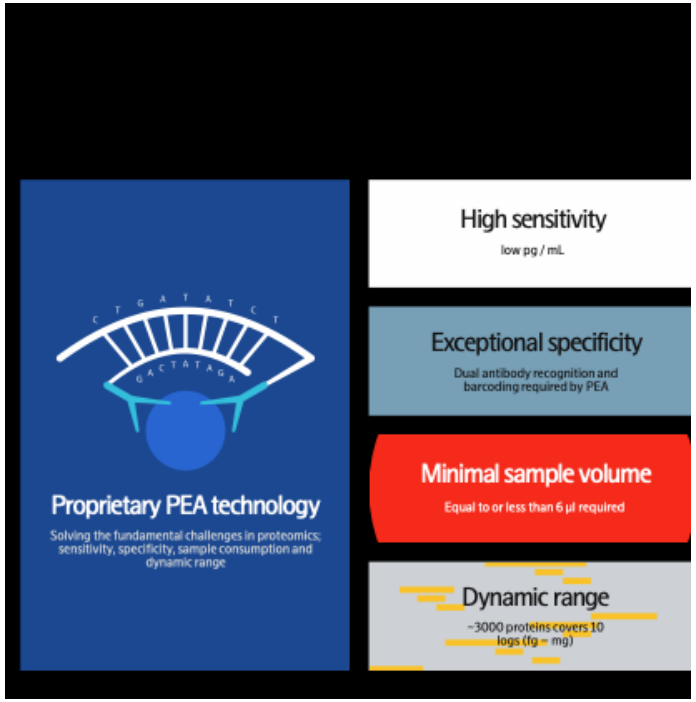
Stabilising buffer is added and the device is shipped ambient to the designated laboratory.

LOCATE Study

LOCATE
Longitudinal Ovarian Cancer Assessment Through Early-detection–
Next Generation Plasma Proteomics for Early Detection of High-Grade Serous

LOCATE Study
Early Detection of High-Grade Epithelial Ovarian Cancer

- **Aim:** Identify biomarkers and mechanisms of early ovarian cancer development.
- **Approach:**
  - Plasma proteomics profiling.
  - Spatial transcriptomics of STIC (serous tubal intraepithelial carcinoma) lesions.
- **Design:** Retrospective study using biobanked samples from UKCTOCS, NHS Lothian, SHARE, and University of Edinburgh.
- **Chief Investigator:** Dr Neil Ryan.
- **Impact:** Potential to transform early detection strategies and reduce ovarian cancer mortality.



north west cancer research

the eve appeal

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The Liquid Bx

Liquid Biopsy Omics: Enabling Smarter Clinical Decisions

- **Faster initiation of therapy**
  – Blood-based ctDNA testing can identify actionable mutations up to ~16 days earlier than tissue biopsy, enabling quicker treatment starts.
- **Precision therapy matching**
  – ctDNA reveals targetable genetic alterations (e.g., EGFR in lung, BRCA/PARP in ovarian), guiding selection of optimal targeted treatments.
- **Real-time response and relapse monitoring**
  – Serial liquid biopsy can detect residual disease, treatment response, or emerging resistance earlier than imaging.
- **Broader patient access**
  – Minimally invasive and repeatable—especially valuable for patients with inaccessible tumors or those unfit for surgical biopsy.
- **Reduced interventions and cost**
  – Can help avoid unnecessary procedures or chemotherapy in low-risk cases; early modeling suggests potential cost savings for healthcare systems.

Conclusion

- **Inherited risk (BRCA, Lynch):** highest impact population for intervention.
- **Current surveillance:** invasive, imperfect, late detection remains common.
- **Future focus:**
- **Non-invasive liquid biopsies** (blood, urine, vaginal samples).
- Integration of **multi-omics + AI** for sensitivity and specificity.
- **Goal:** Shift from late-stage diagnosis → **true prevention and early detection**.
- **Impact:** Better survival, reduced treatment burden, improved quality of life.


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Thank You
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