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Scottish Referral Guidelines for Suspected Cancer Update – Evidence Review (Gynaecological)

The purpose of this document is to synthesise and critique evidence and insight related to referral guidelines for suspected gynaecological cancer. Key themes have been determined from the literature. For each key theme e.g. symptoms, the papers are summarised separately with some high-level synthesis to provide steer on how this may impact referral guidelines. At the end of the document, a table comparing NICE NG12 and SRG guidelines can be found for reference.

This document includes evidence on the following topics:

- Symptoms (individual and combination)
- Investigations
- Safety netting
- Risk Stratification
- Other topics where the evidence base is weaker but emerging

Background

Gynaecological cancer is an umbrella term, comprised of ovarian, endometrial (uterine), cervical, vaginal and vulval cancers. These cancers tend to present with different symptoms, have different stage distributions and outcomes. Scotland stage at diagnosis data is not publicly available for gynaecological cancers. In 2019, 80% of endometrial cancers and 74% of cervical cancers were diagnosed at early stage (1 or 2) out of those with a known stage at diagnosis, compared to just 42% for ovarian cancers in Wales[1]. Available data from other UK nations demonstrate large differences in survival depending on stage at diagnosis for all gynaecological cancers. In Wales, at least 99% of those diagnosed at the earliest stage will survive their cancer for 1-year or more for cervical, ovarian, and endometrial cancers. This compares to just 47% of those diagnosed at stage 4 for ovarian cancer, 39% for cervical cancer and 35% for endometrial cancer[1]. There are also a significant proportion of gynaecological cancers diagnosed via emergency presentation (England, 2018 data where route to

[1] Cancer Research UK (2022a). Early Diagnosis. [online] crukcancerintelligence.shinyapps.io. Available at: https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/.

diagnosis is known: 28% of ovarian cancers, 11% of cervical cancers and 8% of endometrial cancers), which is associated with later stage at diagnosis and worse survival[1,2].

Recognising gynaecological cancers in primary care can be challenging, as many symptoms (e.g. bloating, pelvic pain) are non-specific and often caused by benign disease[3]. There is no international consensus on the optimum initial assessment and investigation for ovarian cancer in symptomatic women[4]. Findings from International Cancer Benchmarking Partnership (ICBP) research has found that there is a statistically significant correlation between lower readiness to investigate for ovarian cancer in primary care and worse 1-year survival in the UK nations included in the study (England, Wales, Northern Ireland)[5]. Compared to ovarian cancer, there is less evidence investigating other gynaecological cancers diagnosis and outcomes. There is also limited evidence into how inequalities may impact diagnosis of gynaecological cancers. As cancers affecting the reproductive organs, it is important to consider additional barriers along the pathway for people who are transgender. A systematic review aimed to investigate prevalence of reproductive cancers in those who are transgender, but the overall evidence quality was low[6]. Further research is required to understand risk of reproductive cancers in transgender people and any barriers to timely recognition and referral in a symptomatic context.

Additional challenges highlighted in the literature focus on use of investigations in primary care and symptoms included in referral guidelines[7]. Continued review of the evidence underpinning referral guideline recommendations and their use, will help ensure people are referred along the most appropriate route at the right time.

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[2] Athey, R.A., Macdonald, M.C. and Jha, S. (2021). Stage of ovarian cancer at diagnosis. Does presentation as an emergency make a difference? European Journal of Obstetrics & Gynecology and Reproductive Biology, 261, pp.7–11. doi:https://doi.org/10.1016/j.ejogrb.2021.04.001.

[3] Funston, G., O'Flynn, H., Ryan, N.A.J., Hamilton, W. and Crosbie, E.J. (2018). Recognizing Gynecological Cancer in Primary Care: Risk Factors, Red Flags, and Referrals. Advances in Therapy, 35(4), pp.577–589. doi:https://doi.org/10.1007/s12325-018-0683-3.

[4] Funston, G., Van Melle, M., Baun, M.-L.L., Jensen, H., Helsper, C., Emery, J., Crosbie, E.J., Thompson, M., Hamilton, W. and Walter, F.M. (2019). Variation in the initial assessment and investigation for ovarian cancer in symptomatic women: a systematic review of international guidelines. BMC Cancer, 19(1). doi:https://doi.org/10.1186/s12885-019-6211-2.

[5] Rose, P.W., Rubin, G., Perera-Salazar, R., Almberg, S.S., Barisic, A., Dawes, M., Grunfeld, E., Hart, N., Neal, R.D., Pirotta, M., Sisler, J., Konrad, G., Toftegaard, B.S., Thulesius, H., Vedsted, P., Young, J., Hamilton, W., The ICBP Module Working Group, Dawes, D. and Elwood, M. (2015). Explaining variation in cancer survival between 11 jurisdictions in the International Cancer Benchmarking Partnership: a primary care vignette survey. BMJ Open, [online] 5(5), pp.e007212–e007212. doi:https://doi.org/10.1136/bmjopen-2014-007212.

[6] Joint, R., Chen, Z. and Cameron, S. (2018). Breast and reproductive cancers in the transgender population: a systematic review. BJOG: An International Journal of Obstetrics & Gynaecology, 125(12), pp.1505–1512. doi:https://doi.org/10.1111/1471-0528.15258.

[7] Funston, G., Crosbie, E.J., Hamilton, W. and Walter, F.M. (2022). Detecting ovarian cancer in primary care: can we do better? British Journal of General Practice, 72(720), pp.312–313. doi:https://doi.org/10.3399/bjgp22x719825.

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Search Strategy

Search terms: PubMed search for combinations of the following terms: gynaecological, ovarian, endometrial, uterine, cervical, vaginal, vulval, symptom, symptomatic, PPV (positive predictive value), presentation, prevalence, risk, recognition, referral, stage, pelvic mass, pelvic pain, abdominal pain, satiety, distention, urinary retention, urinary frequency, post-menopausal bleeding, inter-menstrual bleeding, discharge, thrombocytosis, haematuria, visible, haemoglobin, blood glucose, lump, ulceration, incidence, comorbidities, demographic, primary care, investigation (ultrasound, CA125, HE4), safety netting, direct access, transgender

Date: 2015 – present. In the table summaries, the only papers included from pre-2015 are those that are relevant for explaining differences between Scottish Referral Guidelines (SRG) and NICE NG12 guidelines. These have been gathered from NICE NG12 Evidence Review document.

Peer-reviewed literature

Note: grey rows in the table represent studies that have already been summarised earlier in the document.
Note: throughout this evidence review, participants' gender is described as in the original study.

Topic: Symptoms
Summary: Paper 4 found no gynaecological cancer symptoms were associated with an increased odds of stage 4 disease as a single symptom (for all cancers), suggesting that symptomatic gynaecological cancers have potential to be diagnosed at an earlier stage, where there are more treatment options and outcomes are better. **Ovarian Cancer** Paper 3 found PPVs for abdominal symptoms (abdominal distension, abdominal pain, change in bowel habit, dyspepsia, dysphagia, and rectal bleeding) do not exceed >1% for ovarian cancer for those aged >30 years. This is likely due to the commonality of these symptoms for benign, as well as malignant conditions. Abdominal symptoms are common symptom presentations for ovarian cancer, particularly abdominal pain, and distention. Abdominal pain and distention are included in NG12 guidelines, and in the SRG 'Good Practice Points' for ovarian cancer.

Ovarian cancer incidence in those with abdominal symptoms increases with age. In paper 2, 2% of women aged 60-69 years with abdominal pain plus abdominal mass were diagnosed with ovarian cancer in the year following symptom presentation, which increased to 7% in those aged 70+. 1.5% of women aged 70+ years with abdominal pain plus change in bowel habit were diagnosed with ovarian cancer in the year following symptom presentation. Both paper 2 and 3 are large-scale cohort studies.

Evidence comparing screen-detected and clinically-detected (defined as all other diagnoses that were not as a result of a positive screening result) ovarian cancers has found that symptom profiles may differ between early and late stage, and that symptoms may present up to two years before ovarian cancer becomes 'clinically apparent'. Paper 1 found early-stage ovarian cancer has a greater association with **gastro-intestinal** and **systemic** symptoms (e.g. change in bowel habits, dyspepsia, lethargy), whereas **gynaecological** symptoms are associated with later stage disease. Abdominal symptoms such as CIBH are included in SRG, but dyspepsia is not. This study included invasive epithelial ovarian and tubal cancers and excluded non-epithelial and borderline epithelial tumours.

Ovarian cancer can be classified into two subtypes:

- **Type 1:** includes low-grade serous, endometrioid, clear-cell, and mucinous carcinomas, alongside rarer subtypes. Type 1 tumours mostly arise from borderline tumours. This type typically presents at an early stage, have better prognosis and lower proliferative activity.
- **Type 2 (more common):** include high-grade serous carcinoma, carcinosarcoma, and undifferentiated carcinoma, which mainly originate from serous tubal (invasive) intraepithelial carcinoma. Type 2 tumours are high-grade tumours and are more likely to be diagnosed at advanced stage. They have high proliferative activity with rapid and aggressive progression[8].

There are some differences in symptoms included between SRG and NG12:

- NG12 recommends considering CA125 for unexplained weight loss or fatigue for ovarian cancer, which is not included in SRG. Paper 5 found 3% of patients diagnosed with ovarian cancer present with unexplained weight loss, and paper 1 suggests systemic symptoms e.g. fatigue are associated with earlier stage disease. This may support inclusion of these symptoms in SRG, either as part of gynaecological cancer guidelines or RCDS pathways.

Endometrial Cancer

Paper 3 found PPVs for abdominal symptoms (abdominal bloating/distension, abdominal pain, change in bowel habit, dyspepsia, dysphagia, and rectal bleeding) do not exceed >1% for endometrial cancer for those aged >30 years.

[8] Kurman RJ, Shih IM. The Dualistic Model of Ovarian Carcinogenesis. The American Journal of Pathology. 2016 Apr;186(4):733–47.

A systematic review (paper 8) found the risk of endometrial cancer in pre-menopausal women with abnormal uterine bleeding was low (0.33%). This increased to 1.31% when considering atypical hyperplasia too. The risk of either atypical hyperplasia or endometrial cancer was reported as 2% for 40–50-year-olds and 14% for those aged 50+.

Post-menopausal bleeding (PMB) is the main presenting symptom of endometrial cancer and results in large numbers of referrals to gynaecology clinics. PMB is often associated with benign conditions, such as endometrial polyps or unscheduled bleeding in women using hormone replacement therapy (HRT). A retrospective, England based, service evaluation found the detection rate for endometrial cancer in those with post-menopausal bleeding (PMB) on HRT is much lower than for those who are not on HRT (paper 6), but a systematic review (paper 7) found that risk associated with PMB in those on HRT is still significant. Paper 6 is based on an English, primary care population, whereas paper 7 has a larger sample size but includes studies from across the world and not all in a primary care setting, which may have over-estimated the risk.

There are some differences in symptoms included between SRG and NG12:

- NG12 recommends direct access to ultrasound for a few different symptom combinations not included in SRG:
    - vaginal discharge + thrombocytosis, or + haematuria
    - visible haematuria + low Hb, or + thrombocytosis, or + high blood glucose levels
- Of all patients diagnosed with uterine/endometrial cancer in Paper 10, 4% experienced haematuria or vaginal discharge. No evidence since 2015 has investigated PPVs of these symptom combinations for endometrial cancer.
- Walker et al (2013) reported the following PPVs for these symptom combinations, some of which have relatively high PPVs:
    - Vaginal discharge and haematuria: **2.2%**
    - Vaginal discharge and low Hb: 0.8%
    - Vaginal discharge and high platelets: 1.4%
    - Vaginal discharge and high glucose: 0.6%
    - Haematuria and low Hb: **2.7%**
    - Haematuria and high platelets: 1.9%

Haematuria and high glucose: 1.1 %

Cervical Cancer (paper 10)

For cervical cancer, the PPV of abnormal bleeding for those aged >55 was >4%. This may warrant inclusion in the guidelines, but it is important to note this estimate is only from one study.

Vaginal/Vulval Cancer Paper 9 reports prevalence of vaginal/vulval cancer symptoms, but no evidence was found estimating PPVs for this cancer type.				
Paper number	**Study**	**Cancer**	**Summary**	**Notes**
1	Dilley, J. (2023). Ovarian cancer symptoms in pre-clinical invasive epithelial ovarian cancer – An exploratory analysis nested within the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). Gynaecologic Oncology, [online] pp.123–130. doi:https://doi.org/10.1016/j.ygyno.2023.11.005.	Ovarian	This study aimed to report on symptoms in women with pre-clinical (screen-detected) cancers (PC) compared to clinically diagnosed (CD) cancers. Most symptomatic women with high grade serous tubo-ovarian cancers (HGSC) had more than one symptom (60% in both PC group and CD group). Abdominal symptoms were the most commonly reported symptom type, both in early and advanced stage disease. **PC:** 62% (16/26) reported abdominal symptoms at early stage, 57% (49/86) at advanced stage **CD:** 53% (42/80) reported abdominal symptoms at early stage, 74% (431/580) at advanced stage In symptomatic early-stage disease, PC women reported statistically significantly more **gastrointestinal** (**35%,** 9/26 PC; **9%,** 7/80 CD, p<0.001) and **systemic** (**27%,** 7/26 PC; **9%,** 7/80 CD, p= 0.017) symptoms, compared to the **CD** group. The gastrointestinal symptoms reported were most commonly **change in bowel habits** and **dyspepsia**. The reported systemic symptoms comprised mostly of **lethargy or tiredness**. Early-stage PC symptomatic patients reported significantly fewer gynaecological (PC: **8%,** 2/26; CD: **39%,** 31/80) symptoms, in particular **vaginal bleeding,**	Nested analysis within RCT: UKCTOCS (UK collaborative trial of ovarian cancer screening) Data from England, Wales, and Northern Ireland N=1,133 diagnosed with ovarian caner Age threshold: 50-74 years **Limitations:** the absolute number of screen detected women with early stage preclinical HGSC who were symptomatic was limited (n=133)

			and none reported a change in appetite/feeling full, a key ovarian cancer alert symptom. In advanced stage disease, symptomatic PC women reported significantly **fewer abdominal** (PC: **57%,** 49/86; CD: **74%,** 431/580) and significantly more **gynaecological** (PC: **20%,** 17/86; CD: **8%,** 48/580) and urinary (PC: **26%,** 22/86; CD**: 12%,** 71/580) symptoms compared to the symptomatic CD group. Specifically, **increase in abdominal size/bloating** was reported less and **urinary frequency/urgency** was reported more compared to CD women. Additionally, fewer late-stage PC women reported **weight loss** and more reported **lethargy and tiredness**. The study reported half the women experience symptoms up to two years prior to the cancer becoming clinically apparent, and the symptom profile differs from that observed in women diagnosed clinically.	
2	Price, S., Gibson, N., Hamilton, W., King, A. and Shephard, E. (2022). Intra-abdominal cancer risk with abdominal pain: a prospective cohort primary-care study. British Journal of General Practice, p.BJGP.2021.0552. doi:https://doi.org/10.3399/bjgp.2021.0552.	Ovarian	This study aimed to quantify cancer risk in primary care patients with abdominal pain. 2% (95% CI: 1-6%) of women aged 60-69 years with abdominal pain plus abdominal mass were diagnosed with ovarian cancer in the year following symptom presentation, which increased to 7% (95% CI: 3-15%) in those aged 70+. 0.5% (95% CI: 1-6%) of women aged 60-69 years with abdominal pain plus change in bowel habit were diagnosed with ovarian cancer in the	Prospective cohort study using English primary care data and Clinical Practice Research Datalink (CPRD) dataset between 2009–2013. N=125,793 Age threshold: >40 years

			year following symptom presentation, which increased to 1.5% (95% CI: 3-15%) in those aged 70+.	**Limitations:** some data may be missing, due to only using coded data in the analysis
3	Herbert A, Rafiq M, Pham TM, Renzi C, Abel GA, Price S, Hamilton W, Petersen I, Lyratzopoulos G. Predictive values for different cancers and inflammatory bowel disease of 6 common abdominal symptoms among more than 1.9 million primary care patients in the UK: A cohort study. PLoS Med. 2021 Aug 2;18(8):e1003708. doi: 10.1371/journal.pmed.1003708.	Ovarian/ Endometrial	This study aimed to estimate the predictive values of common abdominal symptom presentations to primary care for (i) cancer; (ii) IBD; and (iii) the composite outcome of cancer or IBD in the year post-consultation in those aged >30 years. Six symptoms were included: abdominal bloating/distension, abdominal pain, change in bowel habit, dyspepsia, dysphagia, and rectal bleeding. PPVs (95% CI) for **ovarian** cancer: • Abdominal bloating/distention: 0.54 (0.48-0.59) • Abdo pain: 0.19 (0.17, 0.20) • Change in bowel habit: 0.16 (0.13-0.19) • Dyspepsia: 0.12 (0.11-0.13) • Dysphagia: 0.04 (0.02-0.06) • Rectal bleeding: 0.06 (0.05-0.08) PPVs (95% CI) for **endometrial** (uterine) cancer: • Abdominal bloating/distention: 0.05 (0.03-0.06) • Abdominal pain: 0.05 (0.04-0.05) • Change in bowel habit: 0.04 (0.03-0.06) • Dyspepsia: 0.03 (0.03-0.04) • Dysphagia: 0.02 (0.01-0.04)	Retrospective population-based cohort study, using data from The Health Improvement Network (THIN) in the UK (2000–2017) N= 102,785 for abdominal bloating/distension, 909,451 for abdominal pain, 108,698 for change in bowel habit, 528,428 for dyspepsia, 87,971 for dysphagia, and 240,253 for rectal bleeding Age threshold: 30-99 years

			• Rectal bleeding: 0.05 (0.04-0.06)	**Limitations:** analysed data only included coded symptoms, which may underestimate the true prevalence of symptoms. Additionally, PPVs stratified by age were not available for ovarian or endometrial cancer.
4	Koo MM, Swann R, McPhail S, Abel GA, Elliss-Brookes L, Rubin GP, et al. Presenting symptoms of cancer and stage at diagnosis: evidence from a cross-sectional, population-based study. The Lancet Oncology. 2019 Nov;21(1).	Ovarian/ Endometrial	There has been some debate around whether cancers present symptomatically at an early enough stage for meaningful clinical intervention. This study aimed to examine associations between common presenting symptoms of cancer and stage at diagnosis. After adjusting for demographic factors, no gynaecological cancer symptoms were associated with an increased odds of stage 4 disease as a single symptom, suggesting that gynaecological cancers could potentially be diagnosed symptomatically at an earlier stage, where the likelihood of successful treatment is greater. Proportion diagnosed at stage 4, and odds of stage 4 diagnosis associated with symptoms when recorded alone: • PMB: 4% (0.4 (95% CI 0.16-1.02)) • Lower abdominal pain: 35% (1.98 (95% CI 1.00-3.94)) • Abdo pain: 33% (1.45 (95% CI 0.81-2.59)) • LUTS: 15% (0.56 (95% CI 0.35-0.90))	Cross-sectional, population-based study England data using National Cancer Diagnosis Audit (NCDA) data (2014) N=7997 (for all cancers) **Limitation:** this study uses primary care records, which may be incomplete and prone to bias

			Proportion of cancer patients who presented with *x* symptom who were subsequently diagnosed with **ovarian** cancer: • Lower abdominal pain: 21% • Abdominal pain: 13% • CIBH: 8% • PMB, any other symptom: 7% • Fatigue, weight loss: 3% • LUTS: 2% • Cough, dyspnoea, back pain, chest pain, neck lump, rectal bleeding, haematuria: 1% Proportion of cancer patients who presented with *x* symptom who were subsequently diagnosed with **endometrial** cancer: • PMB: 89% • Lower abdominal pain, any other symptom: 4% • Haematuria: 3% • Rectal bleeding, LUTS, CIBH, abdominal pain, fatigue: 1%	
5	Moore SF, Price SJ, Bostock J, Neal RD, Hamilton W. Incidence of "Low-Risk but Not No-Risk" Features of Cancer Prior to High-Risk Feature Occurrence: An Observational Cohort Study in Primary Care. Cancers [Internet]. 2023 Aug 2;15(15):3936.	Ovarian/ Endometrial	This study aimed to investigate the number and percentage of patients with a PPV ≥ 3% feature who also presented with a 2–2.99% or 1–1.99% feature in the preceding year. Of 160 patients with >3% risk symptom for **ovarian cancer**, 8 presented with a 2-2.99% PPV symptom in the previous year, suggesting earlier opportunities for recognition of ovarian cancer. 0 presented with a 1-1.99% symptom in the previous year. Abdominal distention was the only 2-2.99% feature present in the year preceding a 3% symptom. (*Note*: small sample size).	Cross-sectional study English primary care data from 2015-2016 N= 150,921 for all cancers combined N=7,108 patients with >3% risk symptom **Note:** PPVs derived from a list of features of cancer from the

			Median time between presenting with 2-2.99% symptom and >3% symptom was 94 days (IQR: 30-235). Of 110 patients with >3% risk symptom for **endometrium cancer,** 0 presented with either a 2-2.99% or 1-1.99% PPV symptom in the previous year.	systematic reviews published in NG12 2015 update for each of the cancer sites. **Limitation:** only coded data was used for this analysis, so there may be underestimation of threshold for symptoms, due to missing data in free text.
6	Buchanan, C., Robinson, M. and Macdonald, M.C. (2022). Endometrial cancer rate in Hormone replacement therapy users with postmenopausal bleeding: Retrospective cohort study. Post Reproductive Health, 28(3), pp.143–148. doi:https://doi.org/10.1177/20533691221116171.	Endometrial	This study aimed to establish the endometrial cancer detection rate in women using hormone replacement therapy presenting with postmenopausal bleeding. 214 women were using HRT when they experienced PMB and only one of these had endometrial cancer. The cancer detection rate for HRT users with PMB was 0.47%. 25 of the 1124 women who were not using HRT were diagnosed with endometrial cancer after presenting with PMB, giving a cancer detection rate of 2.18%. Of the remaining 213 referred due to PMB, 1 was diagnosed with ovarian cancer.	Retrospective service evaluation in a single gynaecology outpatient department between 2019-2020. N=1363 Age threshold: <60 years **Limitations:** the study sample is restricted to one area of England so may lack generalisability to

			This study reports a much higher detection rate for endometrial cancer in those who are not using HRT.	current landscape in Scotland.
7	Clarke, M.A., Long, B.J., Del Mar Morillo, A., Arbyn, M., Bakkum-Gamez, J.N. and Wentzensen, N. (2018). Association of Endometrial Cancer Risk With Postmenopausal Bleeding in Women. JAMA Internal Medicine, [online] 178(9), p.1210. doi:https://doi.org/10.1001/jama internmed.2018.2820.	Endometrial	This study aimed to determine prevalence of PMB in endometrial cancer and the risk of endometrial cancer in women with PMB. The analysis reported a pooled prevalence of 91% for PMB in women with endometrial cancer. This study found the pooled risk of endometrial cancer in those with PMB was 9% (95% CI: 8%-11%). This was significantly higher among studies that excluded women using HRT (12% compared to 7%). There was no significant difference in prevalence of PMB between stage at diagnosis.	Systematic review and meta-analysis N=40,790 patients in 129 studies included published from 1977-2017 **Limitations:** this meta-analysis includes studies from across the world (including UK), so may limit applicability to UK setting.
8	Pennant, M., Mehta, R., Moody, P., Hackett, G., Prentice, A., Sharp, S. and Lakshman, R. (2016). Premenopausal abnormal uterine bleeding and risk of endometrial cancer. BJOG: An International Journal of Obstetrics & Gynaecology, 124(3), pp.404–411. doi:https://doi.org/10.1111/1471-0528.14385.	Endometrial	This study aimed to establish the risk of endometrial cancer and atypical hyperplasia in premenopausal women with abnormal uterine bleeding. In all studies of premenopausal women with abnormal uterine bleeding, the risk of cancer was low: 0.33% (95% CI 0.23–0.48%, n=97 cases). The risk of endometrial cancer was lower for women with heavy menstrual bleeding (HMB): 0.11% (95% CI 0.04–0.32%, n= n = 8352; 9 cases) than for women with inter menstrual bleeding (IMB): 0.52% (95% CI 0.23–1.16%, n = 3109; 14 cases)	Systematic review, papers included up to 2015 65 studies (n =29,059) Studies were conducted in Europe, North America, Australasia and non-Western countries. **Limitations:** despite large numbers

			31 studies reported rates of atypical hyperplasia and endometrial cancer. These reported a combined risk of 1.31% (95% CI 0.96–1.80). In those with abnormal uterine bleeding diagnosed with endometrial cancer alone (n=12 studies), there was an increase in risk with age group, but this was insignificant: • <40 years: 0.33% (95% CI 0.16–0.70%, n=2401, 8 cases) • 40–50 years: 0.51% (95% CI 0.34–0.77%, n = 6662, 31 cases) • >50 years: 1.04% (95% CI 0.24–4.41, n = 277, 2 cases). In those with abnormal uterine bleeding diagnosed with either endometrial cancer or atypical hyperplasia (n=4 studies), the increased risk associated with age was significant: • <40 years: 0.81 (95% CI 0.56–1.17, n = 1240, 10 cases) • 40–50 years: 1.99% (95% CI 1.59–2.48, n= 5131, 102 cases) • >50 years: 14.12% (95% CI 8.20–23.24, n=85, 12 cases).	included in the study there are relatively few cases of endometrial cancer in the sample. Additionally, studies predominately included populations of women referred to secondary care, so they are therefore unlikely to reflect typical populations of women presenting in primary care.
9	Zakkak N, Barclay ME, Swann R, McPhail S, Rubin G, Abel GA, et al. The presenting symptom signatures of incident cancer: evidence from the English 2018 National Cancer Diagnosis Audit. British Journal of Cancer [Internet]. 2024 Feb 1 [cited 2024 Feb 1];130(2):297–307.	Gynae	This study aimed to (1) examine the relative frequency of presenting symptoms by cancer site (the 'symptom signature' of each cancer site), and (2) to examine the relative frequency of cancer sites by presenting symptom (the 'cancer site case-mix' of each symptom), among incident cancer cases. The proportion of patients with gynaecological cancer presenting with the following symptom groups was: • Female specific: 52% • Lower abdominal: 29% • None recorded: 10% • Non-specific: 10% • Urological: 8%	Data from 2018 National Cancer Diagnosis Audit (England) N=55,122 (total cohort) **Limitations:** this is a case-only analysis (only patients with diagnosis of cancer were included), so

			• Upper abdominal: 7% • Respiratory: 2% • MSK: 2% Of all patients diagnosed with **ovarian cancer**, the proportion that experienced *x* symptom are as follows: • Distension: 28% • Abdominal pain: 19% • Lower abdominal pain: 16% • Weight loss: 9% • Pelvic pain: 7% • LUTS, constipation, CIBH, loss of appetite: 6% • Post-menopausal bleeding, nausea/vomiting, other: 5% • Fatigue, other vaginal bleeding, diarrhoea, upper abdominal pain: 4% • Dyspnoea: 3% • Vaginal discharge, back pain, dysuria, UTI, dyspepsia: 2% • DVT, fever, night sweats, early satiety, reflux, chest infection, chest pain, cough, rectal bleeding, haematuria, loin pain, renal colic, breast lump, vaginal mass: 1% Of all patients diagnosed with **cervical cancer**, the proportion that experienced *x* symptom are as follows: • Other vaginal bleeding: 35% • PMB: 25% • Vaginal discharge: 9% • Lower abdominal pain: 8% • Pelvic pain: 5% • Haematuria: 4%	cannot make inferences about PPV

			• Vulval bleeding, vaginal mass, back pain, UTI, abdominal pain, weight loss, fatigue: 3% • LUTS, dysuria, constipation, loss of appetite, other: 2% • DVT, nausea/vomiting, CIBH, diarrhoea, distention, rectal bleeding, vulval mass: 1% Of all patients diagnosed with **uterus/endometrial cancer**, the proportion that experienced *x* symptom are as follows: • PMB: 57% • Other vaginal bleeding: 19% • Lower abdominal pain, Vaginal discharge, haematuria: 4% • Abdo pain, pelvic pain: 3% • Vulval bleeding, back pain, distention, weight loss: 2% • Fatigue, other, loss of appetite, nausea/vomiting, upper abdominal pain, CIBH, rectal bleeding, dysuria, LUTS, UTI, vaginal mass: 1% Of all patients diagnosed with **vulval/vaginal** cancer, the proportion that experienced *x* symptom are as follows: • Vulval mass: 32% • Vulval ulcer: 22% • Vulval bleeding: 10% • Other vaginal bleeding: 6% • Other, vaginal mass, PMB: 5% • Pruritus, dysuria: 4% • Local lymphadenopathy, leukoplakia, LUTS, vaginal discharge: 2% • Loss of appetite, pelvic pain, haematuria, UTI, BCC-like lesion: 1%	

10	Walker, S. and Hamilton, W. (2017). Risk of cervical cancer in symptomatic women aged ≥40 in primary care: A case-control study using electronic records. European Journal of Cancer Care, 26(3), p.e12706. doi:https://doi.org/10.1111/ecc.12706.	Cervical	This study aimed to identify the features of cervical cancer in primary care and to quantify the risk of cancer for these features. Nine features (seven symptoms and two investigations) were determined to be predictive of cervical cancer. 48% of cases presented with at least one of these features in the year before diagnosis of cancer, compared to 13% of controls. PPVs for those aged >40 years (and 95% CI): • Post-menopausal bleeding: 0.46 (0.28-0.75) • Low Hb: 0.03 (0.03-0.04) • High white cell count: 0.06 (0.04-0.09) • Abdominal pain: 0.03 (0.02-0.04) • Vaginal discharge/vaginitis: 0.09 (0.06-0.13) • Inter-menstrual bleeding: 0.05 (0.02-0.13) • Irregular menstruation: 0.06 (0.03-0.12) • UTI: 0.03 (0.02-0.04) • Haematuria: 0.07 (0.04-0.14) PPVs for those aged >55 years (and 95% CI): • PMB: **4.6** (2.5-8.3) • Low Hb: 0.2 (0.15-0.26) • High white cell: 0.36 (0.23-0.56) • Abdominal pain 0.21 (0.15-0.30) • Vaginal discharge/vaginitis: 0.94 (0.52-1.7) • UTI: 0.17 (0.12-0.24) • Haematuria: 0.59 (0.29-1.2) **Note:** inter-menstrual bleeding and irregular menstruation were merged with PMB for this age category	Case–control study using data from the Clinical Practice Research Database (CPRD) in the UK between 2000-2009. n=4,016 eligible women (885 cases and 3,131 controls) Age threshold: 40+ **Limitations:** the data used is relatively dated, which may limit applicability to current practice. Also, the data cannot be used to make inferences for those aged <40.

Created by: Strategic Evidence, Cancer Research UK
Date created: March 2024

Topic: Investigation findings

Summary:

Ovarian Cancer:
CA125 is currently recommended in the guidelines as a diagnostic aid for ovarian cancer. Performance estimates at 35 U/ml cut off (standard threshold used in research and suggested by NG12) from recent, UK based studies are as follows: PPV: **10.1-24.9%,** NPV: **99.8-94.4%,** Sensitivity: **77.0-81.4%,** Specificity: **93.8%-56.8%** and AUC (overall accuracy): **0.92.** The AUC, PPV, sensitivity and specificity were all greater in those aged >50 years. Evidence found the test-to-diagnosis interval was longer if the patient had a CA125 result that did not meet the threshold for further investigation (<35U/ml). Additionally, 'below threshold' CA125 was found to be associated with early-stage disease. Borderline tumours were the most common type in women with CA125 results 'below threshold' (49%), and invasive epithelial cancers were the most common type in women with CA125 results above set threshold (81%).

Paper 11 also includes performance characteristics that suggest there may be a role for CA125 as a diagnostic aid for other cancers. See **'Other insights'** section later in the document for further information.

Cervical cancer:
Visualising the cervix is recommended in the guidelines as first line investigation for cervical cancer. There is limited evidence determining the accuracy of this, but one study reported that findings from visualisation were not commonly documented in medical notes, and rarely leads to onward referral or investigation. Further research is needed to optimise cervical cancer investigation in primary care. Paper 15 investigates the use of cytology as a diagnostic aid and estimates performance characteristics for cytology performed in a symptomatic cohort (sensitivity: 96.2% and specificity: 84.6% for very high-grade cell changes).

For any gynaecological cancer, some research suggests a statistically significant association between raised level of pre-diagnostic thrombocytosis, later stage at diagnosis and worse survival.

Paper number	Study	Cancer	Summary	Notes
11	Funston G, Hamilton W, Abel G, Crosbie EJ, Rous B, Walter FM. The diagnostic performance of CA125 for the	Ovarian	This study aimed to evaluate the performance of CA125 in primary care for the detection of ovarian and non-ovarian cancers.	Retrospective cohort study, using English data from Clinical Practice Research Datalink and

	detection of ovarian and non-ovarian cancer in primary care: A population-based cohort study. PLoS Med. 2020 Oct 28;17(10):e1003295. doi: 10.1371/journal.pmed.1003295		The most commonly reported symptom was abdominal pain (49%) and abdominal distension/bloating (23%). Multiple symptoms were recorded in 1,477 (6.1%) women. Ovarian cancer incidence in the cohort was 0.9% (n=456) and was 3 times higher in the >50 years group than the <50 years group. At or above the 35 U/ml cutoff, CA125 demonstrated the following performance characteristics for ovarian cancer: PPV: 10.1% (95% CI: 9.1–11.2) NPV: 99.8% (95% CI: 99.7–99.8) Sensitivity: 77.0% (95% CI: 72.8–80.8%) Specificity: 93.8% (95% CI: 93.6–94.0) AUC: 0.92 (95% CI: 0.90–0.93). The AUC, PPV, sensitivity and specificity were all greater in the >50-year age group. This study also includes performance characteristics for CA125 for other cancers, see 'Other insights' below.	cancer registry data, between 2011-2014 N=50,780 with CA125 result **Limitations:** large confidence intervals are seen at the extremes of age and CA125 level, and so the cancer probabilities for very old and young women and those with very low CA125 levels may have limited reliability
12	Funston, G., Mounce, L. T., Price, S., Rous, B., Crosbie, E. J., Hamilton, W. and Walter, F. M. (2021) CA125 test result, test-to-diagnosis interval, and stage in ovarian cancer at diagnosis: a retrospective cohort study using electronic health records. *British*	Ovarian	The aim of this study was to compare time between initial primary care CA125 test and diagnosis (test-to-diagnosis interval), tumour morphology* and stage, in women with normal (<35U/ml) and abnormal (≥35U/ml) CA125 prior to ovarian cancer diagnosis. Median test-to-diagnosis interval in the cohort was 42 days (IQR: 25-62 days). This was longer for those with CA125 result <35U/ml, compared to those with CA125 results >35U/ml (64 days (IQR: 42-127 days) vs 35 days (IQR: 21-53 days).	Retrospective cohort study using English data from Clinical Practice Research Datalink and cancer registry data between 2011-2014. **Note:** same dataset as study above

	Journal of General Practice, 71(707), pp. e465-e472.		Invasive epithelial cancers were the most common type in women with CA125 results above set threshold (81%) while borderline tumours were the most common type in women with CA125 results below set threshold (49%). In those with recorded stage data (n=381), 106 (35%) of those with CA125 >35U/ml were diagnosed with early-stage disease compared to 66 (86%) of those with CA125 <35U/ml. In adjusted analysis, the odds of being diagnosed with early-stage disease were 12.1 times higher in women with CA125 <35U/ml, compared to those with CA125 >35U/ml. After excluding borderline tumours, there was still a significant association between CA125 <35U/ml and diagnosis at an early stage (OR 9.0, 95% CI: 4.0-19.8)	N=456 diagnosed with ovarian cancer within year of CA125 result **Limitations:** this study cannot account for severity of symptoms in this analysis. CA125 is more likely to be elevated in women with later stage disease, which often presents with more severe symptoms, so this may act as a confounder.
13	Olsen, M., Lof, P., Stiekema, A., Broek, D., Wilthagen, E.A., Bossuyt, P.M. and Lok, C.A.R. (2021). The diagnostic accuracy of human epididymis protein 4 (HE4) for discriminating between benign and malignant pelvic masses: a systematic review and meta-analysis. Acta Obstetricia et Gynecologica Scandinavica, 100(10),	Ovarian	This study aimed to obtain summary estimates of the accuracy of human epididymis protein (HE4) for diagnosing ovarian cancer and to compare the performance of HE4 with CA125 (see Risk Stratification table below for HE4 results). **CA125:** Mean sensitivity: 81.4% (95% CI 74.6%-86.2%) Mean specificity: 56.8% (95% CI 47.9%-65.4%), at a cut-off of 35 U/ml. NPV: 94.4% (95% CI 92.3%-96.0%), at 15% prevalence PPV: 24.9% (21.1%-29.2%), at 15% prevalence	Systematic review N=17 studies included 3404 patients from 11 countries **Limitations:** all studies were set in a specialised setting, which may over-estimate the performance characteristics

	pp.1788–1799. doi:https://doi.org/10.1111/aogs.14224.			compared to their use in primary care
14	Lim, A.W.W., Hamilton, W., Hollingworth, A., Stapley, S. and Sasieni, P. (2016). Performance characteristics of visualising the cervix in symptomatic young females: a review of primary care records in females with and without cervical cancer. British Journal of General Practice, 66(644), pp.e189–e192. doi:https://doi.org/10.3399/bjgp16x683833.	Cervical	This study aimed to assess visualisation of the cervix for detection of cervical cancer in primary care in young females with gynaecological symptoms. In primary care records, 52%* (56 of 107) of women with cervical cancer had gynaecological symptoms recorded in the year before diagnosis. Of these, 39% (22 of 56) had a documented cervical examination at the time of symptomatic presentation. This resulted in specialist referral for a clinically suspicious cervix in 4 females (18%, 95% CI: 5%-40%). 2 other women whose cervix was not documented as 'suspicious' were also referred for urgent assessment: their findings on examination were recorded as 'normal' or 'red and friable'. Visualisation identified 1 out of 8 stage 1A, and 3 out of 14 stage 1B or worse cervical cancers. *this percentage was reportedly much higher (89%) in interviews. In the CPRD dataset, between 0.6% and 1.6% of females aged 20–29 years who presented with a gynaecological symptom had documented evidence of cervical examination within 14 days. None resulted in colposcopy referral.	Mixed-method study using multiple datasets: nationwide interview-based study of young females aged 18–29 years diagnosed with cervical cancer in England between 2010-2012 Also utilised GP primary care record data, cervical screening history (from the national screening database Exeter Call/Recall System), CPRD data from 1990-2010 N= 45,484 consultation data available Women aged 20-29 included

				Limitations: the study sample has a small number of cervical cancer cases. Primary care records tend to underreport unexplained symptoms, and CPRD data only includes coded symptoms, so this may be an underestimation of cervical cancer symptoms and investigations in primary care.
15	Lim, A.W., Landy, R., Castanon, A., Hollingworth, A., Hamilton, W., Dudding, N. and Sasieni, P. (2016). Cytology in the diagnosis of cervical cancer in symptomatic young women: a retrospective review. British Journal of General Practice, 66(653), pp.e871–e879. doi:https://doi.org/10.3399/bjgp16x687937.	Cervical	Cervical cancer in young women represents a diagnostic challenge because gynaecological symptoms are common, but disease is rare. Cytology has a well-established role in cervical cancer prevention but not in diagnosis. This study explored the potential of cytology as a diagnostic aid for cervical cancer in young women. 22 of 107 women with primary care record data had a symptomatic cytology test. Symptoms reported ahead of tests were: postcoital bleeding (n=17), intermenstrual bleeding (n=6), vaginal discharge (n=7), heavy or frequent periods (n=4), and dyspareunia (n=1). **Sensitivity determined using primary care records:** Sensitivity of high-grade cytology (borderline high risk, or moderate dyskaryosis, or worse): **90.9%** (95% CI = 70.8-98.8)	Data utilised with four datasets: primary care records, national audit of cervical cancer, whole population cytology from national screening and Clinical Practice Research Datalink (CPRD) Data included from 2007-2014

			Sensitivity of very high grade (severe or worse) cytology: **81.8%** (95% CI= 59.7-94.8). None of these 22 women had negative cytology. **Sensitivity determined using national audit data:** From the national audit, 36% (26/72) had a cytology test before their first screening invitation (this was presumed by the authors to be in response to symptoms, but this cannot be ascertained from the study). The sensitivity of cytology for high grade was **96.2%** (95% CI = 80-99%), and **84.6%** (95% CI = 65-96%) for very high grade. None of these women had negative cytology. The sensitivity in symptomatic women calculated from national audit data was similar to that in all women (screened and symptomatic). PPVs were calculated in this study using national audit data and CPRD data, but they included those diagnosed via symptomatic route and screening: • High-grade cytology for invasive cervical cancer was 1.01% (95% CI =0.8-1.2). • High grade (aged 25–29 years): 1.74% (95% CI = 1.6 to 1.9). • Very high grade (aged 20-24) was 2.0% (95% CI = 1.6 to 1.9) • Very high grade (aged 25-29) was 3.15% (95% CI = 2.9 to 3.4) These PPVs were derived from a cohort comprised of mostly screening data	N=107 from primary care data with symptomatic cytology test N=72 from audit data diagnosed with cervical cancer N= 1842 cytology tests in CPRD **Limitations:** Whole-population cytology from the national screening database was not recent (2007 to 2010), and the sample includes relatively small numbers of symptomatic presentations
16	Andersen, C.L., Eskelund, C.W., Siersma, V.D., Felding, P., Lind, B., Palmblad, J., Bjerrum, O.W., Friis, S., Hasselbalch, H.C. and de Fine Olivarius, N. (2015). Is thrombocytosis a valid indicator of advanced stage	Gynae	This study aimed to examine the stage distribution and prognosis of gynaecologic cancer according to levels of pre-diagnostic platelet count. Definitions used in this study: • no thrombocytosis: 150–400 × 109/L • mild: 400–550 × 109/L • severe: 550 × 109/L	Analysis of Copenhagen Primary Care Differential Count (CopDiff) Database contains details of complete blood cell counts (n=1,308,022) requested

	and high mortality of gynecological cancer? Gynecologic Oncology, [online] 139(2), pp.312–318. doi:https://doi.org/10.1016/j.ygyno.2015.09.017.		For gynaecological cancer overall, there was a significant association between the level of pre-diagnostic thrombocytosis and advanced stage of gynaecological cancer. For mild pre-diagnostic thrombocytosis, the adjusted OR for non-localised gynaecological cancer was 2.36 (95% CI 1.33–4.19), compared to patients with normal pre-diagnostic platelet count. For severe thrombocytosis, this increased to 4.54 (95% CI: 1.55–13.27). These analyses also revealed worse outcomes from gynaecological cancer with increasing level of pre-diagnostic thrombocytosis. Those with mild pre-diagnostic thrombocytosis showed a hazard ratio (HR) for death of gynaecological cancer of 1.51 (95% CI: 1.08–2.12), compared to 3.15 (95% CI: 1.95–5.08) for those with severe pre-diagnostic thrombocytosis.	by GPs for 555,039 individuals between 2000-2010 N=139 women (23.9%) with cervical cancer n=218 (37.5%) with endometrial cancer n=224 (38.6%) with ovarian cancer **Limitations:** this study is based in primary care but in Denmark, so may limit applicability to UK context. Additionally, this sample includes anybody who had a platelet count up to 3 years prior a gynaecological cancer diagnosis. Therefore, not all blood tests may have been investigating a suspected gynaecological cancer.

Topic: Safety Netting

Created by: Strategic Evidence, Cancer Research UK
Date created: March 2024

Summary:

People who have been investigated along an urgent pathway for gynaecological or breast cancer are at greater risk of being diagnosed with gynaecological cancers in the years 1-5 following referral, which could provide opportunities for earlier recognition of this higher risk group.

The sensitivity estimates summarised in the **'Investigations'** summary table suggest between 19-23% of those with ovarian cancer will have a 'below threshold' CA125 result. Clear guidance and safety netting strategies are required to ensure adequate follow up and investigations for this patient group.

Paper number	Study	Summary	Notes
17	Scott SE, Gildea C, Nicholson BD, Evans RE, Waller J, Smith D, et al. Future cancer risk after urgent suspected cancer referral in England when cancer is not found: a national cohort study. The Lancet Oncology [Internet]. 2023 Nov 1 [cited 2024 Jan 26];24(11):1242–51.	This study aimed to investigate the risk of cancer occurrence within 1-5 years of finding no cancer following an urgent suspected cancer referral. In years 1-5 post urgent referral for suspected gynaecological cancer, people who were not diagnosed with gynaecological cancer had a higher incidence rate of any subsequent cancer than the rate expected in the general population (incidence ratio 1·24 (95% CI: 1·20–1·27)), and a higher incidence rate of gynaecological cancer than the rate expected in the general population (incidence ratio 2·01 (95% CI: 1·88–2·15). Breast and gynaecological cancers made up around half of cancers occurring when no cancer was found in the first year after referral on the gynaecological pathway, and a similar proportion following referral on the breast referral pathway (Breast pathway: 40% of subsequent diagnoses were breast, 9% were gynaecological. Gynaecological pathway: 31% of subsequent diagnoses were breast, 20% were gynaecological)	National cohort study (England) Data from Cancer Waiting Times dataset and National Cancer Registration Dataset from April 2013 – March 2014 N= 63,112 subsequent cancers **Limitations:** Clinical context has changed since the data collection e.g. guideline changes which may limit the applicability of the results to current setting.

Topic: Risk Stratification

Summary:

Endometrial Cancer

Increasing age, BMI and nulliparity are associated with increased risk of endometrial cancer in those with abnormal vaginal bleeding.

Ovarian Cancer

HE4 is an emerging ovarian cancer biomarker which can be detected in both blood (serum) and urine[9]. Most evidence to date has focused on the use of serum HE4. As far as we are aware, this is not currently recommended in any referral guidelines. Sensitivity for serum HE4 ranges from 79.4%-90.2% and specificity from 75.6%-84.1% for cut-off values between 67-72 pmol/L. This data may be overestimating performance characteristics, as both studies (papers 21 and 23) used data from specialised centres or enriched primary care data.

In Paper 23, HE4 demonstrated a higher sensitivity but lower specificity than CA125. When stratified by age, HE4 demonstrated a better diagnostic performance than CA125 in women aged <50. In women aged >50, CA125 performed significantly better. When combining the two tests, sensitivity is much improved, but this impacts on specificity. Age-adjusted HE4 cut-offs (in use with CA125) improved both sensitivity and specificity for ovarian cancer in those aged >50, but only improved sensitivity in those aged <50. ROMA (Risk of Malignancy Algorithm, combination of menopausal status, CA125 and HE4) demonstrated the best diagnostic performance for both early- and late-stage disease, compared to CA125 or HE4 alone. As mentioned above, this study used enriched primary care data which may have impacted the results, but it does appear that test combinations may be superior to CA125 alone in certain patient groups.

Risk stratification tools are being developed using investigations (CA125, HE4, ultrasound), symptoms and patient factors (age, menopausal status). A model consisting of CA125 and age alone demonstrated high accuracy (AUC: 0.938) for the identification of ovarian cancer in women presenting to primary care with relevant symptoms. In Paper 24, four risk stratification tools are compared. ADNEX (a combination of menopausal status and USS findings) had the best sensitivity for both pre- and post-menopausal women, whereas the Risk of Malignancy Index (RMI, a combination of menopausal status, USS findings and CA125) had the best specificity for both pre-and post-menopausal women. Most studies included in this review used samples from specialist centres, so may not be applicable to primary care, especially those who do not have direct access to ultrasound.

[9] NHS Cancer Programme, supported by SBRI, has awarded funding to Modality LLP to evaluate a new diagnostic pathway for primary & secondary care using an algorithm that combines HE4 and CA125 tests and evidence-based numerical thresholds to guide referral decisions.

A population-based cohort study (paper 11) reported that CA125 levels equating to a 3% probability of being diagnosed with ovarian cancer were higher (53 U/ml) than the threshold typically used in guidelines (35 U/ml), and differ significantly by age:

- For those aged 40: 104 U/ml
- For those aged <50: 89 U/ml
- For those aged >50: 39 U/ml
- For those aged 70+: 32 U/ml.

Currently, CA125 is not age stratified in the guidelines.

Paper number	Study	Cancer	Summary	Notes
18	Verbakel, J.Y., Heremans, R., Wynants, L., Epstein, E., De Cock, B., Pascual, M.A., Leone, F.P.G., Sladkevicius, P., Alcazar, J.L., Van Pachterbeke, C., Jokubkiene, L., Fruscio, R., Bourne, T., Van Calster, B., Timmerman, D. and Van den Bosch, T. (2022). Risk assessment for endometrial cancer in women with abnormal vaginal bleeding: Results from the prospective IETA-1 cohort study. International Journal of Gynecology & Obstetrics. doi:https://doi.org/10.1002/ijgo.14097.	Endometrial	This study aimed to investigate the association between personal history, lifestyle characteristics and endometrial malignancy in women with abnormal vaginal bleeding. Age (increasing), BMI (increasing), and parity (nulliparity) were associated with higher risk of endometrial malignancy in women with abnormal uterine bleeding.	Diagnostic cohort study, part of the International Endometrial Tumour analysis (IETA) -1 prospective observational multicentre study (conducted between 2012-2015 across 9 European countries) N=2417 with abnormal vaginal bleeding **Limitations:** this study sample is restricted to those with bleeding already referred for ultrasound, which may limit the applicability to a primary care setting

19	Wise, M.R., Jordan, V., Lagas, A., Showell, M., Wong, N., Lensen, S. and Farquhar, C.M. (2016). Obesity and endometrial hyperplasia and cancer in premenopausal women: A systematic review. American Journal of Obstetrics and Gynecology, 214(6), pp.689.e1–689.e17. doi:https://doi.org/10.1016/j.ajog.2016.01.175.	Endometrial	This study aimed to systematically review the literature on the association between obesity and endometrial hyperplasia or cancer in premenopausal women. Of the 6 studies that adjusted for other clinical factors, 5 studies found that BMI was still an independent risk factor for endometrial hyperplasia or cancer. A dose-response relationship of BMI and increased risk of endometrial cancer was present. For the 2 studies that reported on women with BMI >25, the pooled OR was 3.85 (95% CI: 2.53-5.84). For the 3 studies that reported on women with BMI >30, the pooled OR was 5.25 (95% CI, 4.00-6.90). For the single study that reported on women with BMI >40, the pooled OR was 19.79 (95% CI: 11.18-35.03).	Systematic review Papers published up to 2015 N=9 studies included, mostly case-control studies of moderate quality **Limitations:** not all studies adjusted for all factors known to be associated with the development of endometrial cancer. For example, diabetes was adjusted for in only 1 of the studies, which may have impacted the conclusions. Additionally, the study period for many studies included is relatively dated, which may limit applicability to current UK setting.
20	Funston G, Abel G, Crosbie EJ, Hamilton W, Walter FM. Could Ovarian Cancer Prediction Models Improve the Triage of Symptomatic Women in Primary Care? A Modelling Study Using Routinely Collected Data. Cancers (Basel). 2021 Jun	Ovarian	This study aimed to (1) develop a comprehensive diagnostic prediction model from primary care data (2) compare the diagnostic performance of this model with that of a simpler model comprising age and CA125 (3) explore the potential implications of implementing different model risk thresholds on ovarian cancer detection in primary care. 279 (0.9%) were diagnosed with ovarian cancer in the 12 months following CA125 testing.	Retrospective cohort study using Clinical Practice Research Datalink (CPRD), Hospital Episode Statistics dataset and cancer registry data. English data only between 2011-2014

	9;13(12):2886. doi: 10.3390/cancers13122886.		Predictor variables included in model: age, ethnicity, BMI, height, abdominal/pelvic pain, abdominal distension, CA125 level, platelet level, and albumin level. A model consisting of CA125 and age alone demonstrated excellent discrimination and calibration for the identification of ovarian cancer in women presenting to primary care with relevant symptoms (AUC: 0.938). Including additional baseline risk factors, symptom type, and routine blood test results did not significantly improve model performance.	Note: same dataset was used as papers 11 and 13 N= 29,962 **Limitations:** to include symptoms as predictor variables, 19,691 women were excluded from the study who likely had relevant symptoms that were not coded, potentially impacting the results
21	Olsen, M., Lof, P., Stiekema, A., Broek, D., Wilthagen, E.A., Bossuyt, P.M. and Lok, C.A.R. (2021). The diagnostic accuracy of human epididymis protein 4 (HE4) for discriminating between benign and malignant pelvic masses: a systematic review and meta-analysis. Acta Obstetricia et Gynecologica Scandinavica, 100(10), pp.1788–1799. doi:https://doi.org/10.1111/aogs.14224.	Ovarian	This study aimed to obtain summary estimates of the accuracy of serum human epididymis protein (HE4) for diagnosing ovarian cancer and to compare the performance of HE4 with CA125. **HE4:** Mean sensitivity: 79.4% (95% CI: 74.1%-83.8%) Mean specificity: 84.1% (95% CI 79.6%-87.8%), for cut-off values of 67-72 pmol/L. PPV: 46.9% (40.4%-53.4%), at 15% prevalence NPV: 95.8% (95% CI 94.4%-96.7%), at 15% prevalence	Systematic review N=17 studies included, 3404 patients from 11 countries **Limitations:** all studies were set in a specialised setting, which may over-estimate the performance characteristics compared to their use in primary care

22	Davenport, C., Rai, N., Sharma, P., Deeks, J.J., Berhane, S., Mallett, S., Saha, P., Champaneria, R., Bayliss, S.E., Snell, K.I. and Sundar, S. (2022). Menopausal status, ultrasound and biomarker tests in combination for the diagnosis of ovarian cancer in symptomatic women. Cochrane Database of Systematic Reviews, 2022(7). doi:https://doi.org/10.1002/14651858.cd011964.pub2.	Ovarian	This study aimed to establish the accuracy of combinations of menopausal status, ultrasound scan (USS) findings and biomarkers for the diagnosis of ovarian cancer in pre- and postmenopausal women and compare the accuracy of different test combinations. **Definitions:** **LR2:** combination of menopausal status and USS findings **ADNEX:** combination of menopausal status and USS findings **Risk of Malignancy Index (RMI):** combination of menopausal status. USS findings and CA125 **Risk of Ovarian Malignancy Algorithm (ROMA):** combination of menopausal status and two serum biomarkers (CA125 and HE4). Sensitivity was higher in post-menopausal women, and specificity was lower in post-menopausal women, compared to pre-menopausal women, across all tests at all thresholds. The authors suggest this may reflect highly selected patient cohorts in the included studies. **Pre-menopausal women sensitivity:** ADNEX: 95.5% (95% CI 91.0% to 97.8%) LR2: 83.3% (95% CI 74.7% to 89.5%) ROMA: 77.4% (95% CI 72.7% to 81.5%) RMI: 57.2% (95% CI 50.3% to 63.8%) **Pre-menopausal women specificity:** RMI: 92.5% (95% CI 90.3% 94.2%) LR2: 90.4% (95% CI 84.6% to 94.1%) ROMA: 84.3% (95% CI 81.2% to 87.0%)	Systematic review N=59 studies included 41 studies were conducted in Europe, 12 in the Asia/Pacific region, five in North America and one in South America. **Limitations:** the studies included were conducted in a range of healthcare settings, so may not represent performance characteristics in a primary care setting.

			ADNEX: 77.8% (95% CI 67.4% to 85.5%) **Post-menopausal women sensitivity:** ADNEX: 97.6% (95% CI 95.6% to 98.7%) LR2: 94.8% (95% CI 92.3% to 96.6%) ROMA: 90.3% (95% CI 87.5% to 92.6%) RMI 78.4% (95% CI 74.6% to 81.7%). **Post-menopausal women specificity:** RMI: 85.4% (95% CI 82.0% to 88.2%) ROMA: 81.5% (95% CI 76.5% to 85.5%) LR2: 60.6% (95% CI 50.5% to 69.9%) ADNEX: 55.0% (95% CI 42.8% to 66.6%).	
23	Barr, C.E., Funston, G., Jeevan, D., Sundar, S., Mounce, L.T.A. and Crosbie, E.J. (2022). The Performance of HE4 Alone and in Combination with CA125 for the Detection of Ovarian Cancer in an Enriched Primary Care Population. Cancers, [online] 14(9), p.2124. doi:10.3390/cancers14092124. This paper is also summarised above, see paper 14.	Ovarian	This study aimed to assess whether HE4 would improve ovarian cancer diagnosis in women with symptoms in primary care. In women without ovarian cancer, CA125 was significantly higher in those under 50 years, whereas serum HE4 was significantly higher in women over 50 years. **36%** (190/525) of women without ovarian cancer over 50 years of age had a raised HE4 compared to only **11%** (65/622) of those under 50 years, suggesting age impacts serum HE4 levels. As a single biomarker, HE4 had a higher sensitivity (90.2% (95% CI 81.7–95.7) vs. 80.5% (95%CI 70.3–88.4), but lower specificity (75.6% (95%CI 73.0–78.0) vs. 92.2% (95%CI 90.4–93.6) than CA125. Risk of Ovarian Malignancy Algorithm (ROMA) includes HE4, CA125 and menopause status. This performed better in terms of AUC,	Prospective observational study in English primary care between 2018-2019 in Manchester, England N= 1229 N=82 were women with ovarian cancer **Limitations:** the sample size was enriched with secondary care data, which may have impacted the sensitivities reported. Additionally, there are relatively few cases of

			sensitivity, and specificity (sensitivity: 87.8% (95%CI 78.7–94.0) and specificity: 80.8% (95%CI 78.4–83.1), AUC: 0.959), compared to CA125 or HE4 alone. When stratified by age, HE4 demonstrated a better diagnostic performance than CA125 in women aged under 50 years (AUC 0.99 vs. AUC 0.934, p=0.06). In women aged over 50 years, CA125 performed significantly better (AUC 0.936 vs. AUC 0.869, p<0.001). **Combination of HE4 and CA125** A combination of HE4 and CA125, using a strategy where either marker was positive, proved to have the best sensitivity (92.7%, 95% CI: 84.8–97.3). However, this combination reduced specificity (70.0%, 95% CI: 67.3–72.6). In women **<50 years of age**, the combination of HE4 and CA125 where either was positive performed the best, improving sensitivity (100%, 95%CI 81.5–100) but reduced specificity (80.1%, 95%CI 76.7–83.1), which, in the study cohort would lead to an additional 67 referrals for further evaluation, of which 2 (3%) would have ovarian cancer (1 in 34), compared to using CA125 alone. In women **>50 years of age**, the combination of CA125 and HE4 where either was positive also had high sensitivity (90.6%, 95% CI: 80.7–96.5); but led to much lower specificity (58.1%, 95% CI: 53.7–62.4), which would lead to 197 extra referrals to secondary care, 1 in 28 of whom would have a malignancy (4%), compared to CA125 alone.	ovarian cancer included in this sample.

			Age and Adjusted Serum HE4 Thresholds HE4 cut-offs of 68 pmol/L and 96 pmol/L maximised the sensitivity and specificity for women under and over 50 years of age, respectively. **In women <50 years of age**, age-adjusted HE4 cut-off has the same sensitivity as standard threshold (77 pmol/L), but a lower specificity, both alone (80.4% vs. 88.4%) and in combination with CA125 (either positive: 73.5% vs. 80.1%, both positive: 97.3% vs. 98.7%). **In women >50 years of age**, the age-adjusted HE4 cut-off demonstrated a better balance of sensitivity and specificity compared to standard care threshold, with a superior specificity, both alone (74.7%vs. 60.4%) and in combination with CA125 (either positive: 71.8 vs. 58.1%, both positive: 97.1% vs. 96.6%), and with minimal reduction in sensitivity. A combination of CA125 and age-adjusted HE4 where either test was positive would lead to fewer additional referrals to secondary care than a threshold of 77 pmol/L (123 vs. 197). The combination would also diagnose an additional 5 cancers (1 in 25) compared to CA125 alone, which is 2 fewer than would be diagnosed at a HE4 threshold 77 pmol/L. ROMA had the best diagnostic performance for both early- and late-stage disease. There was no difference in the performance of CA125 and HE4 for either early- or late-stage detection.	

24	Owens, G.L., Barr, C.E., White, H., Njoku, K. and Crosbie, E.J. (2022). Urinary biomarkers for the detection of ovarian cancer: a systematic review. Carcinogenesis, [online] 43(4), pp.311–320. doi:https://doi.org/10.1093/carcin/bgac016.	Ovarian	This study aimed to review the diagnostic accuracy of urinary biomarkers for the detection of ovarian cancer. Diagnostic accuracy of urinary biomarkers varied significantly. The sensitivity and specificity of single protein/peptide assays ranged from 3.3-100% and 66.7-100%, respectively. Most biomarkers were only assessed in one or two studies, except for HE4. HE4 had a sensitivity of 51.1–89.5% and specificity of 75–100% across five independent studies.	Systematic review Papers included up until 2021 N=27 studies included Nine studies originated from North America, ten from Europe, seven from Asia and one from Australia. **Limitations:** there is significant heterogeneity between studies included in the analysis
-	Funston G, Hamilton W, Abel G, Crosbie EJ, Rous B, Walter FM. The diagnostic performance of CA125 for the detection of ovarian and non-ovarian cancer in primary care: A population-based cohort study. PLoS Med. 2020 Oct 28;17(10):e1003295. doi: 10.1371/journal.pmed.1003295 This paper is also summarised above, see paper 11.	Ovarian	This study aimed to evaluate the performance of CA125 in primary care for the detection of ovarian and non-ovarian cancers. A CA125 level of 53 U/ml equated to a probability of 3% (95% CI: 2.6–3.5) for ovarian cancer, which is higher than recommended cut-off in guidelines. Cut-offs that equated to a 3% probability varied by age: • For those aged 40: 104 U/ml • For those aged <50: 89 U/ml • For those aged >50: 39 U/ml • For those aged 70+: 32 U/ml	See above. **Limitations:** large confidence intervals are seen at the extremes of age and CA125 level, and so the cancer probabilities for very old and young women and those with very low CA125 levels may have limited reliability

Emerging Topics

Risk prediction tools

Diagnostic prediction models have been developed to improve earlier detection of ovarian cancer. These include combinations of test results, ovarian cancer risk factors and symptoms, e.g. Q Cancer Ovarian (combined symptom variables with demographics, family history and routine blood test results). Several of these tools have been incorporated into clinical computer systems which automatically alert the clinician to consider ovarian cancer investigations when relevant symptoms are present or when the risk of undiagnosed cancer reaches a certain level. However, a systematic review comparing ovarian cancer prediction models from across the world found many have not been externally validated and require further research into cost-effectiveness[10].

Alternative referral routes

Evidence investigating alternative access routes such as one-stop clinics and direct access to ultrasound is relatively limited. Smaller scale service evaluations have found over half (56%) of those referred to an ovarian one-stop clinic were able to be discharged[11]. There is limited UK based evidence investigating the impact of direct access to ultrasound for gynaecological cancers. Evidence from Denmark suggests direct access to ultrasound could be an important pathway to ensure fast evaluation of women presenting with vague non-specific symptoms of potential ovarian cancer[12,13]. Future studies should explore the impact of these pathways on patient experience, cancer outcomes, and health economics.

Academic insights:

[10] Funston, G., Hardy, V., Abel, G., Crosbie, E.J., Emery, J., Hamilton, W. and Walter, F.M. (2020). Identifying Ovarian Cancer in Symptomatic Women: A Systematic Review of Clinical Tools. Cancers, 12(12), p.3686. doi:https://doi.org/10.3390/cancers12123686.

[11] Ashmore, A.A., Gnanachandran, C., Luqman, I. and Horrocks, K. (2021). One-stop clinic for patients with suspected ovarian cancer: results from a retrospective outcome study of the referral pathway. BMC Women's Health, 21(1). doi:https://doi.org/10.1186/s12905-021-01540-w.

[12] Ladegaard Baun, M.-L., Dueholm, M., Heje, H.N., Hamilton, W., Petersen, L.K. and Vedsted, P. (2021). Direct access from general practice to transvaginal ultrasound for early detection of ovarian cancer: a feasibility study. Scandinavian Journal of Primary Health Care, [online] 39(2), pp.230–239. doi:https://doi.org/10.1080/02813432.2021.1922831.

[13] Ingeman, M.L., Ormstrup, T.E. and Vedsted, P. (2015). Direct-access to abdominal ultrasonic investigation from general practice--the role in earlier cancer diagnosis. Family Practice, [online] 32(2), pp.205–210. doi:https://doi.org/10.1093/fampra/cmv004.

- Findings from Garth Funston's work[14] found that of women with a CA125 level ≥35 U/ml, aged ≥50 years and were not diagnosed with ovarian cancer, 20.4% were subsequently diagnosed with a non-ovarian cancer. This suggests that consideration should be taken to highlight the risk of other cancers in guidelines if CA125 result is high, but ultrasound is normal. Health professionals may want to consider other cancer pathways, non-specific symptom pathways or alternative investigations.

Suspected Gynaecological Cancer Referral Guidelines: NICE and SRG

SRG	NICE NG12
Ovarian cancer • Abnormal ultrasound scan and/or CA125 level. • Ascites and/or ultrasound-confirmed pelvic or abdominal mass (that is not obviously uterine fibroids, gastrointestinal or urological in origin). **Endometrial cancer** • Any woman on hormone replacement therapy (HRT), presenting with persistent or unexplained postmenopausal bleeding, after cessation of HRT for 4 weeks. • Unscheduled vaginal bleeding in a patient taking tamoxifen • Postmenopausal bleeding. • Persistent intermenstrual bleeding, especially with other risk factors despite a normal pelvic examination • A woman presenting with a palpable abdominal or pelvic mass on examination that is not obviously uterine fibroids, gastrointestinal or urological in origin should be referred urgently for ultrasound scan and, if significant concern,	**Ovarian cancer** The recommendations for ovarian cancer apply to women aged 18 and over. Make a referral to a gynaecological cancer service using a suspected cancer pathway referral if physical examination identifies ascites and/or a pelvic or abdominal mass (which is not obviously uterine fibroids). Carry out tests in primary care if a woman (especially if aged 50 or over) reports having any of the following symptoms on a persistent or frequent basis – particularly more than 12 times per month: • persistent abdominal distension (women often refer to this as 'bloating') • feeling full (early satiety) and/or loss of appetite • pelvic or abdominal pain • increased urinary urgency and/or frequency.

[14] Funston G, Hamilton W, Abel G, Crosbie EJ, Rous B, Walter FM. The diagnostic performance of CA125 for the detection of ovarian and non-ovarian cancer in primary care: A population-based cohort study. PLoS Med. 2020 Oct 28;17(10):e1003295. doi: 10.1371/journal.pmed.1003295

simultaneously to a specialist. Awaiting results of the ultrasound scan should not delay referral.
Cervical cancer
• Any woman with clinical features (vaginal discharge, postmenopausal, postcoital and persistent intermenstrual bleeding) and abnormality suggestive of cervical cancer on examination of the cervix.
Vulval cancer
• Any unexplained vulval lump found on examination.
• Vulval bleeding due to ulceration.
• Any suspicious abnormality of the vagina on speculum examination.
Vaginal Cancer
• Any suspicious abnormality of the vagina on speculum examination
 	
Good practice points
 	
An abdominal palpation should be undertaken, CA125 blood serum level measured and urgent pelvic ultrasound scan carried out in:
 	
• any woman over 50 years who has experienced new symptoms within the last 12 months that suggest irritable bowel syndrome or
• women (especially those over 50 years) with one or more unexplained and recurrent symptoms (most days) of:
  ○ abdominal distension or persistent bloating
  ○ feeling full quickly or difficulty eating
  ○ loss of appetite
  ○ pelvic or abdominal pain
	Consider carrying out tests in primary care if a woman reports unexplained weight loss, fatigue or changes in bowel habit.
	
	Advise any woman who is not suspected of having ovarian cancer to return to her GP if her symptoms become more frequent and/or persistent.
	
	Carry out appropriate tests for ovarian cancer in any woman aged 50 or over who has experienced symptoms within the last 12 months that suggest irritable bowel syndrome (IBS), because IBS rarely presents for the first time in women of this age.
	
	Measure serum CA125 in primary care in women with symptoms that suggest ovarian cancer.
	
	If serum CA125 is 35 IU/ml or greater, arrange an ultrasound scan of the abdomen and pelvis.
	
	If the ultrasound suggests ovarian cancer, make a referral to a gynaecological cancer service using a suspected cancer pathway referral.
	
	For any woman who has normal serum CA125 (less than 35 IU/ml), or CA125 of 35 IU/ml or greater but a normal ultrasound:
	• assess her carefully for other clinical causes of her symptoms and investigate if appropriate
	• if no other clinical cause is apparent, advise her to return to her GP if her symptoms become more frequent and/or persistent.

○ increased urinary urgency and/or frequency ○ change in bowel habit A full pelvic examination, including speculum examination of the cervix, should be carried out in women presenting with: • significant alterations in their menstrual cycle • intermenstrual bleeding • postcoital bleeding • postmenopausal bleeding • vaginal discharge, or • pelvic pain A vulval examination should be carried out for any woman presenting with any vulval symptom **If there is significant concern, awaiting the results of any investigation should not delay referral.**	**Endometrial cancer** Refer women using a suspected cancer pathway referral for endometrial cancer if they are aged 55 and over with post-menopausal bleeding (unexplained vaginal bleeding more than 12 months after menstruation has stopped because of the menopause). Consider a suspected cancer pathway referral for endometrial cancer in women aged under 55 with post-menopausal bleeding. Consider a direct access ultrasound scan to assess for endometrial cancer in women aged 55 and over with: Unexplained symptoms of vaginal discharge who: • are presenting with these symptoms for the first time or • have thrombocytosis or • report haematuria Visible haematuria and: • low haemoglobin levels or • thrombocytosis, or • high blood glucose levels. **Cervical cancer** Consider a suspected cancer pathway referral for women if, on examination, the appearance of their cervix is consistent with cervical cancer. **Vulval cancer** Consider a suspected cancer pathway referral for vulval cancer in women with an unexplained vulval lump, ulceration or bleeding.

	Vaginal cancer Consider a suspected cancer pathway referral for vaginal cancer in women with an unexplained palpable mass in or at the entrance to the vagina.