NICE NG12 2026 UPDATE

Suspected Ovarian and Endometrial Cancer CA125 age-specific thresholds, HRT-associated bleeding and new referral pathways

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WHY WAS NG12 UPDATED?

NICE reviewed two areas where practice had evolved substantially:

Ovarian cancer

New evidence regarding CA125 performance

Risk varies significantly by age

Single threshold of 35 IU/ml no longer optimal

Endometrial cancer

Huge increase in HRT prescribing

More women presenting with unscheduled bleeding on HRT

Concern regarding large numbers of referrals through PMB pathways

Need to distinguish unexplained PMB from bleeding likely attributable to HRT

NICE specifically noted the 47% rise in HRT prescribing and the need for clearer guidance around HRT-associated bleeding.

OVARIAN CANCER CHANGES-WHY THIS MATTERS

Ovarian cancer remains challenging to diagnose

Most lethal gynaecological cancer and 6th most common cause of cancer death in women

Per year-In the UK **7,700 women are diagnosed** with ovarian cancer **3,900 women die** from ovarian cancer.

Symptoms are common and non-specific

Early-stage disease has excellent survival

- 5 year survival stage 1 = 95%
- 5 year survival stage 4 = 15%

Primary care plays a critical role in earlier diagnosis

- At least 50% of women are still presenting with stage 3 or 4 disease (excluding an additional 20% where the stage is unknown but likely to be advanced and incompletely staged)

Key message: The NG12 update aims to improve sensitivity of the diagnostic pathway while reducing false reassurance

NG12 OVARIAN CANCER GUIDANCE CHANGES

New age-specific CA125 thresholds

New recommendations for women under 40

Greater emphasis on ultrasound

Explicit safety-netting recommendations

Clarification that CA125 should not be viewed as simply "normal" or "abnormal"

The previous "CA125 ≥35" approach for all adults has changed

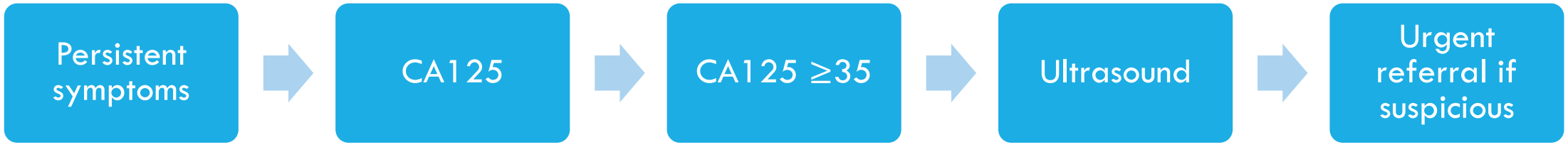
CURRENT SYMPTOMS SUGGESTIVE OF OVARIAN CANCER- UNCHANGED

- Persistent abdominal distension ("bloating")
- Early satiety
- Loss of appetite
- Pelvic or abdominal pain
- Increased urinary urgency/frequency

Consider ovarian cancer particularly when symptoms are:

- Frequent
- Persistent
- New in onset

THE PREVIOUS PATHWAY



Issues:

- Threshold derived decades ago
- Performance varies substantially with age
- Risk associated with a given CA125 changes significantly across age groups

WHY REVISIT CA125?

The same CA125 level carries different cancer risks depending on age.

CA125 of 30 in a woman aged 75 may be more concerning than the same result in a woman aged 45.

- A 35year old would have to have a CA125 of 160 before the ovarian cancer risk reaches 3% whereas a 65 year old would only need a CA125 of 37 to have a 3% risk.
- A CA125 of 100 in a 35 year old would confer approx 1-2% risk whereas in a 70 year old this would confer approx 15-20% risk

Younger women have many benign causes of elevated CA125.

Older women have a higher background risk of ovarian cancer

THE NEW NICE RECOMMENDATIONS

Age <40 years
Do not use CA125 in isolation.
Consider:
Direct urgent ultrasound
Clinical judgement
Robust safety-netting
CA125 is considered insufficiently accurate in this age group

NB CA125 is a triage tool, not a diagnostic test

BENIGN GYNAECOLOGICAL CAUSES

Condition	Typical CA125
Fibroids	35–100
Adenomyosis	35–200
Endometriosis	50–500+
Endometrioma	Often >100

Endometriosis
Adenomyosis
Uterine fibroids
Pelvic inflammatory disease
Benign ovarian cysts
Ovarian endometriomas
Menstruation
Pregnancy

BENIGN NON-GYNAECOLOGICAL CAUSES

Not an exhaustive list- Anything that irritates mesothelial surfaces:

Abdominal

- Diverticulitis
- Appendicitis
- Pancreatitis
- Inflammatory bowel disease
- Peritonitis

Hepatic

- Cirrhosis
- Chronic liver disease
- Ascites

Renal

- Renal impairment

Cardiopulmonary Causes

- Heart failure
- Pleural effusion
- Pneumonia
- Pulmonary embolism
- Chronic lung disease

Autoimmune / Inflammatory Disorders

- Systemic lupus erythematosus
- Rheumatoid arthritis
- Sjögren syndrome
- Vasculitis

OTHER MALIGNANCIES

- Endometrial cancer
- Fallopian tube cancer
- Primary peritoneal cancer
- Cervical adenocarcinoma
- Pancreatic cancer
- Gastric cancer
- Colorectal cancer
- Breast cancer
- Lung cancer
- Lymphoma

A CA125 OF 100- WHAT MIGHT IT REPRESENT?

35-year-old woman

Endometriosis

Endometrioma

Adenomyosis

Fibroids

Pregnancy

PID

Ovarian cancer (uncommon)

70-year-old woman

Ovarian cancer

Endometrial cancer

Gastrointestinal malignancy

Heart failure/ascites

Liver disease

Persistent symptoms

Measure CA125

Use age-specific thresholds

Arrange urgent ultrasound if threshold reached

PATIENTS AGED 40 AND ABOVE

NEW AGE-SPECIFIC CA125 THRESHOLDS EQUIVALENT TO APPROX 3% RISK OF OVARIAN MALIGNANCY

Age	Threshold
40–49	≥35 IU/ml
50–59	≥31 IU/ml
60–69	≥24 IU/ml
70–79	≥25 IU/ml
≥80	≥31 IU/ml

This is **not the risk in the general population,** nor in an asymptomatic woman having a CA125 checked incidentally. It is the estimated risk in the population for whom NICE intended the test to be used: women presenting with symptoms suggestive of ovarian cancer in primary care.

WHAT TO DO WITH AN ELEVATED CA125 AND A NORMAL SCAN?

COMMON SENSE NOT HARD AND FAST RULES

- Could this reasonably be being caused by something else?
- How elevated is the CA125?
- Review patient in 4-6 weeks
  - Are the symptoms persistent, better, worse?
- Repeat CA125 in 6 weeks?
  - What is the trend?
- Repeat the US in 6 weeks?
  - Can we see anything to explain it now?

Or

- I'm really worried (symptoms family hx etc)
- I don't have another explanation
- The CA125 is very raised (remember thresholds but typically over 100)
- 2ww Referral to Gyne or NSS or straight to test CT

ENDOMETRIAL CANCER: WHAT HAS CHANGED?



Previous NICE Guidance

For many GPs the message was simple:

Postmenopausal bleeding = urgent referral



This resulted in:

High numbers of referrals

Many women referred despite obvious HRT-related bleeding

Significant variation in practice

THE NEW NICE RECOMMENDATION

For women aged ≥55: Refer via the suspected cancer pathway if they have:

- Unexplained postmenopausal bleeding that cannot be attributed to HRT.

For women aged <55:

- Consider referral for unexplained PMB that cannot be attributed to HRT.

The key phrase added in 2026 is: **"cannot be attributed to HRT“**

NICE reviewed the evidence and found:

- Very little direct evidence
- Increasing use of HRT
- Existing practice already guided by British Menopause Society recommendations

The committee therefore decided that HRT-related bleeding should be managed differently from unexplained PMB and explicitly signposted clinicians to BMS/ BGCS guidance

WHAT IS UNSCHEDULED BLEEDING?

Bleeding occurring-



AFTER STARTING HRT



FOLLOWING A CHANGE IN HRT REGIMEN



OUTSIDE EXPECTED WITHDRAWAL BLEEDS



ON CONTINUOUS COMBINED HRT

This is common & does not automatically indicate endometrial cancer

THE PRACTICAL CONSEQUENCE IS:

Assess first rather than immediately referring every woman with bleeding.

Questions include:

- What type of HRT?
- When was it started?
- Has the dose recently changed?
- Is the bleeding expected?
- Are there risk factors for endometrial cancer?

The expectation is that primary care undertakes an initial assessment and optimisation of HRT before cancer referral in many cases.

BRITISH MENOPAUSE SOCIETY APPROACH

Women at low risk of endometrial cancer with bleeding:

- Shortly after starting HRT
- Following dose adjustment
- Without concerning symptoms

Can usually be managed conservatively with:

- Review of regimen
- Adjustment of progestogen dose
- Observation period

Rather than immediate urgent referral

WHEN SHOULD WE STILL WORRY?

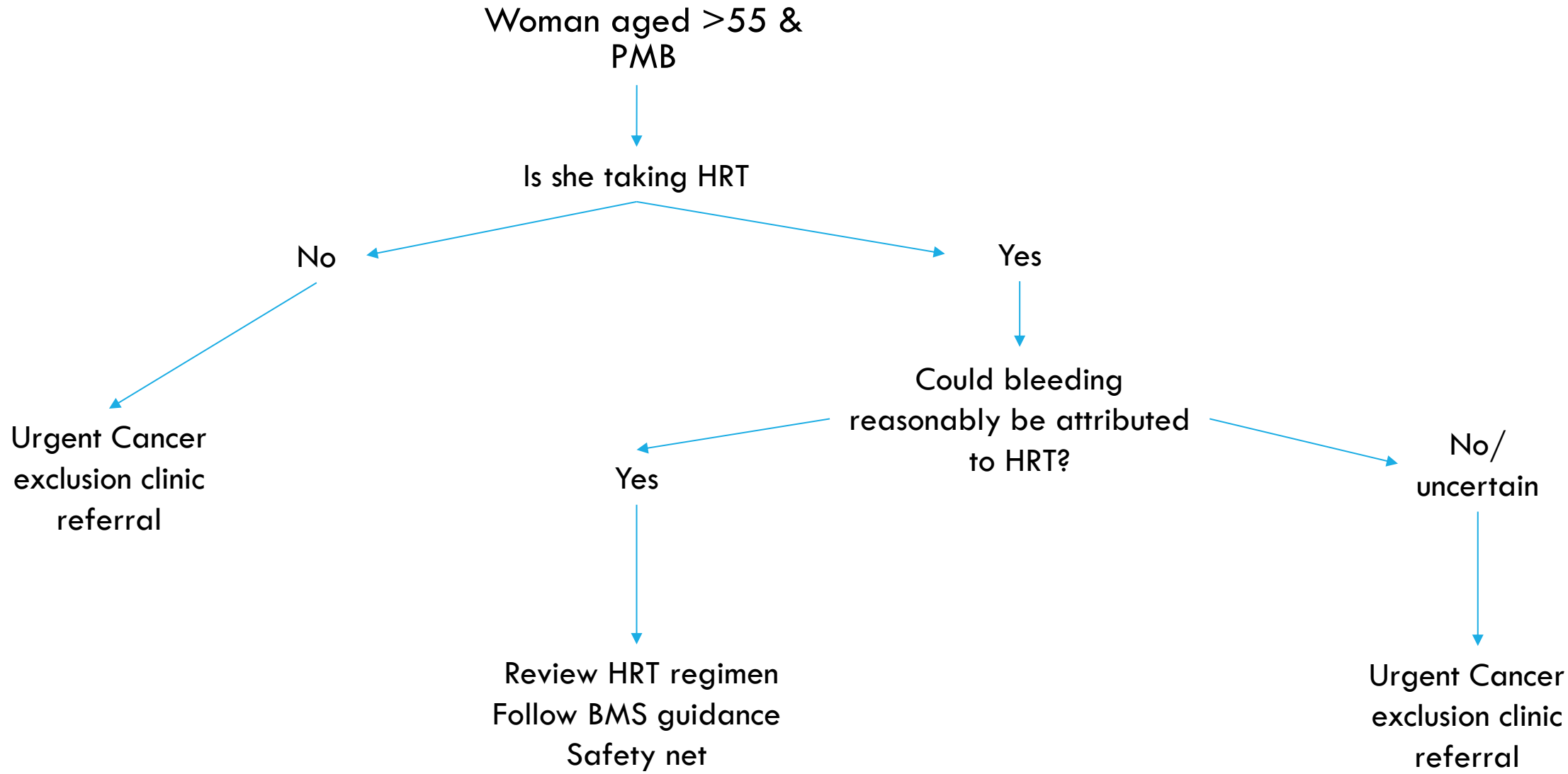
Urgent investigation should be considered if:

- Bleeding persists despite HRT adjustment
- Heavy or prolonged bleeding
- New bleeding after prolonged amenorrhoea
- Significant endometrial cancer risk factors
- Suspicious examination findings

Examples of risk factors:

- Obesity
- Diabetes
- Lynch syndrome
- Tamoxifen exposure
- Previous endometrial hyperplasia

SUGGESTED GP ALGORITHM



HOW ARE WE MANAGING THIS IN GWH?

Direct access US available (NB no current tracking of time with this)

Suspected endometrial cancer referral comes from GP

Referral and US are triaged

Patient allocated to discharge, telephone clinic, pipelle only clinic or hysteroscopy clinic

Suspected ovarian cancer referral come from GP

Referral form, tumour markers and US are triaged

Low risk- Seen directly in cancer exclusion clinic- surveillance or local surgery

High risk- additional imaging CT and/or MRI, followed by MDT, followed by appt with gyne oncology subspecialist consultant & CNS

WHAT GPS NEED TO KNOW

New referral form that reflects NG12 changes to exclude women whose PMB is attributable to HRT.

If Unscheduled bleeding algorithm followed please use US referral criteria

If referring on PMB pathway please examine patient as still may not be seen face to face as part of the referral

Please don't promise a hysteroscopy- we are moving towards biopsy only in many cases

If referring on PMB pathway please request US as per faster diagnosis standards

New referral form that reflects NG12 changes to include new CA125 thresholds

- Helpful if US requested/ done prior to referral, don't refer with raised CA125 or physical examination alone as leads to delay

CURRENT GWH REFERRAL FORM

C:\Users\Amy.Keightley\Desktop\RAC triage stuff\GWH 2ww pro forma Endometrial & Ovarian.docx

CAN WE DO BETTER THAN SYMPTOMS AND ULTRASOUND?

Current pathways rely on:

- Symptoms
- Ultrasound
- Hysteroscopy and biopsy

Challenges include:

- Large number of referrals
- Low conversions of referrals to cancers
- High false-positive rates
- Invasive investigations
- Pressure on diagnostic services

WOMEN'S CANCER RISK IDENTIFICATION — WID-EAZY

A simple outpatient swab may identify molecular changes before imaging abnormalities become obvious.

The test analyses:

- DNA methylation patterns
- Epigenetic changes associated with malignancy

The concept is similar to:

- HPV testing
- Cervical screening

But instead of looking for HPV, the test looks for molecular signatures associated with gynaecological cancers.

WOMEN'S CANCER RISK IDENTIFICATION – WID-EAZY

Potential benefits:

- Faster diagnosis
- Fewer invasive investigations
- Reduced outpatient burden
- Better resource allocation

For endometrial cancer:

- Very high sensitivity reported in initial validation studies
- Good negative predictive value
- Potential utility as a rule-out test

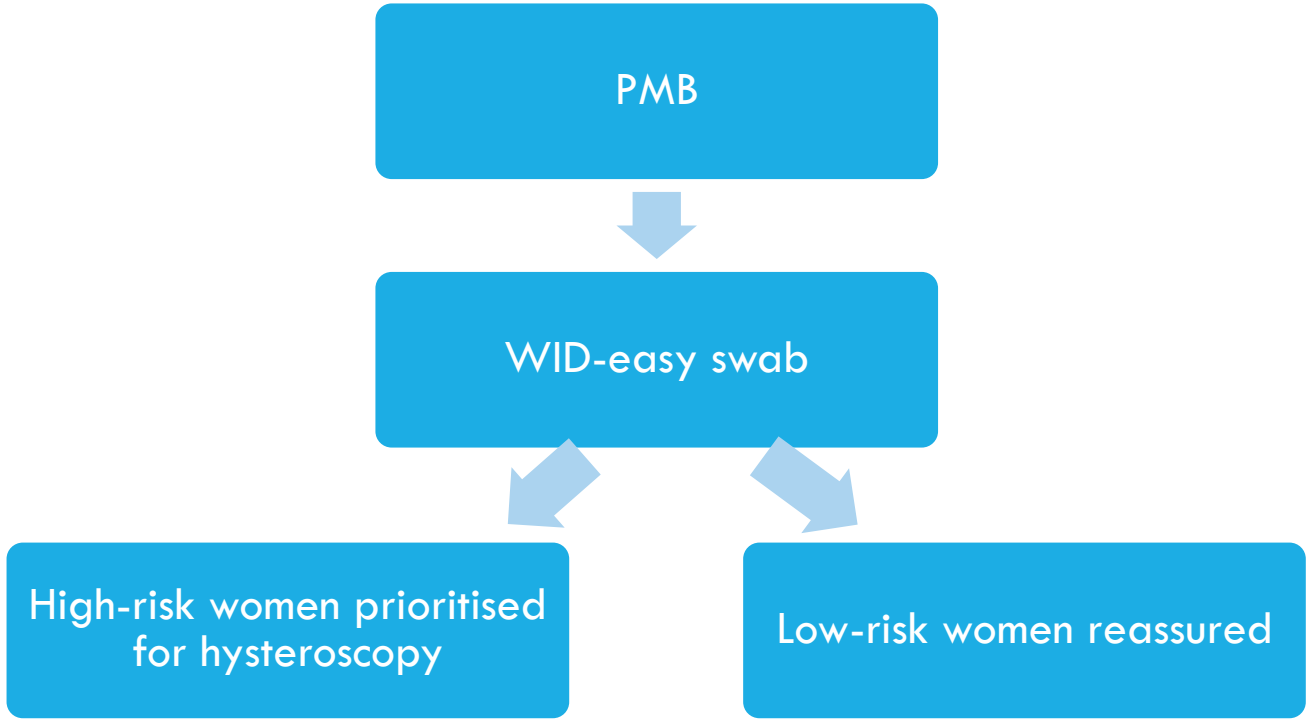
For ovarian cancer:

- Early data are promising
- Further validation ongoing

POTENTIAL FUTURE PATHWAY:

Potential advantages:

- Fewer hysteroscopies
- Reduced waiting times
- Earlier cancer diagnosis
- More sensitive than US triage



FINAL TAKE-HOME MESSAGES

Ovarian Cancer

- CA125 thresholds are now age-specific
- Women over 50 may require ultrasound despite CA125 below 35
- Women under 40 should not be assessed using CA125 alone

Endometrial Cancer

- Bleeding attributable to HRT is no longer automatically a cancer pathway referral
- GPs are expected to assess and optimise HRT before referral in many cases.
- Persistent, unexplained or high-risk bleeding still requires urgent investigation.

Safety-netting is essential