NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Diagnostics Assessment Programme

Tests in secondary care to identify people at high risk of ovarian cancer

Final scope

November 2016

1 Introduction

A surveillance review of NICE's guideline on ovarian cancer: recognition and initial management identified new evidence related to the diagnostic accuracy of serum tumour marker HE4 and the Risk for Ovarian Malignancy Algorithm (ROMA). A decision was made to update the review question 'for women with suspected ovarian cancer, what serum tumour marker tests should be routinely carried out to aid in diagnosis?' The NICE surveillance programme identified this update as potentially suitable for evaluation by the diagnostics assessment programme.

The NICE guideline on ovarian cancer specified that the groups covered are:

- Adults (18 years and older) with epithelial ovarian cancer.
- Adults with fallopian tube carcinoma.
- Adults with primary peritoneal carcinoma.
- Adults with suspected ovarian or primary peritoneal carcinoma.
- Adults with borderline ovarian cancer.

The following groups are not covered:

- Children (younger than 18 years) with ovarian malignancy.
- People with pseudomyxoma peritonei.
- People with relapsed ovarian, fallopian tube or peritoneal cancer.
- People with germ cell tumours of the ovary.
- People with sex cord stromal tumours of the ovary.

The final scope was informed by discussions at the scoping workshop held on 18 October 2016 and the assessment subgroup meeting held on 2 November 2016. A glossary of terms and a list of abbreviations are provided in appendices B and C.

2 Description of the technologies

This section describes the properties of the diagnostic technologies based on information provided to NICE by manufacturers and clinical experts, and on information available in the public domain. NICE has not carried out an independent evaluation of the descriptions.

2.1 Purpose of the medical technologies

Serum tumour markers and ultrasound scans are used in secondary care to help determine if a person referred with suspected ovarian cancer is likely to have an ovarian malignancy. The tests inform decisions about whether they should be referred to a gynaecological oncology multidisciplinary team for further assessment and treatment.

Reducing the number of people with ovarian cancer who are not referred for further specialist care has the potential to avoid delays in confirming diagnosis and initiating treatment. It is particularly important that ovarian cancer is identified as soon as possible because earlier stage ovarian cancer is associated with improved patient prognosis compared with later stage ovarian cancer. Conversely, testing could lead to more accurate recognition of people referred to secondary care with suspected ovarian cancer who do not have the condition. This has the potential to reduce inappropriate referrals to tertiary care for further assessment and treatment, and the costs, potential unnecessary surgery and anxiety that this can cause.

Currently, serum biomarker CA125 (cancer antigen 125) is widely-used. However, patients with early stage epithelial ovarian cancer often do not exhibit elevated CA125 levels. In addition, elevated levels of CA125 are not always indicative of ovarian cancer, because they may be raised because of other causes, such as endometriosis, fibroids, pregnancy or pelvic inflammatory disease

2.2 Product properties

2.2.1 HE4 serum assays

Serum biomarker HE4 (human epididymis protein 4) has been suggested as a more sensitive marker of epithelial ovarian cancer than CA125 (particularly in early stage cancers) and also as being less frequently elevated in benign ovarian tumours and in other conditions such as endometriosis. Elevated levels of HE4 have been reported in epithelial ovarian cancer (although the extent can vary according to the histological subtype) but levels are rarely elevated in non-epithelial ovarian cancer (sex cord stromal tumours and germ cell tumours). Elevated serum HE4 levels have also been detected in people

with renal failure, endometrial cancer, primary lung adenocarcinoma and transitional cell carcinomas (Karlsen et al. 2014).

Risk of Ovarian Malignancy Algorithm (ROMA)

HE4 assays are recommended for use in conjunction with CA125 assays, using the Risk of Ovarian Malignancy Algorithm (ROMA). The ROMA combines a person's serum CA125 and HE4 levels with their menopausal status to produce an estimate of the probability that they have epithelial ovarian cancer. Initially a predictive index (PI) value is calculated using a formula which differs depending on whether the person is pre- or postmenopausal (equations (1) and (2) in table 1). This PI value can then be used to calculate the ROMA score (using equation (3) in table 1; Moore et al. 2009).

Table 1 ROMA equations

Premenopausal people: PI = –12.0 + 2.38 × LN [HE4] + 0.0626 × LN [CA125]	(1)
Postmenopausal people: PI = –8.09 + 1.04 × LN [HE4] + 0.732 × LN [CA125]	(2)
ROMA (%) = exp (PI) / [1 + exp (PI)] × 100%	(3)
Where 'PI' is predictive index; [HE4] is the measured serum concentration of HE4 in pM; [CA125] is the measured serum concertation of CA125 in U/ml; 'LN' is natural logarithm.	

Cut-off values for the ROMA score are set to stratify individuals as being at a high or low risk of having epithelial ovarian cancer. Designated cut-off values can vary between studies; for example, Li et al. 2012, a systematic review of tests that predicted epithelial ovarian cancer, reported cut-off values for ROMA that varied between 7.4% and 13.1% in premenopausal and 10.9% and 27.7% in postmenopausal people. Recommended ROMA cut-off values may vary depending on which HE4 and CA125 assays are being used.

Clinical experts commented that ultrasound scans would be used prior to carrying out ROMA assessment in clinical practice in order to confirm the presence of a pelvic mass.

The ROMA has not been validated for the following patient groups: people previously treated for malignancy, people currently being treated with chemotherapy, and people less than 18 years of age.

Three assays that measure HE4 serum levels using automated immunoassay analysers, and that are available to the NHS, have been identified. Summary characteristics of these assays are provided in table 2 and further details are provided in the following text.

Table 2 Summary of serum HE4 assays

Name of assay	Company	Detection limit	Detection range	Assay time
ARCHITECT HE4	Abbott Diagnostics	15 pmol/L	20 – 1500 pmol/L	28 minutes*
Lumipulse G HE4	Fujirebio Diagnostics	3.5 pmol/L	20-1500 pmol/L	35 minutes**
Elecsys HE4 - Human epididymal protein 4	Roche Diagnostics	15 pmol/L	15-1500 pmol/L	18 minutes***

Abbreviation: pmol/L, picomoles per litre

* Time is for analyser to complete sample analysis once initiated.

** Using the LUMIPULSE G1200 instrument; time is for 1 sample, time for all 42 results is 55 minutes

*** Report time is dependent on whether other tests are carried out on the same sample, but typically take less than 30 minutes.

All the HE4 assays above use anti-HE4 antibodies to capture HE4 and attach a signal-generating label, which can be used to detect the amount of antibody-HE4 complexes in a sample. The signal generating label used differs between assays.

2.2.1.1 ARCHITECT HE4 (Abbott Diagnostics)

The ARCHITECT HE4 assay is a chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of HE4 in human serum. The assay is designed for use on the Abbott ARCHITECT i2000SR or ARCHITECT i1000SR immunoassay analysers.

Additional material required to run the assay are: ARCHITECT HE4 assay software file, ARCHITECT HE4 calibrators, ARCHITECT HE4 controls, ARCHITECT multi-assay manual diluent, ARCHITECT pre-trigger solution, ARCHITECT trigger solution, ARCHITECT wash buffer, ARCHITECT reaction

vessels, ARCHITECT sample cups, ARCHITECT septum and ARCHITECT replacement caps.

Results of the assay are intended to be used in conjunction with the ARCHITECT CA 125 II assay as an aid in estimating the risk of epithelial ovarian cancer in people presenting with a pelvic mass who will undergo surgical intervention. The company recommends that the HE4 assay results are used in the ROMA, using the following cut-off values for ROMA scores, based on obtaining a specificity of 75%:

Premenopausal patients

- ROMA value ≥ 7.4% indicates high risk of finding epithelial ovarian cancer
- ROMA value < 7.4% indicates low risk of finding epithelial ovarian cancer

Postmenopausal patients

- ROMA value ≥ 25.3% indicates high risk of finding epithelial ovarian cancer
- ROMA value < 25.3% indicates low risk of finding epithelial ovarian cancer

These results must be interpreted in conjunction with other methods and clinical data (for example symptoms and medical history) in accordance with standard clinical management guidelines. The company states that additional testing should be done if HE4 results are inconsistent with clinical evidence.

2.2.1.2 Lumipulse G HE4 (Fujirebio Diagnostics)

The Lumipulse G HE4 is a Chemiluminescent Enzyme Immunoassay (CLEIA) for the quantitative measurement of HE4 in human serum. The assay is designed for use on the LUMIPULSE G System (either the LUMIPULSE G1200 or LUMIPULSE G600 immunoassay analysers). Samples are run using immunoreaction cartridges, which contain reagents and into which samples are added. Further materials required for the assay are: Lumipulse G HE4 calibrators, Lumipulse G substrate solution, Lumipulse G wash solution, Lumipulse G specimen diluent I, sampling tips for Lumipulse system, soda lime for Lumipulse system and Lumipulse G dilution cartridges.

The assay is intended for use in conjunction with CA125 levels (measured using the Lumipulse G CA125II assay) as an aid in estimating the risk of epithelial ovarian cancer in premenopausal and postmenopausal women presenting with a pelvic mass who will undergo surgical intervention.

The company recommend the HE4 results are used in the ROMA and suggest the following cut-off values for ROMA scores, based on obtaining a specificity of 75%:

Premenopausal people

- ROMA value ≥ 13.1% indicates high risk of finding epithelial ovarian cancer
- ROMA value < 13.1% indicates low risk of finding epithelial ovarian cancer

Postmenopausal people

- ROMA value ≥ 27.7% indicates high risk of finding epithelial ovarian cancer
- ROMA value < 27.7% indicates low risk of finding epithelial ovarian cancer

Results should be interpreted in conjunction with further methods and clinical data (clinical findings, age, family history and imaging results), in accordance with standard clinical management guidelines.

A further HE4 assay is also available from Fujirebio: the HE4 EIA assay, a manual, enzyme immunometric assay for the quantitative determination of HE4 in human serum. Clinical experts commented that manual kits would be unlikely to be used in routine practice in the NHS; therefore this assay has not been included in the scope of this assessment.

2.2.1.3 Elecsys HE4 immunoassay (Roche Diagnostics)

The Elecsys HE4 is an immunoassay test that uses Roche's ElectroChemiLuminescence (ECL) detection technology to quantity HE4 levels. The assay uses anti-HE4 mouse monoclonal antibodies to capture HE4 in a serum sample and label it with a ruthenium complex. Application of a voltage to the samples then induces chemiluminescent emissions which are measured by a photomultiplier.

The assay is designed for use on the following immunoassay analysers: Modular analytics E170, cobas e 411, cobas e 601/e 602 and cobas e 801. Additional materials required for the HE4 assay are HE4 CalSet, PreciControl HE4 and Diluent MultiAssay. Further materials are also required for the general running of analysers; such as wash and cleaning solutions and disposable consumables.

The assay is intended to be used in conjunction with the Elecsys CA 125 II assay as an aid in estimating the risk of epithelial ovarian cancer in premenopausal and postmenopausal people with a pelvic mass. The company recommend that the HE4 and CA125 assay results are used in the ROMA. The company suggest the following cut-off values for ROMA scores, based on obtaining a specificity of 75%:

Premenopausal patients

- ROMA value ≥ 11.4% indicates high risk of finding epithelial ovarian cancer

- ROMA value < 11.4% indicates low risk of finding epithelial ovarian cancer

Postmenopausal patients

- ROMA value ≥ 29.9% indicates high risk of finding epithelial ovarian cancer
- ROMA value < 29.9% indicates low risk of finding epithelial ovarian cancer

These results must be interpreted in conjunction with other methods and clinical data (for example symptoms and medical history) in accordance with standard clinical management guidelines. The company states that additional testing should be done if HE4 results are inconsistent with clinical evidence.

2.2.2. Simple Rules ultrasound classification system (International Ovarian Tumour Analysis [IOTA] group)

Simple Rules is a morphological scoring system based on the presence of ultrasound features (described as rules) to characterise an ovarian mass as benign or malignant, and was developed by the International Ovarian Tumour Analysis (IOTA) group. There are 5 rules that predict a malignant tumour (M-rules) and 5 rules that predict a benign tumour (B-rules), as described in Timmerman et al. (2008) and summarised in table 4. Terms and definitions used in the classification system are as defined in a previous publication (Timmerman et al. 2000).

Table 4 Simple Rules ultrasound classification system

M-rules (rules for predicting a malignant tumour)	**B-rules** (rules for predicting a benign tumour)
• Irregular solid tumour • Ascites present • Four or more papillary structures • Irregular multilocular solid tumour with largest diameter 100mm or more • Very strong blood flow (colour score 4).	• Unilocular • Solid components present, with largest solid component having a largest diameter of less than 7mm • Acoustic shadows present • Smooth multilocular tumour with largest diameter less than 100mm • No blood flow (colour score 1).

If any M-rules apply (and no B-rules) then the mass is classified as malignant. If any B-rules apply (and no M-rules) then the mass is classified as benign. However, if both M- and B-rules apply, or neither, then the mass is unclassifiable. The group state that there are several options in this situation:

- Classify the mass as malignant,
- Refer the patient to an expert ultrasound investigator for a second opinion,
- The use of alternative imaging techniques is currently being investigated, or

- Use the Simple Rules risk model (Timmerman et al. 2016) to calculate risk of malignancy using the ultrasound features identified in the Simple Rules classification system.

Clinical experts commented that in practice unclassifiable results are likely to be considered as if malignant, and would result in a referral to a gynaecological oncology multidisciplinary team for further assessment.

No specific make or model of ultrasound device is required to carry out the Simples Rules system. A transvaginal probe is required and image quality must be of sufficient quality to allow the ultrasound features specified by the Simple Rules system to be seen. The group state that the approach to evaluating masses required is no more time consuming than a standard ultrasound scan.

The IOTA group organise 1 day courses that teach the terminology for classifying masses required by this system, with participants assessed with a multiple choice test. These courses are organised within relevant conferences with no additional fees charged for the course (beyond conference registration fees). An on-line training tool which will be freely accessible to NHS practitioners is also being developed. In addition to this training, the group also recommend that practitioners should have completed 300 gynaecological scans.

The Simple Rules system is not recommended for use with people who are pregnant. Physiological changes during pregnancy can alter the appearance of ovarian masses which can affect classification using Simple Rules, and the system has not been validated in this group.

2.2.3 The Assessment of Different NEoplasias in the adneXa (ADNEX) model (IOTA group)

The ADNEX model was developed by the IOTA group and contains 3 clinical and 6 ultrasound derived predictors, as described in table 5. Serum CA125 levels are not required to run the model, but are preferable to include because it improves specificity in discriminating between different malignancies. Terminology used in the model is as defined in a previous publication by the IOTA group (Timmerman et al. 2000).

Table 5 Criteria included in the ADNEX model

Clinical predictors	Ultrasound derived predictors
• Age (in years) • Serum CA125 level (U/ml) • Type of centre (oncology centre or	• Maximum diameter of lesion (mm) • proportion of solid tissue (ratio of the maximum diameter of the

other hospital)*	largest solid component and the maximum diameter of the lesion) • more than 10 cyst locules (yes or no) • number of papillary projections (0, 1, 2, 3 or >3) • acoustic shadows (yes or no) • ascites (yes or no)
* 'oncology centres' defined as tertiary referral centres with a specific gynaecology oncology unit (Van Calster et al. 2014).	

Based on these predictors, the ADNEX model estimates the probability that a pelvic tumour is benign or malignant. In addition, the model also estimates probabilities that a tumour is borderline, stage I cancer, stage II-IV cancer, or secondary metastatic cancer. This can be used to inform decisions about treatment, as described in Van Calster et al. (2015).

The ultrasound variables required for the ADNEX model require B mode imaging (that is, there is no requirement for Doppler or 3D imaging). The group state that any modern ultrasound machine can be used, as long as it has a high frequency (more than 6Hz) transvaginal probe.

The IOTA group organise 1 day courses which teach the terms, definitions and measurement techniques required to assess pelvic masses required for the ADNEX model. The course is followed by a multiple choice test; the group state that participants passing the test should be capable of assessing the ultrasound features required for the ADNEX model. In addition, online lectures and educational materials are available on the IOTA website and an online training tool specifically for NHS practitioners is being developed, and will be available in the near future.

The ADNEX model formulas are available in published literature (Van Calster et al. 2014; appendix D). An ADNEX model programme is also freely available from the IOTA group website. An ADNEX model app for smartphones is also available for download at a cost.

The ADNEX model has not been validated for use in people who are pregnant.

2.2.4 Risk of Malignancy Index I (RMI I)

The RMI I tool combines 3 pre-surgical features (measured serum CA125 levels, ultrasound imaging and menopausal status) to create an index score - as shown in equation (4) below (from Appendix D in the NICE guideline on ovarian cancer). Notably, RMI I scores are zero if none of the specified features of the ultrasound score (U) are present.

RMI I score = U x M x CA125 (4)

U: ultrasound score – 1 point scored for the presence of each of the following features: multilocular cysts, solid areas, metastases, ascites, bilateral lesions. U=0 (0 points), U=1 (1 point) or U=3 (2-5 points).

M: menopause score – M=1 (premenopausal) or M=3 (postmenopausal). The classification of 'post-menopausal' is a woman who has had no period for more than 1 year or a woman over 50 who has had a hysterectomy.

CA125: serum CA125 concentration – measured in IU/ml

The NICE guideline on ovarian cancer recommends that people with an RMI I score of 250 or greater should be referred to a specialist multidisciplinary team (see the comparator for this assessment – section 4). However, this guideline also includes a research recommendation stating that further research should be undertaken to determine the optimum RMI I threshold that should be applied in secondary care to guide the management of people with suspected ovarian cancer. The guideline notes that there was variation in the evidence base at that time with regard to the optimum RMI I threshold to use in secondary care, and that the value used will have implications for the management options considered, and the number of people who will be referred for specialist treatment.

The Scottish Intercollegiate Guidelines Network (SIGN) guideline on the management of epithelial ovarian cancer (SIGN 135) recommends referring people with an RMI I score greater than 200 to a gynaecological oncology multidisciplinary team. In addition, the Royal College of Obstetricians and Gynaecologists (RCOG) guideline on ovarian cysts in postmenopausal women recommends the use of 200 as a threshold to predict the likelihood of ovarian cancer, although noting that the threshold of 250 is equally acceptable.

2.2.5 OVA2/Overa (Vermillion)

The Overa assay is a CE marked qualitative serum test that combines the results of 5 immunoassays into a single numeric result (the Overa Risk Score). The 5 biomarkers included in the test are:

- Follicle-stimulating Hormone (FSH),
- Human Epididymis Protein 4 (HE4),
- Apolipoprotein A-1 (Apo A-1),
- Transferrin (TRF), and
- Cancer Antigen 125 (CA 125).

The levels of these biomarkers present in serum are determined using immunoassays run on the Roche cobas 6000 system. The Overa Risk Score is generated by the company's OvaCalc software, with results ranging between 0.0 and 10.0. A risk score of less than 5.0 indicates a low probability of malignancy and a score of 5.0 or more indicates a high probability of malignancy.

The assay is indicated for use in people over the age of 18 years with a pelvic mass for whom surgery may be considered. It is intended for use as part of preoperative assessment to help decide if a person presenting with a pelvic mass has a high or low risk of ovarian malignancy.

The company state that test results must be interpreted in conjunction with an independent clinical and imaging evaluation, and that test is not intended for use in screening or as a stand-alone assay.

3 Target condition

3.1 Ovarian cancer

Ovarian cancer arises from cells in, or near, the ovaries - a pair of organs situated in the pelvis that form part of the female reproductive system. There were approximately 7,200 new cases of ovarian cancer in the UK in 2013, accounting for 2% of all new cancer cases. The incidence of ovarian cancer increases with age, with more than half of cases between 2011-2013 occurring in people aged 65 years and over. There were approximately 50 new cases in people under 19 years old in this time period, approximately 550 new cases in people under 40 years and approximately 1,300 new cases in people under 50 years (Cancer Research UK, Ovarian cancer statistics).

Pelvic masses can also be caused by ovarian cysts – fluid filled sacs that develop on, or in, an ovary. While most ovarian cysts will be benign, some can become malignant. The Royal College of Obstetricians and

Gynaecologists (RCOG) management of suspected ovarian masses in premenopausal women guideline states that the incidence of a symptomatic ovarian cyst in a premenopausal person being malignant is approximately 1 in 1000 (rising to 3 in 1000 at the age of 50).

3.1.1. Types of ovarian cancer

Primary ovarian tumours are classified based on the tissue that they develop from, with 3 main types:

- epithelial ovarian tumours
- sex cord-stromal tumours of the ovary
- germ cell tumours of the ovary.

Epithelial tumours are the most common and occur in several different histological subtypes; including serous, endometrioid, clear cell and mucinous. Each subtype of tumour can be benign, malignant or intermediate (borderline malignant). Approximately 90% of primary ovarian cancers are malignant epithelial tumours (epithelial carcinomas). Serous carcinomas are the most common, with different epithelial histology cancers exhibiting varied behaviours and expression of markers.

Non-epithelial ovarian cancers include malignant germ cell tumours and malignant sex cord-stromal tumours, and make up a higher proportion of ovarian cancer in people who are premenopausal (Myers et al. 2006; Colombo et al. 2009).

3.1.2. Stages of ovarian cancer

Ovarian cancer is staged using the FIGO system, which uses 4 stages to describe ovarian cancer. A simplified description is provided below:

- Stage 1 – cancer is only in the ovaries,
- Stage 2 – cancer has grown outside of the ovaries but is still within the pelvis
- Stage 3 – cancer has spread outside the pelvis into the abdominal cavity, or into lymph nodes in the upper abdomen, groin or behind the womb
- Stage 4 - cancer has spread to other organs (such as the lungs, liver, spleen, lymph nodes in the groin).

In addition, ovarian cancer can also be graded based on how differentiated cells appear; either grade 1 (well differentiated), grade 2 (moderately differentiated) or grade 3 (poorly differentiated/undifferentiated). Grading can give an indication of how likely it is that the cancer will spread. Further detail

on staging ovarian cancer can be found on the Cancer Research UK website (stages of ovarian cancer) or Prat et al. (2015).

Ovarian cancer is often only diagnosed at later stages, due to variable presentation and the difficulty in recognising early stage symptoms, which can be attributed to other conditions such as irritable bowel syndrome or pre-menstrual syndrome (NHS choices, Ovarian cancer - Symptoms). Of the people for whom stage of ovarian cancer at diagnosis is known, 63% were diagnosed at stage II, III or IV in England in 2013 (Cancer Research UK, Ovarian cancer statistics).

The prognosis of people diagnosed with ovarian cancer is strongly dependent on their stage at diagnosis. Of people diagnosed at stage I in England in 2012, 97% survived for at least 1 year, compared with 53% of people diagnosed at stage IV (Public Health England; Cancer Survival in England by stage, 2014).

3.2 Diagnostic and care pathway

Several guidelines provide recommendations on the diagnosis and management of ovarian cancer:

- NICE guideline on Ovarian cancer: recognition and initial management (CG122)
- NICE guideline on Suspected cancer: recognition and referral (NG12)
- Scottish Intercollegiate Guidelines Network (SIGN) guideline on the management of epithelial ovarian cancer (135)
- The RCOG guideline on the management of suspected ovarian masses in premenopausal women
- The RCOG guideline on Ovarian Cysts in Postmenopausal Women
- The Royal College of Radiologists' iRefer referral guidelines
- British Gynaecological Cancer Society (BGCS) Guidelines for Epithelial Ovarian / Fallopian tube / Primary Peritoneal Cancer: Recommendations for Practice (draft – currently in development)

The diagnosis and management of ovarian cancer is further described in the NICE pathway on ovarian cancer and in NICE's quality standard on ovarian cancer.

A NICE guideline on the diagnosis and management of endometriosis, a condition which can lead to false positive results in tests for ovarian cancer, is currently in development (expected publication in September 2017).

3.2.1 Initial assessment

Primary care

The NICE guideline on ovarian cancer recommends an urgent referral if a physical examination in primary care identifies ascites and/or a pelvic or abdominal mass (which is not obviously uterine fibroids). The scope of this guideline includes adults (18 years and older) with epithelial ovarian cancer, but does not cover people with either germ cell or sex cord stromal tumours of the ovary. Recommendations from this guideline have also been incorporated in the NICE guideline on suspected cancer.

Testing is recommended for people (especially if 50 years or over) having any of the following symptoms on a persistent or frequent basis (particularly more than 12 times per month):

- persistent abdominal distension (often referred to as 'bloating')
- feeling full (early satiety) and/or loss of appetite
- pelvic or abdominal pain
- increased urinary urgency and/or frequency.

Testing is also recommended for any woman of 50 years or over who has experienced symptoms within the last 12 months that suggest irritable bowel syndrome. The guideline also recommends considering further testing in primary care if a woman reports unexplained weight loss, fatigue or changes in bowel habit.

For people presenting to primary care with symptoms that suggest ovarian cancer, serum CA125 levels should be measured. If serum CA125 is 35 IU per millilitre or greater, an ultrasound scan of the abdomen and pelvis should be arranged. If this ultrasound suggests ovarian cancer, then the person should be urgently referred to secondary care for further investigation. An internet-based survey of GPs in the West Midlands (Moss et al. 2013) reported that an urgent referral to secondary care is often made in the event of raised CA125 levels even if an ultrasound scan doesn’t suggest ovarian cancer.

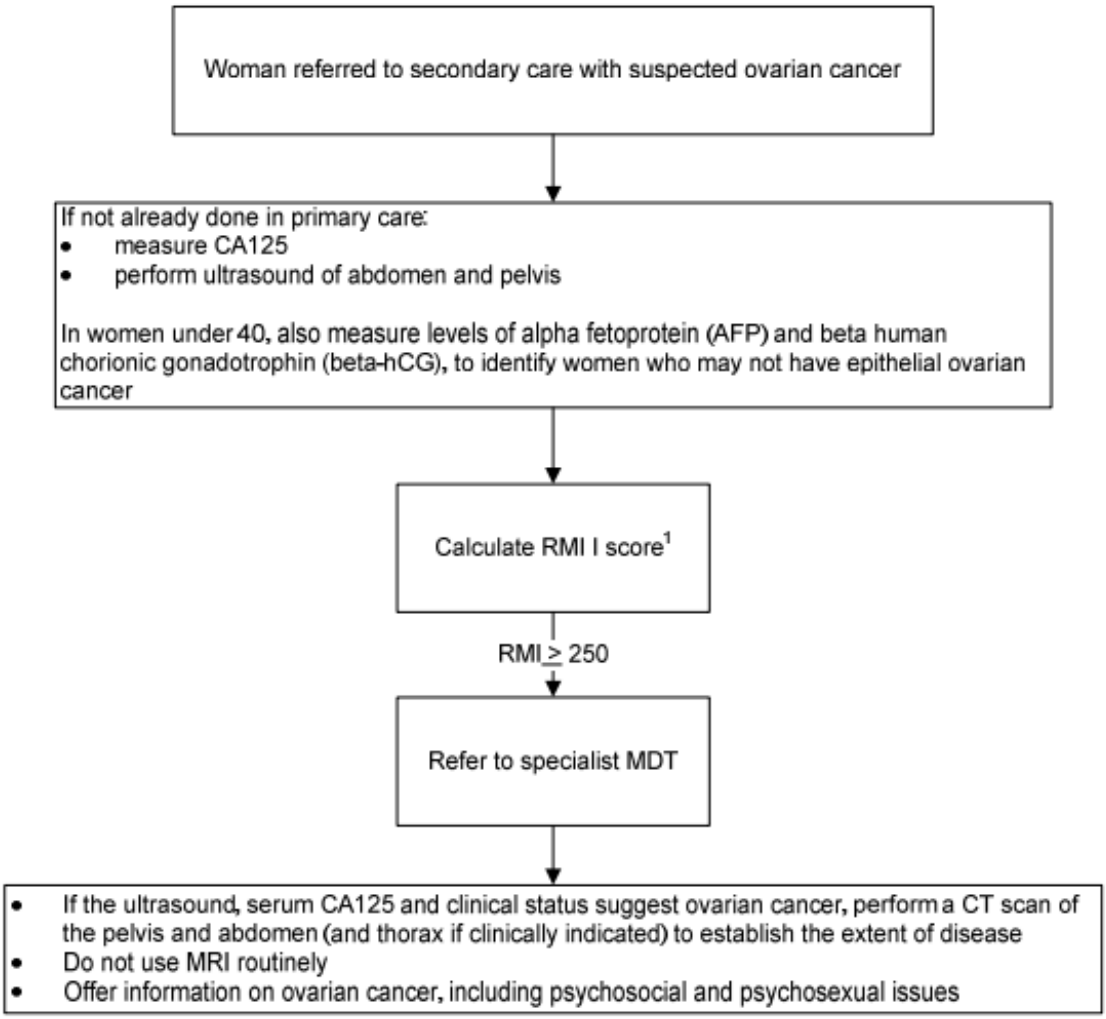
An algorithm describing this pathway is provided in Appendix A.

Secondary care

The NICE guideline on ovarian cancer provides recommendations on establishing a diagnosis of suspected ovarian cancer in secondary care. This is summarised in figure 1 below. An ultrasound of the abdomen and pelvis is

recommended as the first imaging test in secondary care for people with suspected ovarian cancer (if not already performed in primary care).

Figure 1 Algorithm describing testing in secondary care for people referred with suspected ovarian cancer (from NICE CG122 full guideline). [1] Risk of malignancy index (RMI I) calculated as described in Appendix D of NICE CG122.



After performing an ultrasound, the guideline recommends calculating a risk of malignancy index I (RMI I) score. This score is based on observed ultrasound characteristics, CA125 serum levels and menopausal status. People with an RMI I score of 250 or greater should be referred to a specialist multidisciplinary team. The SIGN guideline on management of epithelial ovarian cancer also recommends using the RMI I score to predict the likelihood of ovarian cancer. However, referral to a gynaecology-oncology multidisciplinary team is recommended if the produced score is greater than 200.

Clinical experts commented that people are sometimes referred to multidisciplinary teams solely on the basis of observed ultrasound features (that is, without raised CA125 levels). This is because CA125 levels are often not raised in non-epithelial ovarian cancers, and also in some cases of epithelial cancer (particularly early stage). In addition, referrals to tertiary care are also sometimes made solely on the basis of elevated CA125 levels. Clinical experts also commented that RMI I scores are often only used if malignancy can't be readily determined from CA125 levels or ultrasound scans alone.

Clinical experts also commented that borderline ovarian tumours should be considered by gynaecological oncology multidisciplinary teams, as management and follow-up can be complex.

The RCOG guideline on the management of suspected ovarian masses in premenopausal women recommends the use of a pelvic ultrasound as the single most effective way of evaluating an ovarian mass, with transvaginal ultrasonography noted as preferable to transabdominal ultrasound because of higher sensitivity. This guideline also states that if the clinical picture and ultrasonography findings indicate that malignant disease is a possibility, then referral to a gynaecological oncology multidisciplinary team is appropriate. The RCOG guideline on ovarian cysts in postmenopausal women also recommends the use of a transvaginal pelvic ultrasound to evaluate ovarian cysts in postmenopausal people, and provides further recommendations related to ultrasound scanning.

These 2 guidelines from the RCOG also suggest that the IOTA Simple Rules classification system can be used as an alternative to the RMI I index for practitioners experienced in using this technique. People with an ovarian mass with any of the M-rules ultrasound findings should be referred to a gynaecological oncology service. If an ovarian cyst is not classifiable using this system, further investigation by a specialist in gynaecological ultrasound is required.

The Royal College of Radiologists' iRefer radiological investigation guidelines tool states that most ovarian lesions are initially identified based on clinical examination or ultrasound scan. The guideline recommends a combination of transabdominal ultrasound and transvaginal ultrasound (supplemented by colour Doppler). In addition, the use of MRI is recommended for specialised investigation and is noted as useful for problem-solving, for example when pelvic lesions appear indeterminate on ultrasound scans.

Non-epithelial ovarian cancer

The NICE guideline on ovarian cancer recommends measuring the levels of alpha fetoprotein (AFP) and beta human chorionic gonadotrophin (beta-hCG), in addition to CA125, in people under 40 years with suspected ovarian cancer to identify non-epithelial ovarian cancer. The RCOG guideline on the management of suspected ovarian masses in premenopausal women recommends measuring lactate dehydrogenase (LDH), AFP and hCG levels in people aged under 40 years with a complex ovarian mass because of the possibility of germ cell tumours.

The BGCS draft ovarian cancer guidelines recommends measuring AFP, beta-hCG, hormonal levels (such as oestrogen, testosterone, prolactin, sex hormone-binding globulin, and thyroid hormones) and inhinin, in addition to CA125, to identify non-epithelial ovarian cancer in people under 40 years with suspected ovarian cancer (especially if there is radiological suspicion of a germ cell tumour).

3.2.2. Further imaging and tissue diagnosis

Imaging is used to characterise the extent and spread of ovarian cancer. This information can be used for staging of the cancer and influencing management decisions, and can facilitate image-guided biopsy to enable histological confirmation of diagnosis.

If the ultrasound, serum CA125 and clinical status suggest ovarian cancer, the NICE guideline on ovarian cancer recommends performing a CT scan of the pelvis and abdomen (and thorax if clinically indicated) to establish the extent of disease. MRI is not recommended for routine use for assessing people with suspected ovarian cancer.

The Royal College of Radiologists iRefer radiological investigation guidelines tool recommends that CT of the abdomen and pelvis has a role in identifying people who may benefit from chemotherapy or cytoreductive surgery. MRI of the abdomen and pelvis is recommended for specialised investigation when enhanced CT is contraindicated or for problem-solving. PET-CT is indicated as a specialised investigation for difficult management situations.

The NICE guideline on ovarian cancer recommends tissue diagnosis by histology to confirm ovarian cancer. Tissue samples are often obtained during surgery; therefore, a histological diagnosis is often not made until after surgery. Clinical experts commented that pre-operative biopsies are used for tissue diagnosis in cases of advanced stage ovarian cancer; however in cases of early stage ovarian cancer, tissue diagnosis would typically be made following removal of ovaries. In people where cancer appears to be confined

to one ovary and who wish to conserve fertility, conservative surgery is considered.

If surgery has not been performed, other options for obtaining tissue for histology may be used, such as percutaneous image-guide biopsy or laproscopic biopsy. Cytotoxic chemotherapy is only recommended following a confirmed tissue diagnosis of ovarian cancer in all but exceptional cases.

3.2.3. Management

The NICE guideline on ovarian cancer contains recommendations for the management of early (stage I) and advanced (stages II-IV) ovarian cancer. NICE technology appraisal guidance has also been published on treatment of ovarian cancer:

- Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer
- Olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy
- Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer
- Bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer
- Guidance on the use of paclitaxel in the treatment of ovarian cancer

In addition, NICE interventional procedure guidance provides recommendations on the use of ultra-radical (extensive) surgery for advanced ovarian cancer.

Benign ovarian masses

The RCOG guidelines on the management of suspected ovarian masses in premenopausal women and ovarian cysts in postmenopausal women provide recommendations for management of benign ovarian masses. Ovarian cysts with low risk of malignancy can either be treated conservatively (with surveillance) or with surgery, depending on the observed features. Typically, people with a low risk of ovarian malignancy are managed in a general gynaecology unit. However, if malignancy is identified during surgery (or from subsequent histology), referral to a gynaecological oncologist for further management is recommended.

3.2.4. Reference standard

Histopathology is used as the reference standard for assessing the accuracy of tests to identify people at high risk of ovarian cancer. In addition to distinguishing between malignant and benign tumours, this testing can also determine the type of ovarian cancer present. Where tissue samples are not taken, clinical follow-up may be required to determine the presence, or absence, of ovarian cancer.

3.3 Patient issues and preferences

It is not anticipated that there will be any substantial difference to patients in terms of timing or methodology through the use of HE4 serum testing alongside CA125 serum testing, as both require blood samples to be taken. However, any improvement in test accuracy will have patient benefits. Improved recognition of ovarian cancer at an earlier stage will improve patient survival and may also reduce the extent of surgery or chemotherapy that would be required, compared with if ovarian cancer was initially missed and recognised at a later stage. Earlier referral to specialist gynaecological oncology teams will ensure optimal surgery and treatment.

Improved recognition of benign ovarian tumours in secondary care will reduce the number of people inappropriately referred to specialist gynaecological oncology multidisciplinary teams. This could reduce the incidence of unnecessary surgery (which may affect fertility) and also procedures used to obtain tissue for diagnosis, and consequently the complications associated with these procedures. For example, needle biopsies can cause complications such as local bruising and discomfort.

The amount of time that it takes for tests to be run is also an important issue for patients. Quicker results will reduce the amount of time patients spend in uncertainty about their condition and the anxiety that this can cause. A further issue for patients will be the number of operations required and potentially the amount of time off work that will be required for operations. Repeated surgery may be required if, for example, ovarian cancer is diagnosed following an initial operation to remove a mass which was thought to be benign. Preserving fertility is a further potentially important issue for some patients. Any aspect of patient testing or management that can improve the likelihood of conservative surgery for ovarian cancer could therefore be of considerable benefit.

4 Comparator

The comparator for this assessment is the Risk of Malignancy Index I (RMI I) used at a threshold of 250, as currently recommended in the NICE guideline

on ovarian cancer. The RMI I tool combines 3 pre-surgical features (measured serum CA125 levels, ultrasound imaging and menopausal status) to create an index score. It is described in greater detail in section 2.2.4 and in Appendix D in the NICE guideline on ovarian cancer.

5 Scope of the assessment

Table 6 Scope of the assessment

Decision question	What is the clinical and cost effectiveness of tests in secondary care (ADNEX, Overa, RMI I, ROMA and Simple Rules) to identify people who are at high risk of ovarian cancer and who should be referred to a specialist multidisciplinary team?
Populations	People who are referred to secondary care with suspected ovarian cancer. Potential subgroups include: • People who are premenopausal • People who are postmenopausal
Possible interventions	• ADNEX • OVA2/Overa • RMI I testing (with a value other than 250 as a cut-off for referral or incorporating HE4 serum levels) • ROMA • Simple Rules ultrasound-based testing
Comparator	RMI I testing (with a score of 250 as a cut-off for referral)
Healthcare setting	Secondary care
Outcomes	Intermediate measures for consideration may include: • Diagnostic accuracy of testing • Time to test result • Number of inconclusive results • Stage of ovarian cancer at diagnosis • Number of people referred to gynaecological oncology multidisciplinary teams • Number of cross sectional imaging scans for people with suspected ovarian cancer • Number of people who have ovarian cancer whose initial surgery to remove a pelvic mass is not carried out by a gynaecological oncologist • Adverse events from biopsy or surgery

	Clinical outcomes for consideration may include: • Morbidity associated with ovarian cancer (or surgery for suspected ovarian cancer) • Mortality associated with ovarian cancer (or surgery for suspected ovarian cancer) • Survival
	Patient-reported outcomes for consideration may include: • Health related quality of life
	Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include: • Cost of equipment, reagents and consumables • Cost of staff and associated training • Costs of procedures, including biopsy, histological examination and surgery (including secondary surgery) and including any time related costs associated with these procedures • Costs associated with treatment and subsequent testing to confirm diagnosis • Costs arising from adverse events
	The cost-effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.
Time horizon	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

6 Other issues for consideration

Studies assessing relevant tests usually focus on diagnostic accuracy rather than longer term clinical outcomes. Therefore it is likely that a linked-evidence modelling approach will need to be used in this assessment.

The prevalence of ovarian cancer in people referred to secondary care who are pre- and postmenopausal is likely to differ. In addition, the incidence of non-cancer pathologies, non-epithelial ovarian cancers and borderline ovarian tumours is potentially higher in people who are premenopausal. All these factors may cause the accuracy of tests to differ significantly between these groups.

There will also be heterogeneity in the characteristics of people referred to secondary care with suspected ovarian cancer, in terms of the symptoms they exhibit and also previous testing (for example, CA125 and ultrasound).

An NIHR-funded primary research project (ROCkeTS - Refining Ovarian Cancer Test Accuracy Scores) is currently under way, with a preliminary publication date for reporting of April 2019. The results of this work are likely to be directly relevant to the decision problem.

Many studies reporting on the accuracy of tests for identifying ovarian malignancy are based on populations of patients who have already been selected for surgery for their pelvic mass, potentially because tissue samples obtained from surgery are needed to confirm the accuracy of tests. Because the population for this assessment includes people with suspected ovarian cancer *before* a decision about whether they should have surgery has been made, such studies may introduce bias to estimates of test accuracy if applied to this population

The population with suspected ovarian cancer will include people with epithelial and non-epithelial ovarian cancer. Therefore modelling may not capture all the benefits of tests include in this assessment that would identify people with non-epithelial cancer as well as epithelial ovarian cancer.

If tests rely on potentially subjective interpretation of imaging, there is likely to be operator-dependant variability in test accuracy. This will particularly be the case if studies are carried out with test operators that differ in expertise from those in secondary care in the NHS.

7 Potential equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

All people with cancer are covered under the disability provision of the Equality Act (2010) from the point of diagnosis.

The Simple Rules classification system and the ADNEX model have not been validated for use with people who are pregnant. The use of transvaginal ultrasound probes for scans may also be inappropriate for people under 18 years.

The ROMA has not been validated for use with people under 18 years. In addition, the OVA2/Overa test is only indicated for use with people 18 years and older.

8 Potential implementation issues

Current use of serum markers

Pathways involving the use of CA125 are in widespread use and are well established in current practice. CA125 levels are frequently measured in primary care prior to referral to secondary care with suspected ovarian cancer. The RMI I score is also commonly used to decide if people should be referred to a specialist gynaecological oncology multidisciplinary team for further assessment. In contrast, HE4 is not in routine use in either primary or secondary care, although some private laboratories do offer this assay.

HE4 testing is likely to be used at the same point in the care pathway as CA125 and will also require a blood sample to be taken. It is anticipated that the volume of blood currently drawn for CA125 testing will be sufficient for HE4 testing to also be carried out.

Analysers and CA125 assays

Currently CA125 assays are widely used by laboratories, and a range of different analysers are available to run the assays. HE4 assays from different manufacturers may require particular analyser platforms to run the assay, which may differ from analysers currently used by laboratories to run CA125 assays. In addition, manufacturers will often recommend that particular CA125 assays are used with their HE4 assays to calculate ROMA scores, which may differ from CA125 assays currently used by laboratories.

Training

Expertise required to carry out and interpret ultrasound scans according to Simple Rules and ADNEX requirements may not be widely available, or may require training before they can be routinely used. In addition, while protocols for obtaining samples for HE4 assays, and running the assay, may be similar to existing CA125 protocols, expertise in interpreting results (such as ROMA scores) may not be widely available.

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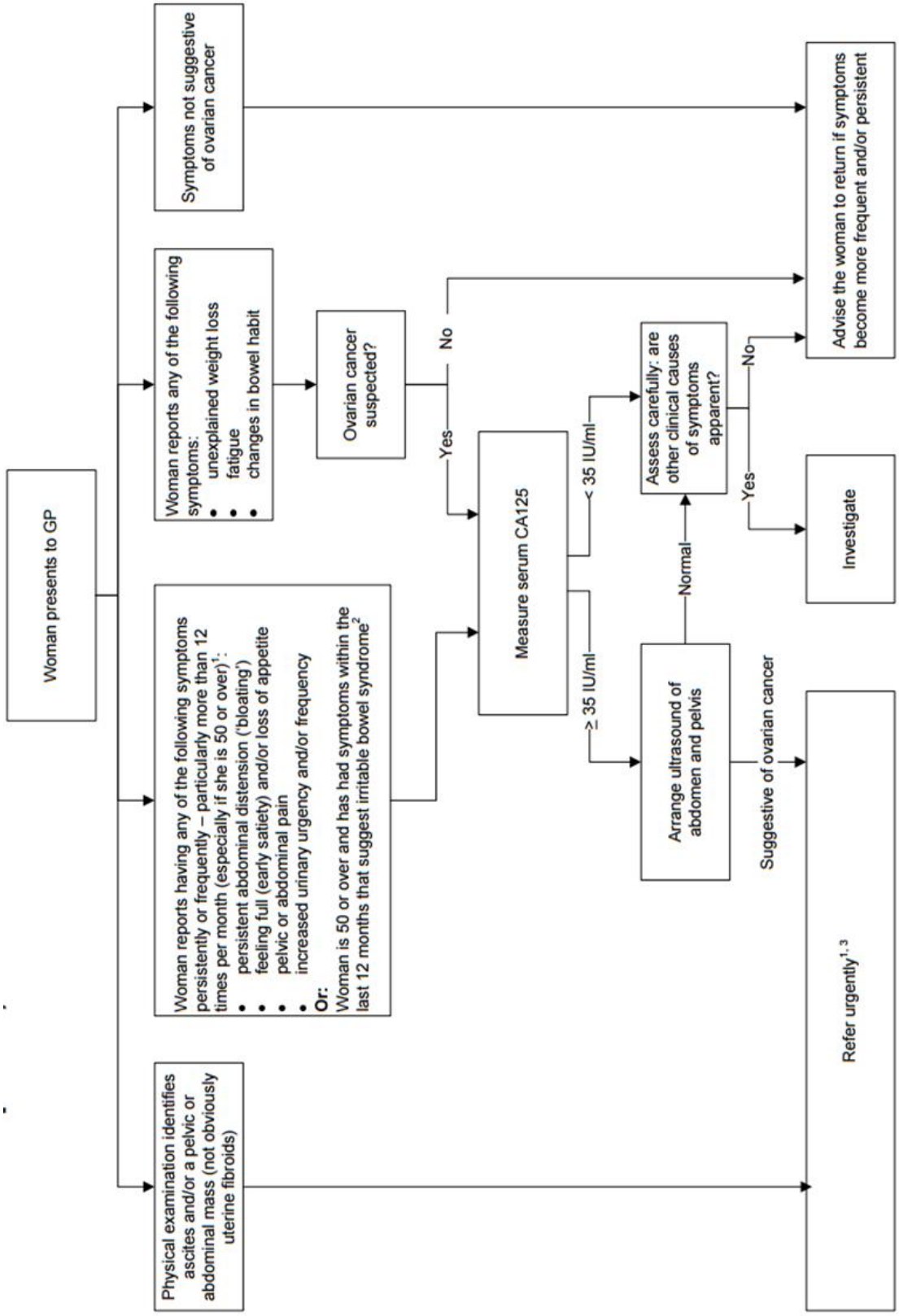
Appendix A Detection in primary care – care pathway algorithm (from NICE CG122 full guideline)



Appendix B Glossary of terms

Ascites
A build-up of fluid in the peritoneal cavity.

Endometriosis
A condition where tissue that behaves like the lining of the womb (the endometrium) is found outside the womb.

Uterine fibroids
Non-cancerous growths that develop in or around the womb (uterus).

Appendix C Abbreviations

ADNEX
Assessment of Different NEoplasias in the adneXa

CA125
Cancer antigen 125

HE4
Human epididymis protein 4

IOTA
International ovarian tumour analysis group

RMI
Risk of malignancy index

ROMA
Risk of ovarian malignancy algorithm

Appendix D References

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