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Guideline No. 403: Initial Investigation and Management of Adnexal Masses

(En français : Évaluation initiale et prise en charge des masses annexielles)

The English document is the original version. In the event of any discrepancy between the English and French content, the English version prevails.

This joint Clinical Practice Guideline was prepared by the Society of Gynecologic Oncology of Canada (GOC) Guidelines Committee. It was reviewed by the Society of Obstetricians and Gynaecologists of Canada (SOGC) Gynaecology Clinical Practice Committee, Family Physicians Advisory Committee, Canadian Paediatric and Adolescent Gynaecology and Obstetrics Committee, and Guideline Management and Oversight Committee and approved by the boards of the GOC and the SOGC.

Authors
Shannon Salvador, MD, Montréal, QC
Stephanie Scott, MD, Halifax, NS
Phyllis Glanc, MD, Toronto, ON
Lua Eiriksson, MD, Hamilton, ON
Ji-Hyun Jang, MD, Vancouver, BC
Alexandra Sebastianelli, MD, Québec, QC
Erin Dean, MD, Winnipeg, MB

2019 GOC Guidelines Committee: Shannon Salvador, Alexandra Sebastianelli, Lua Eiriksson, Erin Dean, Stephanie Scott, and Ji-Hyun Jang

2019 SOGC Gynaecology Clinical Practice Committee: Olga Bougie, Annette Bullen, Innie Chen, Devon Evans, Susan Goldstein, Joann James, Sari Kives, Ally Murji, Jessica Papillon-Smith, Leslie Po, Elizabeth Randle, David Rittenberg (co-chair), Jackie Thurston, Wendy Wolfman (co-chair), Grace Yeung, Paul Yong (co-chair), and Andrew Zakhari

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Corresponding Author: Shannon Salvador, shannon.salvador@mcgill.ca

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This document reflects emerging clinical and scientific advances as of the publication date and is subject to change. The information is not meant to dictate an exclusive course of treatment or procedure. Institutions are free to amend the recommendations. The SOGC suggests, however, that they adequately document any such amendments.

Informed Consent: Everyone has the right and responsibility to make informed decisions about their care together with their health care providers. In order to facilitate this, the SOGC recommends that they provide their patients with information and support that is evidence-based, culturally appropriate, and personalized.

Language and Inclusivity: This document uses gendered language in order to facilitate plain language writing but is meant to be inclusive of all individuals, including those who do not identify as a woman/female. The SOGC recognizes and respects the rights of all people for whom the information in this document may apply, including but not limited to transgender, non-binary, and intersex people. The SOGC encourages health care providers to engage in respectful conversation with their patients about their gender identity and preferred gender pronouns and to apply these guidelines in a way that is sensitive to each person's needs.

RECOMMENDED CHANGES IN PRACTICE

1. Use improved ultrasound criteria for distinguishing benign adnexal masses from malignant adnexal masses.
2. Make use of additional tumour markers to aid in diagnosis.

KEY MESSAGES

1. The International Ovarian Tumor Analysis group's simple rules are a preoperative classification system for ovarian tumours that consists of 5 features for benign masses (B-features) and 5 features for malignant masses (M-features) and that allows sonographers with varying degrees of expertise to accurately classify adnexal masses.
2. Women <40 years of age with masses with malignant features should undergo further testing of tumour markers: human chorionic gonadotropin, lactate dehydrogenase, and alpha-fetoprotein.
3. Measurement of cancer antigen 125 should not be used as a screening tool for asymptomatic women not presenting with an adnexal mass.

ABSTRACT

Objectives: To aid primary care physicians, emergency medicine physicians, and gynaecologists in the initial investigation of adnexal masses, defined as lumps that appear near the uterus or in or around ovaries, fallopian tubes, or surrounding connective tissue, and to outline recommendations for identifying women who would benefit from a referral to a gynaecologic oncologist for further management.

Intended Users: Gynaecologists, obstetricians, family physicians, general surgeons, emergency medicine specialists, radiologists, sonographers, nurses, medical learners, residents, and fellows.

Target Population: Adult women 18 years of age and older presenting for the evaluation of an adnexal mass.

Options: Women with adnexal masses should be assessed for personal risk factors, history, and physical findings. Initial evaluation should also include imaging and laboratory testing to triage women for management of their care either by a gynaecologic oncologist or as per SOGC guideline no. 404 on the initial investigation and management of benign ovarian masses.

Evidence: A search of PubMed, Cochrane Wiley, and the Cochrane systematic reviews was conducted in January 2018 for English-language materials involving human subjects published since 2000 using three sets of terms: (i) ovarian cancer, ovarian carcinoma, adnexal disease, ovarian neoplasm, adnexal mass, fallopian tube disease, fallopian tube neoplasm, ovarian cyst, and ovarian tumour; (ii) the above terms in combination with predict neoplasm staging, follow-up, and staging; and (iii) the above two sets of terms in combination with ultrasound, tumour marker, CA 125, CEA, CA19-9, HE4, multivariable-index-assay, risk-of-ovarian-malignancy-algorithm, risk-of-malignancy-index, diagnostic imaging, CT, MRI, and PET. Relevant evidence was selected for inclusion in descending order of quality of evidence as follows: meta-analyses, systematic reviews, guidelines, randomized controlled trials, prospective cohort studies, observational studies, non-systematic reviews, case series, and reports. Additional articles were identified through cross-referencing the identified reviews. The total number of studies identified was 2350, with 59 being included in this review.

Validation Methods: The content and recommendations were drafted and agreed upon by the authors. The Executive and Board of the Society of Gynecologic Oncology of Canada reviewed the content and submitted comments for consideration. The Board of Directors of the Society of Obstetricians and Gynaecologists of Canada approved the final draft for publication. The quality of evidence was rated using the criteria described in the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology framework (Table A1 of Online Appendix A). See Table A2 of Online Appendix A for the interpretation of strong and weak recommendations. The summary of findings is available upon request.

Benefits, Harms, Costs: Adnexal masses are common, and guidelines on how to triage them and manage the care of patients presenting with adnexal masses will continue to guide the practice of primary care providers and gynaecologists. Ovarian cancer outcomes are improved when initial surgery is performed by a gynaecologic oncologist, likely as a result of complete surgical staging and optimal cytoreduction. Given these superior outcomes, guidelines to assist in the triage of adnexal masses and the referral and management of the care of patients with an adnexal mass are critical.

SUMMARY STATEMENTS (GRADE ratings in parentheses)

1. Information from a detailed personal and family history can guide decisions on further testing and evaluation for women with adnexal masses (low).
2. The majority of women with ovarian cancer have symptoms in the year prior to their diagnosis, although these symptoms can be vague (low).
3. Adnexal masses are best evaluated through subjective pattern recognition by an expert sonographer in order to distinguish benign adnexal masses from malignant adnexal masses (moderate).
4. Ultrasound evaluation of adnexal masses with risk prediction models such as the simple rules, developed by the International Ovarian Tumor Analysis group, allows sonographers with varying degrees of expertise to use uniform terminology and accurately classify these masses as "likely malignant," "benign," or "indeterminate" (moderate).
5. Laboratory testing can aid in the differential diagnosis of an adnexal mass. Testing for sexually transmitted infection with results showing leukocytosis can help identify tubo-ovarian abscesses, while a positive pregnancy test can lead to diagnosis of possible ectopic pregnancies (low).
6. Cancer antigen 125 is a non-specific glycoprotein that can be elevated in benign and malignant gynaecologic conditions and in non-gynaecologic conditions (moderate).
7. Only half of all early stage ovarian cancers and 80% of advanced stage ovarian cancers show elevated cancer antigen 125 levels (moderate).
8. The sensitivity and specificity of cancer antigen 125 as a tumour marker are higher in women who are postmenopausal because many of the benign clinical conditions that can increase the level of cancer antigen 125 occur in the premenopausal population, while most cases of epithelial ovarian, fallopian tube, and peritoneal cancer occur in the postmenopausal population (moderate).
9. Despite having gone through several iterations, the risk of malignancy index, which uses cancer antigen 125 and sonographic features along with the patient's menopausal status, is outperformed by the more recent International Ovarian Tumor Analysis group's logistic regression model 2 and simple rules. The sensitivity and specificity of version 2 of the risk of malignancy index for distinguishing

malignant from benign masses are only 75% and 87%, respectively (moderate).

RECOMMENDATIONS (GRADE ratings in parentheses)

1. Take a detailed history for a woman presenting with an adnexal mass. For a woman with a personal history of infertility, endometriosis, or cancer or a family history of cancer, refer the patient to a gynaecologic oncologist for further evaluation if possible (strong, low).
2. Physical examination should include lymph node survey, respiratory examination to rule out pleural effusion or consolidation, breast and axillary examination to rule out breast malignancy, and an abdominal examination to assess for ascites, omental caking, and organomegaly as well as a pelvic examination, including a bimanual and rectovaginal examination, to assess for mass size, contour, mobility, and parametrial, bladder, and rectal abnormality (strong, low).
3. If a woman presents with an adnexal mass, request an initial ultrasound using either pattern recognition or the risk prediction model developed by the International Ovarian Tumour Analysis group (strong, moderate).
4. Promptly refer to a gynaecologic oncologist any patient who presents with a mass with any of the following sonographic features, suggestive of malignancy: (i) solid component with strong or central colour flow, (ii) ≥4 papillary projections (defined as >3 mm in height), (iii) thick multiple irregular septations, or (iv) ascites and peritoneal nodularity. While awaiting a gynaecologic oncologist consult, where resources permit, pursue further investigations, including tumour marker levels and computed tomography scan of the chest, abdomen, and pelvis, as appropriate (strong, moderate).
5. Women with adnexal masses with indeterminate features should be evaluated by ultrasound conducted by an expert sonographer (if available) or by magnetic resonance imaging or be referred to a gynaecologic oncologist (strong, low).
6. Do not use cancer antigen 125 testing as a screening tool in asymptomatic women without a pelvic or adnexal mass (strong, moderate).
7. The initial ultrasound characterization can be done using either pattern recognition (best in the hands of an expert sonographer) or risk prediction algorithms, such as simple rules, which have been demonstrated to work well for practitioners with varying degrees of expertise. If the lesion is suspicious for malignancy, prompt referral to a gynaecologic oncologist is recommended (strong, moderate).
8. In women <40 years of age with an adnexal mass, rare forms of ovarian cancer must be considered and further tumour marker measurements, including human chorionic gonadotropin, lactate dehydrogenase, and alpha-fetoprotein, should be obtained (strong, low).
9. Further tumour marker testing, including carcinoembryonic antigen, cancer antigen 19-9, and cancer antigen 15-3, along with referral to a gynaecologic oncologist are recommended for women presenting with bilateral masses with features of malignancy (strong, moderate).

INTRODUCTION

Adnexal masses (i.e., lumps that appear near the uterus or in or around the ovaries, fallopian tubes, or surrounding connecting tissues) are common and frequently detected by primary care providers and gynaecologists. Although the majority of these masses are benign, the primary goal of assessment is to rule out ovarian cancer. Ovarian cancer affects 2800 women annually in Canada and is the fifth leading cause of cancer death in women.[1] Ovarian cancer outcomes are improved when initial surgery is performed by a gynaecologic oncologist as opposed to a general gynaecologist or general surgeon, likely as a result of appropriate surgical staging and optimal cytoreduction.[2,3] As a result, guidelines to assist in the triage of adnexal masses and the management of the care of patients with an adnexal mass are critical.

The earlier version of this guideline, published in 2009,[4] outlined the importance of ultrasound, cancer antigen 125 levels, and the risk of malignancy index (RMI). See Online Appendix B for an overview of this index. However, since its publication, there has been considerable research on additional individual tumour markers, marker panels, radiologic criteria, and algorithms to assist in the triage of adnexal masses and the management of the care of patients with an adnexal mass. In addition, our understanding of the diversity of ovarian cancers, their risk factors, and genetic predisposition has also evolved considerably and warrants attention.

Two marker panels have been approved by the U.S. Food and Drug Administration (FDA) and warrant discussion: the risk of ovarian malignancy algorithm[5,6] and the multivariate index assay.[7,8] In order to assist physicians in the initial evaluation of an adnexal mass, guidelines should provide indications for the use of not only these new markers and marker panels of epithelial ovarian cancers but also traditional markers for germ cell and sex-cord stromal tumours.

The usefulness of ultrasound in distinguishing benign versus malignant features of an adnexal mass is emphasized, considering that tumour markers can be unreliable in early stage malignancy and are histology dependent.[9] Ultrasound criteria such as those developed by the International Ovarian Tumor Analysis (IOTA) group have been shown to outperform the RMI[10] and demand further exploration and discussion in contemporary guidelines.

SUMMARY STATEMENT 1 and RECOMMENDATION 1

PATIENT RISK FACTORS

In patients with an isolated adnexal mass, a detailed review of medical and family history can assist with determining the risk of malignancy. For patients with a family or personal history of cancer or relevant personal risk factors, referral to a gynaecologic oncologist may be indicated, even in the absence of an elevated risk of malignancy based on imaging and biomarker testing alone.

Patients with a history of gastrointestinal, breast, hepatobiliary, or gynaecologic cancer, particularly those with advanced stage disease or high-risk features, may present with an adnexal mass or masses consistent with metastatic disease to the ovaries.[11] Tailored biomarker testing may be useful to further estimate risk, in addition to doing supplementary investigations as directed by history and clinical presentation such as computed tomography (CT) scanning and mammography or diagnostic evaluations such as colposcopy, gastroscopy, and colonoscopy. For patients with evidence of diffuse metastatic disease who are awaiting consultation with a gynaecologic oncologist, it may be useful to request an image-guided biopsy. If possible, the biopsy should be compared with the histology of the previous malignancy. Biopsy is not recommended in the case of an isolated adnexal mass.

A personal history of endometriosis or infertility may suggest an epithelial ovarian neoplasm with clear cell or endometrioid histology.[12,13] These tumour types are less commonly associated with an elevation in cancer antigen 125 and commonly present as an isolated adnexal mass.[14]

Patients with a family history of ovarian, breast, colorectal, or endometrial cancer may have increased risk of ovarian cancer owing to a cancer susceptibility syndrome such as Lynch syndrome (hereditary nonpolyposis colorectal cancer) or breast and ovarian cancer syndrome.[15,16] Patients with a high-risk family history or those with a confirmed hereditary cancer syndrome in their family may benefit from referral to a gynaecologic oncologist for possible management of their care at a cancer centre with access to genetic counselling.[17–19]

Table 1. International Ovarian Tumor Analysis group simple rules for tumour identification: malignant and benign sonographic features

Malignant (M) Rules	Benign (B) Rules
M1: Irregular solid tumour	B1: Unilocular cyst
M2: Presence of ascites	B2: Presence of solid components, with largest diameter <7 mm
M3: Presence of at least 4 papillary structures	B3: Presence of acoustic shadows
M4: Irregular multilocular-solid tumour, with largest diameter ≥100 mm	B4: Smooth multilocular tumour, with largest diameter <100 mm
M5: Very strong blood flow (colour score 4)	B5: No blood flow (colour score 1)

SOURCE: International Ovarian Tumor Analysis group. Available at www.iotagroup.org/iota-models-software/iota-simple-rules-and-srrisk-calculator-diagnose-ovarian-cancer.

SUMMARY STATEMENT 2 and RECOMMENDATION 2

CLINICAL PRESENTATION

Women presenting with an adnexal mass often have symptoms that can help in the diagnosis. Fevers, chills, and vomiting may be signs of a tubo-ovarian abscess, while acute pain is often associated with an ectopic pregnancy or ovarian torsion. Acute or chronic dysmenorrhea and pelvic pain could be evidence of an endometrioma. While symptoms of ovarian cancer may be vague, 93% of women report having some type of symptoms in the year prior to diagnosis.[20] Symptoms of ovarian cancer range from bloating, abdominal fullness, pain, abdominal distension, gastrointestinal and urinary dysfunction, dyspnea, and dyspareunia to a palpable abdominal mass.[20–22] Such symptoms should therefore prompt the workup of potential adnexal or gastrointestinal malignancy.

When an adnexal mass is suspected or identified, a tailored physical examination should include a lymph node survey with palpation of supraclavicular and inguinal lymph nodes, respiratory examination with focus on pleural effusion or consolidation, breast and axillary examination to assess for breast malignancy, and an abdominal examination to assess for ascites, omental caking, and organomegaly. Complete pelvic examination is also recommended, including visual inspection of the vulva, cervix, and vagina, in addition to a bimanual and rectovaginal examination to assess for mass size, contour, mobility, and parametrial, bladder, and rectal abnormality. An endometrial biopsy is recommended in cases of abnormal uterine bleeding.

SUMMARY STATEMENTS 3, 4 and RECOMMENDATIONS 3, 4, 5

IMAGING

Ultrasound is the first-line imaging modality for an initial evaluation of adnexal masses. It is recommended that a transabdominal and transvaginal pelvic ultrasound be performed in combination with colour Doppler ultrasound. Two approaches are recommended for the evaluation of adnexal masses. The first is subjective pattern recognition by an sonographer to distinguish benign from malignant masses (most accurate method to evaluate masses in the adnexa) and to distinguish ovarian, paraovarian, and fallopian tube masses or cysts.[23] Patients with characteristically benign masses can be managed conservatively with serial sonography as appropriate.[23] Detailed descriptions of these characteristic masses have been extensively published.[23] As ultrasound can be interpreted by practitioners with varying degrees of expertise and confidence; referral to an expert sonographer may be indicated when the evaluation is indeterminate.[24]

The second approach is to use risk prediction models, of which the best validated model is the simple rules, developed by the IOTA group.[25] The simple rules (Table 1) use standardized terminology and comprise 5 features that suggest a malignant mass (M-features) and 5 features that suggest a benign mass (B-features).[26] Sonographic features that are suggestive for malignancy include: (i) solid component with strong or central blood flow (as per elevated colour score), (ii) ≥4 papillary projections (defined as >3 mm in height), (iii) thick, multiple, irregular septations, (iv) ascites and peritoneal nodularity, and (v) masses with largest diameter >10 cm or containing more than 10 locules.[24] These large multicystic masses are associated with an increased risk of malignancy, specifically in borderline ovarian tumours.[27] If 1 or more M-features apply in the absence of a B-feature, the mass is classified as malignant. If 1 or more B-features apply in the absence of M-features, the mass is classified as benign. If both B- and M-features apply or if no rules apply, the mass is considered indeterminate. The simple rules do not apply to as many as 25% of masses.[26] In this case, the IOTA group suggests either referring the patient to an expert sonographer or labelling the mass as possibly malignant given the high prevalence of malignancy.[28] Another risk prediction model, again validated by the IOTA group, is the logistic regression model 2, which incorporates age and 5

ultrasound variables: presence of blood flow in a papillary structure, irregular cyst walls, ascites, acoustic shadows, and maximum diameter of the largest solid component.[29] Additional information on the simple rules and risk prediction modelling can be found at www.iotagroup.org. In addition, clinicians can purchase the IOTA ADNEX app for iPhone or Android ($) or can use the free web application, available at www.iotagroup.org under the **Research** tab.

Patients with a mass suggestive of malignancy should be promptly referred to a gynaecologic oncologist. To facilitate triage and care in a timely fashion and where resources permit, the referring physician should order tests for tumour markers, discussed below in **Laboratory Testing, Markers, and Marker Panels**, at the same time as making the referral. If there is a strong suspicion of metastatic disease or carcinomatosis, the referring physician can also request a CT scan of the chest, abdomen, or pelvis, as appropriate, to help expedite the diagnostic process. Improved survival outcomes in women with ovarian cancer who are referred to a gynaecologic oncologist have been well documented.[2,3] Consideration should be given to the presence of interim growth or change in morphology with the development of solid or vascular components; however, there are no evidence-based guidelines on how much growth or changes in morphology should trigger referral to a gynaecological oncologist. It is important to note that no single sonographic feature should be evaluated in isolation; the overall set of sonographic features and the complete clinical evaluation should be considered.

There are several options for managing the care of patients who show indeterminate masses following an initial ultrasound, including serial ultrasound, referral to a specialized ultrasound consultant such as a radiologist or a specially trained sonographer, application of established risk prediction models, correlation with magnetic resonance imaging (MRI), or referral to a gynaecologic oncologist for further evaluation and consideration of serum biomarkers. Discrimination between benign and malignant masses is highly accurate in the hands of experts, with sensitivity as high as 96.7%.[30] Thus, consideration of referral to a specialized ultrasound consultant may be appropriate. Serial sonography has demonstrated that most adnexal masses will resolve spontaneously over time. Furthermore, Elder et al. demonstrated that serial sonography improves the prediction of ovarian malignancy while decreasing the number of surgical procedures performed for benign masses.[31] A review of established risk prediction models recommended incorporating the IOTA simple rules for preoperative characterization of ovarian masses.[32] MRI can be used as a problem-solving tool in the case of an indeterminant result on ultrasound or when the ultrasound does not adequately characterize an adnexal mass. In the case of an indeterminate mass, MRI decreases the risk of misdiagnosing a benign mass as malignant and increases the specificity of a benign diagnosis.[33] MRI is also highly sensitive (96.6%) and specific (83.7%–94.0%) for the diagnosis of malignancy.[34] See **Laboratory Testing, Markers, and Marker Panels** for information on the role of serum biomarkers. The decision on the best route for further investigation after an indeterminate result on ultrasound will vary depending both on the experience of the physician and available local resources.[24]

SUMMARY STATEMENTS 5, 6, 7, 8, 9, and RECOMMENDATIONS 6, 7, 8, 9

LABORATORY TESTING, MARKERS, AND MARKER PANELS

Once an adnexal mass has been identified, laboratory testing may assist with the differential diagnosis and identifying women who have an increased likelihood of malignancy and determining whether a gynaecologic oncology assessment is needed. For all women of child-bearing age, the first requirement is a pregnancy test. Any woman with a history of and symptoms suggestive of a tubo-ovarian abscess should undergo testing for gonorrhea and chlamydia. Complete blood count can identify leukocytosis, which may be associated with infection.

The most studied biomarker for the assessment of a pelvic mass is serum cancer antigen 125, a glycoprotein often elevated in patients with epithelial ovarian, fallopian tube, or peritoneal malignancies. This marker is non-specific and can be elevated in both benign and malignant conditions. Many gynaecologic conditions (menstruation, pregnancy, endometriosis, benign pelvic masses, and pelvic inflammatory disease) and non-gynaecologic conditions (cirrhosis) can result in an elevated cancer antigen 125 level.[35] Cancer antigen 125 testing is not recommended as a screening tool. Multiple large population-based trials evaluating cancer antigen 125 screening in combination with ultrasound imaging concluded that: (i) screening increases interventions in the screened women, with resulting morbidity, (ii) there is no statistical difference in the level of mortality from ovarian cancer between the control group and screened patients, and (iii) routine screening in asymptomatic women is not recommended at this time.[36,37] When used to distinguish between benign and malignant masses,

Table 2. Serum biomarkers to aid in diagnosing ovarian germ cell and sex-cord stromal tumours

Tumour type	Serum biomarkers					
	hCG	AFP	LDH	CA 125	Inhibin	Testosterone/androstenedione
Dysgerminoma	+	–	+	–	–	–
Endodermal sinus tumour	–	+	–	–	–	–
Embryonal carcinoma	+	+	–	–	–	–
Polyembryoma	+	+	–	–	–	–
Choriocarcinoma	+	–	–	–	–	–
Immature teratoma	–	±	±	±	–	–
Granulosa cell tumour	–	–	–	–	+	Rare
Sertoli–Leydig cell	–	–	–	–	–	+

AFP: alpha-fetoprotein; CA 125: cancer antigen 125; hCG: human chorionic gonadotropin; LDH: lactate dehydrogenase.

cancer antigen 125 testing has been found in meta-analyses to have a sensitivity of 73% to 79% with a specificity of 82% to 86% when using a cut-off value of 35 U/mL.[38–40] Of note, only half of all early ovarian cancers had elevated-cancer antigen 125 levels, compared with 80% of advanced ovarian cancers.[41] The sensitivity and specificity of cancer antigen 125 as a tumour maker are higher in women who are postmenopausal because many of the benign clinical conditions that can increase the level of cancer antigen 125 occur in the premenopausal population, while most cases of epithelial ovarian, fallopian tube, and peritoneal cancer occur in the postmenopausal population.[39,40]

Evaluations have been done on the use of cancer antigen 125 marker combined with other tests in order to increase the sensitivity and specificity for distinguishing malignant masses from benign masses. The risk of malignancy index (RMI), which incorporates sonographic features, menopausal status, and cancer antigen 125 level, has gone through several iterations in an effort to improve its diagnostic accuracy (see online appendices B and C).[42–45] According to a meta-analysis, performance characteristics of version 1 RMI, which has a cut-off value of 200, demonstrate a sensitivity of 72% with a specificity of 92% for malignancy, while RMI versions 2, 3, and 4 perform similarly (sensitivity of 75%, 70%, and 68%, respectively, and specificity of 87%, 91%, and 94%, respectively).[32] A second meta-analysis confirmed these values for versions 1 to 3 of the RMI, with sensitivity of 71% to 75% and specificity of 87% to 92%.[46] A meta-analysis comparing the RMI with the simple rules and logistic regression model 2 found the simple rules and logistic regression model 2 outperformed the RMI, with higher sensitivities (91% and 93%, respectively, for the simple rules and logistic regression model 2 vs. 75% for version 2 of the RMI).[46]

Human epididymis protein 4 is another FDA-approved biomarker for assessing the risk of ovarian malignancy and is used in combination with cancer antigen 125 in the risk of ovarian malignancy algorithm (ROMA).[47] In Canada, ROMA testing is not available in the public system and, based on research available, is currently not recommended. In 2009, the FDA approved a panel of markers for the triage of pelvic masses—OVA1, a multivariate index assay. However, it is not available in the public system in Canada and, based on available research, is currently not recommended. The OVA1 panel comprises five markers: cancer antigen 125-II, transferrin, transthyretin (prealbumin), apolipoprotein A-I, and beta-2 microglobulin.[48] For further information about the research, specificity, and sensitivity of these markers, see Online Appendix C.

The differential diagnosis of an adnexal mass in women under the age of 40 should include the possibility of germ cell tumours of the ovary and epithelial ovarian neoplasms. Similarly, younger patients may present with sex-cord stromal tumours. Serum biomarkers, including human chorionic gonadotropin, lactate dehydrogenase, alpha-fetoprotein, and inhibin (not routinely available), may assist in the evaluation and follow-up of these patients (Table 2).[49]

Bilateral adnexal masses may represent tumour metastases, which should also be considered in patients with risk factors or symptoms suggestive of an alternative primary site cancer. Additional tumour markers such as carcinoembryonic antigen, cancer antigen 19-9, and cancer antigen 15-3 may aid diagnosis. Tumours with mucinous histology such as gastrointestinal adenocarcinomas, especially those originating from the pancreas, may result in elevated cancer antigen 19-9 levels.[50] Carcinoembryonic antigen is also elevated in tumours with mucinous histology and is usually

significantly elevated in colon cancers with metastasis to the ovaries.[51] Cases with a cancer antigen 125/carcinoembryonic antigen (Ca125/CEA) ratio above 25 are usually associated with primary ovarian tumours, whereas a Ca125/CEA ratio below 25 suggests metastasis to the ovary from another site.[52] Metastatic breast cancer can present with bilateral ovarian tumours and significantly elevated cancer antigen 15-3 with a slightly elevated cancer antigen 125.[53]

CONCLUSION

An important first step during the initial assessment of a patient with an adnexal mass is the ability to appropriately triage her care by either referring the patient to a gynaecologic oncologist for suspected malignancy or continuing to provide care as per SOGC's companion guideline no. 404 on the initial investigation and management of benign ovarian masses. The optimal prediction method of triage is imaging with ultrasound by an expert sonographer or in conjunction with clinical judgement informed by the patient's medical and family history and clinical findings. Assessment using additional imaging and tumour marker tests may be indicated. The opinion of a gynaecologic oncologist should be sought for any indeterminate cases, with immediate referral for suspected malignancy.

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APPENDIX A

Table A1. Key to Grading of Recommendations, Assessment, Development and Evaluation

Strength of Recommendation	Definition
Strong	High level of confidence that the desirable effects outweigh the undesirable effects (strong recommendation for) or the undesirable effects outweigh the desirable effects (strong recommendation against)
Conditional (weak)[a]	Desirable effects probably outweigh the undesirable effects (weak recommendation for) or the undesirable effects probably outweigh the desirable effects (weak recommendation against)
Quality of Evidence	**Definition**
High	High level of confidence that the true effect lies close to that of the estimate of the effect
Moderate	Moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect
Very low	Very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] Do not interpret conditional (weak) recommendations to mean weak evidence or uncertainty of the recommendation. Adapted from GRADE Handbook (2013), Table 5.1, available at gdt.gradepro.org/app/handbook/handbook.html.

Table A2. Implications of Strong and Conditional (Weak) Recommendations, by Guideline User

Perspective	Strong Recommendation • "We recommend. . ." • "We recommend to not. . ."	Conditional (Weak) Recommendation • "We suggest. . ." • "We suggest to not. . ."
Guideline panel	The net desirable effects of a course of action outweigh the effects of the alternative course of action.	It is less clear whether the net desirable effects of a strategy outweigh the alternative strategy.
Patients	Most individuals in the situation would want the recommended course of action, while only a small proportion would not.	The majority of individuals in the situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the course of action.	Recognize that patient choices will vary by individual and that clinicians must help patients arrive at a care decision consistent with the patient's values and preferences.
Policy makers	The recommendation can be adapted as policy in most settings. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	The recommendation can serve as a starting point for debate with the involvement of many stakeholders.

Adapted from GRADE Handbook (2013), Table 6.1, available at gdt.gradepro.org/app/handbook/handbook.html.

APPENDIX B

Table B1. Risk of Malignancy Index, Versions 1 to 4

RMI version	Ultrasound score (U)	Menopausal status (M)	Size (S)	Calculation	Cut-off values
1	0 features = 0 1 feature = 1 ≥2 features = 3	Pre = 1 Post = 3	NA	U × M × CA 125	200
2	0 or 1 feature = 1 ≥2 features = 4	Pre = 1 Post = 4	NA	U × M × CA 125	200
3	0 or 1 feature = 1 ≥2 features = 3	Pre = 1 Post = 3	NA	U × M × CA 125	200
4	0 or 1 feature = 1 ≥2 features = 4	Pre = 1 Post = 4	<7 cm = 1 ≥7 cm = 2	U × M × S × CA 125	450

CA 125: cancer antigen 125; NA: not applicable; RMI: risk of malignancy index.

Sonographic features suggestive of malignancy, each worth 1 point: the presence of a multilocular cystic mass, solid areas, bilateral masses, ascites, intra-abdominal metastases. One point was given for each feature. Postmenopausal status defined as more than 1 year of amenorrhea or age greater than 50 years in women who had undergone hysterectomy.

APPENDIX C. ADDITIONAL INFORMATION ON THE RISK OF OVARIAN MALIGNANCY ALGORITHM AND THE MULTIVARIATE INDEX ASSAY

Human epididymis protein 4 is a biomarker approved by the US Food and Drug Administration and used along with cancer antigen 125 in the risk of ovarian malignancy algorithm (ROMA) to assess the risk of ovarian malignancy.[1] In Canada, ROMA testing is not available in the public system and, based on current research, is not recommended. For evaluating a woman presenting with a pelvic mass, the use of human epididymis protein 4 (HE4) alone, which has a changing cut-off value based on menopausal status, was shown in a variety of meta-analyses to have a sensitivity ranging from 76% to 83% and specificity ranging from 85% to 93%.[2–7] When evaluated against cancer antigen 125, the sensitivity of HE4 is similar; however, the specificity is better than that of cancer antigen 125 in premenopausal women, likely due to a rise in cancer antigen 125 from many benign conditions in premenopausal women.[2,7]ROMA, which combines cancer antigen 125, human epididymis protein 4, and menopausal status, is found to be more sensitive, but less specific, than the use of HE4 alone (which has a sensitivity and specificity similar to cancer antigen 125 when used alone).[2,8] There is a significant increase in sensitivity of ROMA (90%) when used for postmenopausal women, making it most useful in this population.[2] There are several prospective trials comparing ROMA to the RMI, which have conflicting results. In a study involving 457 women, Moore et al. found that ROMA predicted epithelial ovarian cancer in women with a pelvic mass with a sensitivity of 94.3%, compared with 84.7% for the RMI.[9] However, a larger prospective trial (n = 1218) by Karlsen et al. found that the performance of ROMA and the RMI were equivalent.[10] Further evaluation is needed in order to determine the clinical utility of ROMA in the context of the currently available RMI and risk prediction models, including the International Ovarian Tumor Analysis group's simple rules. In studies that compared the International Ovarian Tumor Analysis methods with the RMI and ROMA in the same study population, logistic regression model 2 and simple rules provided greater diagnostic accuracy than did the RMI or ROMA.[11–14]

In 2009, the U.S. Food and Drug Administration approved a panel of markers for the triage of pelvic masses—the multivariate index assay, which includes cancer antigen 125-II, transferrin, transthyretin (prealbumin), apolipoprotein AI, and beta-2 microglobulin[15] (this panel is not available in the public health system in Canada and, based on current research, we do not recommend it at this time). The initial evaluation of the multivariate index assay in 524 women enrolled in an OVA1 trial with a pelvic mass demonstrated a sensitivity of 93% when used alone; sensitivity increased to 96% when combined with physician assessment. However, the specificity was poor, at 43%, and there were many false positives.[15] The high sensitivity (92%) but poor specificity (49%) was confirmed by Longoria et al. in a prospective trial involving 1016 women.[16] Clinicians should not substitute the results of biomarker testing for clinical judgment and decision-making.

APPENDIX C REFERENCES

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