Gynecologic Biopsy for Molecular Profiling: A Review for the Interventional Radiologist

Bradley R. Corr, MD¹ Kian Behbakht, MD¹ Monique A. Spillman, MD, PhD¹

¹Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Colorado School of Medicine, Aurora, Colorado

Address for correspondence Monique A. Spillman, MD, PhD, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Colorado School of Medicine, 12631 E. 17th Avenue, Campus Box B198-4, Aurora, CO 80045 (e-mail: monique.spillman@ucdenver.edu).

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Abstract

Keywords

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- molecular profiling

The interventional radiologist is often asked to obtain multiple biopsies of gynecological malignancies for genetic profiling. This article reviews the current indications for gynecological biopsy as well as how the information gained contributes to a personalized medicine plan for the individual patient. The specific focus of this review is the current knowledge and practice of molecular profiling for gynecological malignancies.

Gynecological biopsies are often requested for the diagnosis of malignancy or, in the case of known malignancy, for further characterization. The most common origin for gynecological malignancy biopsy requests to the interventional radiologist are ovarian, endometrial, and cervical. The surgical and chemotherapy treatments of these malignancies have remained generally consistent over the past few decades; however, over the past decade, the ability to perform molecular profiling has led to advancements in treatment through pathway targeted agents. This article reviews the current state and future outlook of molecular profiling of gynecological malignancies and how this information is useful to the interventional radiologist. To best understand these advancements, a background primer in gynecologic malignancy is necessary. The three most common gynecologic malignancies will be discussed in this review: ovarian, endometrial, and cervical.

Ovarian Cancer

One in 73 women will be diagnosed with epithelial ovarian cancer in their lifetime. It is estimated that 22,240 women will be diagnosed with, and 14,030 will die of, ovarian cancer in 2013.¹ Ovarian cancer is often diagnosed in the late stages and there is currently no effective screening method. Though its prevalence is low, the mortality is high. At 5 years after

diagnosis, survival is only 44%; 60% of patients will have recurrence after the initial remission.^{2,3} First-line therapy often includes surgery and a chemotherapy combination of cisplatin or carboplatin and paclitaxel. Recurrence rates and prognosis are strongly correlated with initial platinum-based chemotherapy response.⁴ Although some second-line chemotherapy agents carry FDA approval, there are currently no standard of care second-line regimens. Clinicians currently pick second-line chemotherapy regimens based on professional experience, without objective evidence tailored to an individual patient.⁵

Initial surgery for ovarian cancer is prognostic as well as therapeutic. Ovarian cancer is surgically staged based on the Federation of Gynecology and Obstetrics (FIGO) staging criteria (► **Table 1**). Prognosis is strongly correlated with initial disease stage, as 10-year overall survival ranges from 73% for stage I disease compared with less than 5% for stage IV.⁶ Initial surgery often entails a vertical midline incision for removal of the uterus, fallopian tubes, and ovaries. Pelvic washings or ascites are collected for cytology. Pelvic and periaortic lymph nodes may also be removed. The omentum may be removed if there is visible disease, or biopsied if not. Random peritoneal biopsies may be obtained at the discretion of the surgeon. Any visible tumor is removed from the abdominal and pelvic cavities. A main focus of the surgery is to attempt “optimal” surgical tumor cytoreduction, which refers to less than 1-cm

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Table 1 FIGO staging of ovarian cancer

I	Tumor limited to the ovaries (one or both)
IA	Tumor limited to one ovary; capsule intact, no tumor on ovarian surface; no malignant cells in ascites or peritoneal washings
IB	Tumor limited to both ovaries; capsules intact, no tumor on ovarian surface; no malignant cells in ascites or peritoneal washings
IC	Tumor limited to one or both ovaries with any of the following: capsule ruptured, tumor on ovarian surface, malignant cells in ascites or peritoneal washings
II	Tumor involves one or both ovaries with pelvic extension
IIA	Extension and/or implants on the uterus and/or tube(s); no malignant cells in ascites or peritoneal washings
IIB	Extension to other pelvic tissues; no malignant cells in ascites or peritoneal washings
IIC	Pelvic extension (T2a or T2b) with malignant cells in ascites or peritoneal washings
III	Tumor involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis
IIIA	Microscopic peritoneal metastasis beyond the pelvis (no macroscopic tumor)
IIIB	Macroscopic peritoneal metastasis beyond the pelvis ≤ 2 cm in greatest dimension
IIIC	Macroscopic peritoneal metastasis beyond the pelvis > 2 cm in greatest dimension and/or regional lymph node metastasis
IV	Distant metastasis (excludes peritoneal metastasis)

Abbreviation: FIGO, Federation of Gynecology and Obstetrics.

Source: Adapted from Pecorelli S, Odicino F, Maisonneuve P, et al. Carcinoma of the ovary. FIGO annual report on the results of treatment in gynaecological cancer. *J Epidemiol Biostat* 1998;3:75–102.

diameter of the largest residual tumor. Optimal debulking is important because there is an inverse correlation between volume of residual tumor and overall survival.⁷

The methodology behind initial surgical treatment and evaluation, as well as the FIGO staging system, is based on the typical pattern of spread for ovarian cancer. Ovarian cancer can spread via the lymphatic and/or hematologic system, but it is most commonly spread via direct extension. Ovarian tumor cells shed into the peritoneal cavity and circulate throughout the abdomen and pelvis, eventually implanting along peritoneal surfaces.

Endometrial Cancer

Endometrial cancer is the most common malignancy of the female genital tract with a lifetime risk of 2.69%. It is often diagnosed and treated in early stages and has a 5-year survival rate of 81.5%.¹ Endometrial cancer is classically characterized as either type I or type II, although current molecular analysis is blurring the lines between these types. The majority of endometrial tumors are type I, which are related to excess estrogen. Type II tumors typically have a worse prognosis, as they have more aggressive histologies such as high-grade endometrioid, papillary serous, or clear cell. These type II tumors are not related to hyperestrogenism.

Surgery is the typical first-line therapy and staging is defined by surgical sampling of defined areas per the 2009 FIGO staging criteria (–Table 2). Adjuvant radiation and chemotherapy may be recommended on the basis of tumor size, histologic subtype, and extent of disease spread. The most common sites of metastatic spread are pelvic and

periaortic lymph nodes, fallopian tubes, ovaries, and the vagina. Surgical removal of the uterus and adnexa is necessary, with additional lymphadenectomy of the pelvic and periaortic areas at the surgeons' discretion based on uterine tumor characteristics such as grade and size.⁸

Tumor spread, in order of prevalence, is via direct extension, lymphatic, and less commonly hematologic spread. Direct extension is typically through the myometrium (stage I) and eventually through the serosa to surrounding pelvic tissue (stage III). Commonly, endometrial cancer can involve the cervix if the initial tumor was low lying in the endometrial canal (stage II). Lymphatic spread follows a typical locational progression of pelvic nodes (stage IIIC1) from uterine drainage and may also spread to the periaortic nodes from the ovarian lymphatics (stage IIIC2). Hematologic spread is the most likely source for distant metastasis, most commonly to the lung.

Cervical Cancer

Cervical cancer is still the most prevalent gynecological cancer worldwide; however, it is far less prevalent in industrialized countries. Most cervical cancer originates from high-risk human papillomavirus (HPV), which is a sexually transmitted infection. HPV 16 and 18 are detected in 95% of cervical cancers, and 80% of women demonstrate infection by HPV at some point in their lives.^{9,10} Other risk factors include demographic risks (ethnicity, socioeconomic status, age), behavioral risks (early coitarche, multiple sexual partners, smoking), and medical risk factors (immunosuppression, inadequate Papanicolaou screening, increased parity).

Table 2 FIGO staging of endometrial cancer

I	Tumor confined to the corpus uteri
IA	No or less than half myometrial invasion
IB	Invasion equal to or more than half of the myometrium
II	Tumor invades cervical stroma but does not extend beyond the uterus
III	Local and/or regional spread of the tumor
IIIA	Tumor invades the serosa of the corpus uteri and/or adnexae
IIIB	Vaginal and/or parametrial involvement
IIIC	Metastases to pelvic and/or para-aortic lymph nodes
IIIC1	Positive pelvic nodes
IIIC2	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
IV	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA	Tumor invasion of bladder and/or bowel mucosa
IVB	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

Abbreviation: FIGO, Federation of Gynecology and Obstetrics.

Source: Adapted from Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet* 2009;105(2):103–104.

The majority of cervical cancers are squamous cell originating at the squamo-columnar junction of the cervix, with the second most common being adenocarcinoma arising from the endocervical columnar cells. Tumor spread is lymphatic following the cervical lymphatic drainage starting in the paracervical and parametrial nodes, and progressing into the obturator then into the internal, external, and common iliac nodes, and finally into the periaortic lymph nodes. Tumor progression, and prognosis, also correlates with lymphovascular space involvement.^{11,12}

Unique among gynecological malignancies, cervical cancer is staged *clinically* (► **Table 3**). Physical exam, colposcopy, cervical or cone biopsy, cystoscopy, lower gastrointestinal endoscopy, barium enema, intravenous pyelography, and chest X-ray are all permissible tools for staging, but suspicious findings need biopsy confirmation. Computed tomography (CT) and magnetic resonance imaging (MRI) are used often to help delineate disease and define radiation treatment fields, but are not used for staging purposes, although the finding of hydronephrosis by ultrasound, CT, or intravenous pyelogram (IVP) does allow upstaging to IIIB without the need for biopsy. Primary therapy depends on the stage at diagnosis; early-stage disease is often treated with radical hysterectomy and pelvic lymphadenectomy, while advanced disease is treated with the combination of cisplatin chemotherapy and radiation.

Considerations for Biopsy

A request for a biopsy of a patient with suspected primary gynecologic malignancy is almost always for the questions “is this malignant” and “what is the cancer of origin.” What may appear as an ovarian mass, for instance, is not always ovarian cancer. Gastrointestinal malignancies, such as gastric or colorectal carcinomas, often metastasize to the ovary and

can easily mimic a primary ovarian malignancy (Krukenberg tumors). Breast carcinoma may also metastasize to the ovary. More rare metastases to the ovary can occur from lymphomas or melanomas.^{13–15} In addition, pelvic infection with tuberculosis or mycobacterium bovis may mimic an ovarian malignancy.

A biopsy may be requested for tissue confirmation of a primary ovarian malignancy before the initiation of chemotherapy. CT may demonstrate omental caking, enlarged lymph nodes, ascites, and a pelvic mass. For diagnostic purposes, it is preferable to obtain a core needle biopsy for histology, rather than ascites for cytology; more usable tissue is obtained from the core needle biopsy, which allows additional diagnostic immunohistochemical staining by the pathologist.

In the setting of a previous ovarian malignancy, a recurrence may be suspected due to a rising tumor marker, cancer antigen 125 (CA-125). CA-125 is sensitive but not specific for ovarian cancer, and many inflammatory or infectious conditions can cause an elevation in this marker. Requests for a biopsy of suspected gynecologic cancer recurrences may also be encountered. Often a CT scan or positron electron tomography (PET)/CT scan demonstrates an area of concern, whether the patient exhibits symptoms or not. The use of PET/CT to demonstrate ovarian cancer recurrence has a specificity of 82 to 87% and sensitivity of 73 to 100%.^{16–18} Similarly for cervical cancer, recurrence detection rates have a specificity of 85 to 90% and a sensitivity of 81 to 87%.^{19,20} Because the sensitivity and specificity are not 100% accurate, a biopsy may be requested for confirmation of recurrence.

Several factors enter into the decision process to perform biopsy or imaging. These include the length of time from initial diagnosis as well as response to first-line treatment(s). If there is a significant length of time from initial treatment or the anatomic location of recurrence is not typical for the

Table 3 FIGO staging for cervical cancer

I	Cervical carcinoma confined to the cervix (disregard extension to the corpus)
IA	Invasive carcinoma diagnosed only by microscopy; stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less; vascular space involvement, venous or lymphatic, does not affect classification
IA1	Measured stromal invasion ≤ 3.0 mm in depth and ≤ 7.0 mm in horizontal spread
IA2	Measured stromal invasion > 3.0 mm and ≤ 5.0 mm with a horizontal spread ≤ 7.0 mm
IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
IB1	Clinically visible lesion ≤ 4.0 cm in greatest dimension
IB2	Clinically visible lesion > 4.0 cm in greatest dimension
II	Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina
IIA	Tumor without parametrial invasion
IIA1	Clinically visible lesion ≤ 4.0 cm in greatest dimension
IIA2	Clinically visible lesion > 4.0 cm in greatest dimension
IIB	Tumor with parametrial invasion
III	Tumor extends to pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or nonfunctional kidney
IIIA	Tumor involves lower third of vagina, no extension to pelvic wall
IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctional kidney
IV	Tumor invades mucosa of bladder or rectum and/or extends beyond true pelvis (bullous edema is not sufficient to classify a tumor as T4)
IVA	Tumor invades mucosa of bladder or rectum (bullous edema is not sufficient to classify a tumor as T4)
IVB	Tumor extends beyond true pelvis

Abbreviation: FIGO, Federation of Gynecology and Obstetrics.

Adapted from Pecorelli S, Zigliani L, Odicino F. Revised FIGO staging for carcinoma of the cervix. *Int J Gynaecol Obstet* 2009;105(2):107–108.

pelvic malignancy, biopsy may help reveal a new primary malignancy. For instance, a recurrence of endometrioid endometrial carcinoma would be suspected if a vaginal mass or pelvic sidewall lymph node were enlarged; however, a new posterior fossa cranial mass is unlikely to arise from an endometrial cancer. Similarly if there is a clinical recurrence but no rise in tumor markers, biopsy may provide more relevant information for the discrepancy.

Biopsy Volume and Type

Beyond the use for purely diagnostic purposes, percutaneous image-guided biopsies may be used to obtain tissue for molecular analysis, which may allow targeted therapy. Studies have shown that fine-needle aspiration (FNA) and core needle biopsy have similar diagnostic accuracies. Malmström demonstrated sensitivities of 92 versus 73% and specificities of 92 versus 100% for FNA versus core biopsy, respectively.²¹ Positive predictive values were relatively similar at 96 and 100% for FNA and core biopsy. However, for cancer recurrence, core biopsy is superior for tissue and histological evaluation.

It is important to understand how the primary team intends to use the tissue before obtaining a biopsy. Specifically, certain diagnostic companies have requirements for adequate tissue processing. Caris Life Sciences (Irving, TX) offers genetic profiling and individual assays for gynecological tumor markers and biomarker tumor analysis for therapy.

The tissue procurement requirements for core needle biopsy are four to six formalin-fixed biopsy specimens, preferably from an 18-gauge needle. If insufficient tissue is obtained, the company is often unable to run the full list of requested tests. Similarly, ChemoFx (Precision Therapeutics, Pittsburgh, PA) is another test that specifically looks at tumor response to chemotherapy agents with the goal of tailoring chemotherapy. Their procurement requirements for core biopsy are two cores from a 14-gauge device, three cores from a 16-gauge device, or four cores from an 18-gauge device. While a single successful core biopsy may yield enough diagnostic tissue for an institution's diagnostic pathologist, it may not be sufficient for the molecular profiling of the tumor for cancer recurrence.

Molecular Analysis of Biopsy Specimens

Gynecological cancers have varying histological subtypes that all behave differently in regard to factors such as growth, survival, recurrence, and response to treatment. While there is still an enormous amount to learn about the molecular profiling involved, there is currently a substantial knowledge of varying cancer biomarkers and pathways that can guide practitioners in personalizing patient treatment. This technology is promising in its potential for significant advancements in disease detection, treatment, and further tumor characterization.

Research in the area of genetic profiling has had a high level of interest over the past two decades because significant advancements in the field have led to promising findings as well as clinical outcomes in the world of cancer. The goal of personalized medicine in oncology is becoming obtainable through these technologies.

Genetic profiling has been significantly advanced by the use of microarray technology. Simply, this is the use of a biochip to measure complementary DNA and the messenger RNA expression of a large number of genes at once. This technology enables investigators to study the expression of many genes that may be related to a cancer on a molecular level. Some biomarkers may be associated with significant amplifications or deletions of chromosomal material, which is detected through cytogenetics. The goal of cytogenetic and expression profiling of tumors is to examine known biomarkers associated with gynecological cancers and predict a possible response of the tumor to targeted chemotherapy treatments.

Ovary

In the field of gynecologic oncology, the most significant focus for molecular profiling has been in the direction of ovarian malignancy. Clinical use is predominantly limited to guiding potential chemotherapy or biologic therapies targeting known cancer pathways as stated above. Advancements in our knowledge of ovarian cancer are improving patient longevity and patients are receiving more chemotherapy courses. As tumor heterogeneity changes over time in response to selection pressure from prior chemotherapeutic agents, the molecular profile also changes. Repeat biopsies are needed to accurately capture the specific tumor composition at a given point in time and indicate which pathways are now driving the recurrent clonal expansion of the tumor.

In the realm of ovarian cancer research, the goals of molecular profiling are to improve diagnosis through the use of biomarkers and to aid in treatment by both predicting chemotherapy response as well as identifying chemotherapy resistance. A research aim of tissue biopsy is to further characterize subtypes of ovarian malignancies to develop a hierarchy of ovarian cancers similar to that developed for breast cancers.²²

Microarray technology has enabled us to further characterize molecular subtypes of ovarian neoplasms. Tothill et al identified six molecular subtypes of ovarian cancer and directly linked them to clinical and pathological features.²³ These subtypes are able to distinguish low malignant potential from higher grade and advanced stage cancers. Multiple other studies have looked to characterize specific histological subtypes such as lower and higher grade disease, serous versus endometrioid, and genetic markers of mucinous, serous, endometrioid, and clear cell histology.²⁴ The molecular classification of ovarian cancer further aids in proper diagnosis and management of patients.

Prognosis of ovarian cancer is highly dependent on time to recurrence as well as multiple tumor-specific factors. The Ovarian Cancer Prognostic Profile developed by Spentzos et al²⁵ is a 115-gene signature that can predict long-term survival as a distinct variable using a combination of estrogen pathways, angiogenesis cytokines, tyrosine kinase receptors,

mesenchymal markers, and proinvasive enzymes. Berchuck et al further developed an expression model that distinguishes short-term (< 3 years) versus long-term (> 7 years) survival of epithelial ovarian cancer patients.²⁶ These studies, each independently validated, demonstrate that gene profiles are directly attributable to patient prognosis. None, however, are currently in use clinically. This knowledge may be useful in determining which patients should be directed toward clinical trials earlier in their treatment and even potentially before first-line therapy.

First-line therapy of platinum and taxane has remained consistent over the past several decades; however, genetic profiling has the potential to offer individualized variations. Spentzos et al identified a 93-gene signature labeled as the chemotherapy response profile that accurately predicts pathologic complete response at second look laparoscopy.²⁷ Importantly, direct evaluation of first-line therapy has found multiple genetic profiles that predict platinum resistance as well as response.^{28–30} Knowledge of *a priori* platinum resistance can limit the toxicity and morbidity from an ineffective treatment. Platinum is commonly used in combination with other chemotherapy in second-line treatment as well.

Additionally, there have been attempts to profile genes related to efficacy of second-line therapies. Direct polymorphism studies have shown various efficacies for patients with or without specific polymorphisms toward drugs such as methotrexate and bevacizumab.³¹ Similarly, Hartmann et al identified a gene signature that is able to predict patients at high risk for early recurrence after first-line platinum and paclitaxel therapy.³² These genetic profiles give the clinician direct patient and tumor-specific information to help optimize both first-line and second-line therapies.

Endometrium

Similar to ovarian cancers, molecular profiling of endometrial cancer has been used for diagnosis, treatment, and further classification. Endometrial cancer is more simply divided into the two subcategories, type I and type II, as described above. Type I, or estrogen related, tumors have been associated with several genetic mutations including PTEN (phosphatase and tensin homolog), KRAS (Kirsten rat sarcoma viral oncogene), β -catenin, PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit α), and microsatellite instability.^{33,34} Type II tumors are typically (~ 90%) associated with p53 (tumor protein 53) mutations but have also been associated with HER2/neu (human epidermal growth factor receptor 2), p16 (cyclin-dependent kinase inhibitor 2A), E-cadherin, and apoptosis deregulation genes. Carcinosarcoma of the uterus has been associated with C-MYC mutations and loss of heterozygosity of the p53 gene.^{33,35} Detection of these genetic mutations and study of their related pathways have led to potential therapies including mammalian target of rapamycin inhibitors such as temsirolimus, everolimus, and deforolimus; epidermal growth factor receptor inhibitors such as gefitinib, erlotinib, and lapatinib; anti-HER2/neu trastuzumab; and monoclonal antibodies targeting vascular endothelial growth factor such as bevacizumab and sorafenib.³³ Knowledge of the genetic profiles and pathways of endometrial cancer has led to tumor-specific therapies.

Cervix

Molecular profiling of cervical cancer is the least studied among gynecological cancers. This may be due to the high volume of knowledge about its precursor virus HPV. However, the area most focused in genetic profiling of cervical cancer relates to which patients infected with HPV progress to cervical cancer. The majority of HPV infections will clear on their own in 1 to 2 years, but certain HPV types are more likely to progress to cancer, including HPV 16 and 18. The suspected genetic associations of cervical cancer progression as well as treatment response are currently incompletely understood; however, viral genes E6 and E7 have been implemented in activating cell proliferation; downregulation of the BAX (BCL-2-associated X protein) and APC (adenomatous polyposis coli) genes have been demonstrated in lymphatic spread; and a high risk of progression model using elevated gene expression of MK167 (human K_i-67), CDKN2A (cyclin-dependent kinase inhibitor 2A), PGR (progesterone receptor), and BAX has been proposed.^{36,37}

Current Use

Caris Molecular Intelligence™ and ChemoFx® tests are widely used, although there are other companies marketing the use of these technologies as well. These companies are examples of two different technologies currently being used with direct patient tissue specimens. The information returned to the clinician is typically in an easy to read format that states which chemotherapy or biologic therapy may have potential benefit or potential lack of benefit. The ChemoFx assay provides results categorized by “responsive,” “intermediate response,” and “nonresponsive.” This assay directly tests chemotherapy on individualized tissue. The Caris assay utilizes cytogenetic testing, microarray, and gene sequencing to provide the clinician with information on potential genetic targets, such as PIK3CA, KRAS, or BRAF (v-raf murine sarcoma viral oncogene), which are related to the specific tumor pathways and can aid in potential direction toward appropriate clinical trials of new agents. Biopsy specimens sent for these tests are typically on recurrent disease, and the information from these reports can help guide second-line therapy toward more effective treatments while avoiding unnecessary toxicities from drugs that will demonstrate no response for that patient.

Cost Effectiveness

Havrilesky et al demonstrated that aside from the observed potential clinical benefit to the patient, there may also be an overall reduced cost of therapy.³⁸ Their group utilized patient data over a 5-year period and studied costs of three groups of patients receiving chemotherapy for recurrent ovarian cancer. The groups were assigned as (1) those who were treated according to a chemotherapy response assay; (2) those who were treated with the oncologist's choice of chemotherapy following chemotherapy response testing; and (3) those who were empirically treated with the most frequently used chemotherapy agents and no assay was used. The cost to the patient, including that of the assay (for those who adhered to the chemotherapy assay recommendations), compared

with empiric treatment was \$23,986 versus \$48,758 for six cycles of therapy, respectively. It is important to recognize that these assays are not instructions on how to treat a malignancy, but rather a guide to which therapies the tumors are more or less likely to be responsive.

Conclusion

Genetic profiling after percutaneous image-guided biopsy is a relatively new technology that many clinicians are using to tailor patient-specific therapies for gynecological malignancies. Although currently there has been no change in first-line therapies, this is an area of high potential for significant advancement in patient care and disease knowledge. Use of genetic profiling may determine the recurrence risk of a tumor, the likely timing of a recurrence, and the predicted efficacy of a chemotherapy agent.

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