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Review

Molecular Signature of Gynecological Malignancies: A Narrative Review

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Abstract

Background: Cancer research is significantly improved by comprehensive DNA sequencing and profiling. Genes involved in diagnostic, prognostic, or therapeutic consequences have been extensively studied using high-throughput sequencing. Thus, precision medicine based on cancer genotype has been developed, leading to improved survival. The fifth edition of the *World Health Organization Classification of Tumors* specified a diagnostic molecular pathology section under each disease category. **Methods**: We highlight the molecular aspects in research and diagnostics of diverse gynecological malignancies using database resources in addition to data mining software tools. **Results**: This review article presents insight into various gynecological cancers and their different characteristics, offering better profiling for switching to better therapeutic options. **Conclusions**: Genomic profiling is evolving as a clinically feasible tool for personalizing treatment. It can provide insight regarding treatment plans for common gynecological cancers.

Keywords: molecular markers; gynecological malignancies; hereditary cancer syndrome

1. Introduction

Cancer is a disease in which a defect occurs in the balance between cell growth and death. It has been reported that several molecules are implicated in oncogenesis, metastasis, and treatment sensitivity. In comparison with other areas of oncology, gynecological oncology has been slow to adopt personalized medicine based on genetics. Current molecular assays can detect genomic alterations, including substitution, insertion or deletion events (indels). In addition, tumor mutational burden (TMB), microsatellite instability (MSI) and homologous recombination deficiency (HRD) can also be assessed.

At the genetic level, most cancer cells are unstable, resulting in accumulated mutations that lead to malignant behavior, such as invasion and metastasis. Alterations in oncogenes, which stimulate cell growth, promote carcinogenesis [1]. Moreover, *KRAS* mutations are among the most common oncogenes. Additionally, *BRAF* is a serine/threonine-specific protein kinase that interacts with Ras proteins to activate the mitogen-activated protein kinase (MAPK) pathway. The *BRAF* V600E mutation has been described in many tumor cases. Mutations in tumor suppressor genes, which present a loss of genetic function, disrupt the regulation of cell cycle progression. The two-hit theory of inactivation involves each allele of these genes. Statistically, the TP_{53} gene is mutated in most human cancers [2].

2. Epithelial Ovarian Cancer

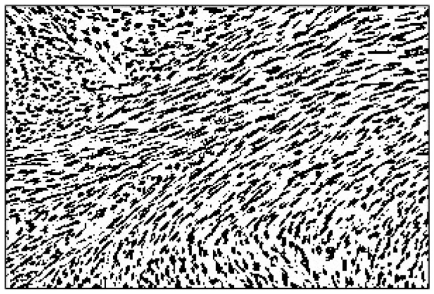
The epithelial subtype of ovarian malignancies represents the most common gynecologic cancer mortality in Western countries [3]. Clinical presentations and treatment responses vary between subtypes based on the internal biology of these tumors.

2.1 High-Grade Serous Ovarian Carcinoma (HGSOC)

The TP_{53} (tumor suppressor gene) mutation characterizes HGSOC. According to the Cancer Genome Atlas (TCGA), most HGSOC harbors *BRCA1/2* (tumor suppressor gene) germline or somatic mutations associated with improved overall survival and better sensitivity to platinum-based chemotherapy [4,5]. In contrast, the *CCNE1* gene amplification exhibits dismal prognosis and treatment resistance [6]. The molecular subtype switches from C2 to C1, which is the main etiology behind the resistance behavior [7].

2.2 Low-Grade Serous Ovarian Carcinoma (LGSOC)

In LGSOC, the two most commonly detected mutations are *BRAF* and *KRAS* (oncogenes), which are mutually exclusive [8]. The estrogen (ER)/progesterone receptor (PR) expression predominates in this category [9]. *BRAF* mutations are uncommon among LGSOC, and their existence frequently does not disturb prognosis compared to the occurrence of a *KRAS* transformation, which has been described as an opposing prognostic feature [10]. Chemotherapy regimens have limited therapeutic interest in LGSOC. The reported MAPK pathway mutations account for approximately 80% of LGSOC, which provides a rationale for using MEK inhibitors in these tumors [11].



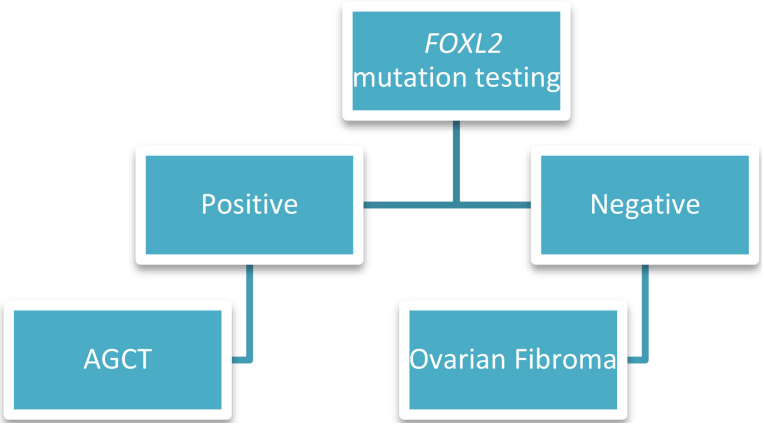


Fig. 1. Differentiating adult granulosa cell tumor (AGCT) versus ovarian fibroma in oophorectomy specimen with pure spindle cell growth and equivocal reticulin stain.

2.3 Clear Cell Carcinoma

The PI3K/Akt and RTK/Ras pathway mutations are the main variants in clear cell carcinomas. Most of these are in *ARID1A* (chromatin remodeling) and *PI3KCA* (phosphorylation) genes [12].

2.4 Ovarian Endometrioid Carcinoma

About half of low-grade endometrial ovarian cancers have mutations in the *CTNNB1* gene that encodes β-catenin (adherent junction protein) [13].

2.5 Mucinous Ovarian Carcinoma

Similar to mucinous colon adenocarcinoma, *KRAS* mutations are the most encountered aberrations in the ovarian counterpart. To a lesser extent, *HER2* amplification is also detected [14]. The *HER2* activation initiates the upstream *KRAS* pathway (promotes the growth of cancer cells). Therefore, trastuzumab may play a role in *HER2* amplified mucinous carcinoma [15].

2.6 Adult Granulosa Cell Tumor (AGCT)

Nearly all AGCTs harbor the recurrent somatic *FOXL2* mutation [16]. It has diagnostic value in cases where AGCTs lack the typical morphology. For example, an AGCT with pure spindle cell growth may result in a differential diagnosis of ovarian cellular fibroma. When the reticulin special stain is equivocal, *FOXL2* mutation testing is indicated. The detected mutation favors rendering an AGCT diagnosis (Fig. 1). However, cellular fibroma cases have an absence of the *FOXL2* mutation. In addition, *FOXL2* testing is useful when distinguishing an AGCT from a juvenile one. Juvenile granulosa cell tumors lack the *FOXL2* mutation [17].

2.7 Small Cell Carcinoma of Hypercalcemic Type

The small cell carcinoma of hypercalcemic type is primarily observed in young women, with an unfavorable outcome. Germline/somatic *SMARCA4* is detected in nearly all tumors [18].

3. Implications of Therapeutics in Advanced Epithelial Ovarian Carcinoma

Poly ADP-ribose polymerase (PARP) inhibitors have resulted in better progression-free survival in ovarian cancer patients. The (2.2021) version of the National Cancer Comprehensive Guidelines recommended PARP inhibitors in homologous recombination deficient cases, which can be defined by either a *BRCA* mutation detection or a genomic instability score of $\geq$42 using myChoice CDx (Myriad Genetics) testing. Furthermore, immunotherapy may be used in mismatch repair deficient (dMMR) cases or tumors with a high mutational burden (TMB-H). Similarly, positively identified *NTRK* gene fusion tumors are candidates for Trk inhibitor–targeted therapies (Fig. 2) [19]. Checkpoint blockade monotherapy has led to only minor advances in gynecologic cancer. Thus, combination therapies with other immunotherapies, targeted drugs, chemotherapy and radiation therapy have been considered in clinical trials [20].

4. American Society of Clinical Oncology Testing Recommendations in Epithelial Ovarian Carcinoma

A germline mutational analysis for the *BRCA1/2* germline should be performed in all patients with epithelial ovarian carcinoma. Negative cases are followed by somatic *BRCA1/2* testing using formalin-fixed, paraffin-embedded tissue. The *BRCA* status plays an important role in guiding decisions about maintenance therapy, as PARP inhibitors work best in *BRCA* mutated cancers. Second, the MMR status should be evaluated in mucinous, endometroid and clear cell ovarian carcinoma. Other histology types are optionally tested. Immunotherapy can target advanced or metastatic cancer, that is, MSI-H or dMMR. Finally, the

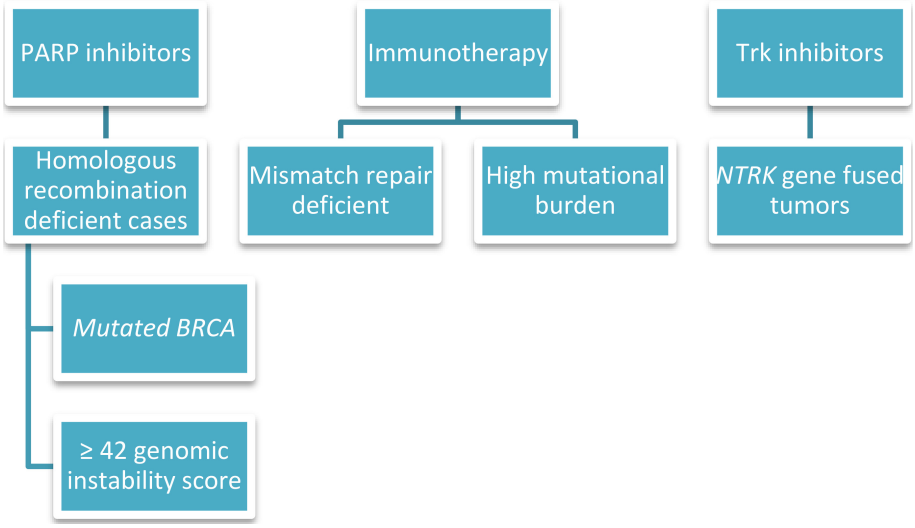


Fig. 2. Molecular testing and its therapeutic implications in advanced epithelial ovarian cancer.

ovarian cancer susceptibility multigene panel should include a minimum of *BRCA1/2*, *RAD51C/D*, *BRIP1*, *MLH1*, *MSH2/6*, *PMS2* and *PALB2* genes [21].

5. Malignant Ovarian Cell Germ Tumors

An i(12)p or 12p amplification is frequently observed in embryonal carcinoma. Similarly, chromosome 12 abnormalities can be observed in mixed germ cell tumors and can also develop in dysgenetic gonads with an aberrant karyotype. In embryonal carcinoma, the gold standard molecular tool for distinguishing nongestational from gestational choriocarcinoma is the short tandem-repeat DNA sequences because the genome in the nongestational subtype resembles that of the host, and no nonmaternal/paternal component is found [22].

6. Cancer of the Endometrium

Postmenopausal bleeding presentation helped discover endometrial carcinoma in its initial stage. One-third of patients present with advanced stage or tumor relapse, which is difficult to treat [21]. Historically, type 1 tumors are associated with *PTEN* loss, *PICK3CA* mutations and ER/PR positivity, whereas type II tumors harbor TP_{53} mutations and *PIK3CA* amplification [23]. Recent evidence from the TCGA group indicates that the following four outlined molecular alterations are important in determining the overall outcomes [24].

(1) Ultra-mutated polymerase epsilon (*POLE*): The *POLE* mutated subtype is more commonly observed in high-grade endometrioid carcinomas presenting at a young age with a favorable prognosis [25]. The improved outcome is justified by neoantigens production caused by the extreme tumor mutational burden, stimulating the immune system and antitumor effects. Recent studies have reported a dramatic response to checkpoint inhibitors (anti-PD1).

(2) MSI hypermutated: Approximately 30% of endometrial carcinoma cases have MSI due to mutations in the *MLH1*, *MSH2*, *MSH6* and *PMS2* genes, leading to MMR loss. Furthermore, immunohistochemistry stains have revealed a good correlation with the MSI status using the polymerase chain reaction [26]. About half of undifferentiated/dedifferentiated carcinomas of the endometrium are dMMR [27]. These tumors may be associated with Lynch syndrome, present at a relatively young age, arising from the lower uterine segment with intense intra/peritumoral infiltrating lymphocytes. Checkpoint inhibitors are recommended for this subtype as well.

(3) The p53 mutant (copy number high): The p53 aberrant expression immunostaining pattern (all or null) is more commonly observed in high-grade serous histology with destructive growth, diffuse cytonuclear atypia, lymphovascular invasion and the worst outcome. The treatment modality combines aggressive surgery (lymphadenectomy and omentectomy), adjuvant chemotherapy and radiotherapy.

(4) No specific molecular profile (NSMP) (copy number low): This entity is MMR proficient with a lack of mutation in the TP_{53} and *POLE* genes. Most wild-type p53 is FIGO Grade 1 or 2 endometrioid carcinomas with frequent squamous differentiation. Hormonal therapy/mammalian target of rapamycin (mTOR) inhibitors may be of value in these cases. Early-stage endometroid endometrial carcinoma, especially in the NSMP group, appears significantly more likely to recur if the *CTNNB1* exon 3 mutations are present [28].

Undifferentiated/Dedifferentiated Carcinoma of the Endometrium

Inactivating mutations involving *SMARCA4/B1*, *ARID1A/B*, or the dMMR status can support the diagnosis of undifferentiated/dedifferentiated carcinoma of the endometrium [29]. Prognosis-wise, Santoro *et al.*

Table 1. Summarizes the hereditary gene associations.

Gene	Syndrome	Morphology
BRCA1 *BRCA2*	Hereditary breast and ovarian cancer syndrome [38]	High-grade serous carcinoma of the ovary, fallopian tubes and peritoneum
MSH2 *MLH1* *MSH6* *PMS2*	Lynch syndrome [40]	Uterus: Endometroid, clear, undifferentiated and dedifferentiated carcinoma Ovary: Endometroid, clear and undifferentiated carcinoma
STK11	Peutz–Jeghers syndrome [41]	Gastric type endocervical mucinous adenocarcinoma (from minimal deviation to malignant), sex cord tumor with annular tubules
PTEN	Cowden syndrome [42]	Low-grade endometrial carcinoma (major criteria), fibroid (minor criteria)
ATM	Ataxia telangiectasia [43]	Dysgerminoma
PRKAR1A	Carney complex [44]	Carney genital lentigines
DICER1	*DICER1* syndrome [45]	Sertoli–Leydig tumor
VHL	Von Hippel–Lindau syndrome [46]	Genital tract papillary cystadenoma, particularly bilateral
FH	Fumarate hydratase deficiency [47]	Uterine leiomyoma with staghorn vasculature, alveolar pattern oedema and prominent eosinophilic nuclei with halo

[30] suggested dividing undifferentiated/dedifferentiated endometrial carcinoma into three risk groups. The SWI/SNF-deficient cases have a dismal prognosis compared to *POLE*-mutant cases. The biological behavior of the other TCGA molecular subtypes appears intermediate [30].

7. Sarcoma of the Endometrium

Although the incidence of uterine sarcomas is rare, recent updates have been made in this group regarding molecular aberrations. Endometrial stromal sarcoma (ESS) is an indolent local recurrent tumor with distant metastases following a prolonged time from the initial diagnosis. Notably, the loss of CD10 and ER/PR expression is a poor prognostic factor. The genetic rearrangement of t (7:17) (p15;q21), leading to a *JAZF1-SUZ12* fusion, occurs in about 50% of low-grade ESS with metastatic tendency [31]. A differentiating factor for high-grade ESS is the t (10;17) (q22;p13) *YWAAE-NUTM* fusion associated with a favorable outcome [32].

8. Cancer of the Cervix

The human papillomavirus (HPV) 16 and 18 are high-risk types known to significantly increase the risk of cervical cancer and high-grade precancerous lesions, followed by the strains HPV31 and HPV33. The incorporation of HPV into the genome of the host cell is crucial for carcinogenesis development [33]. Moreover, E6 and E7 viral oncoproteins disrupt p53 and Rb host cell suppressor genes, respectively, eventually causing replication and cellular division. On the cytological level, majority of high-grade squamous intraepithelial lesions (HSIL) and cervical carcinoma are caused by HPV 16 and 18. In contrast, HPV6 and 11 were described in low-grade squamous intraepithelial lesion (LSIL) specimens. Similar to pap smears, the early detection of HPV integrated atypical squamous cells of undetermined significance (ASCUS)/LSIL cases can be used for early prevention and intervention. The percentage of HPV infection persistence is minor compared to the viral clearance rate. The malignant transformation of cervical lesions requires persistent infection. Further, HPV-negative tumors exhibit *KRAS*, *ARID1A* and *PTEN* mutations [34].

The *PIK3CA* mutations are commonly detected in cervical cancers. However, the TP_{53} mutation, a common occurrence in many malignancies, is not observed in cervical cancers or cervical intraepithelial neoplasia. Additional genes, some of which have been linked to cancer development, including *PTBP3*, *ESX1*, *PER3* and *CIP2A*, were simultaneously mutated in cervical cancers and cervical intraepithelial neoplasia [35].

9. Vulvar Squamous Cell Carcinoma

Most vulvar malignancies have squamous morphology. The severe morbidity during treatment adds an additional layer of complexity. A better molecular prognostic stratification instrument has been described to reduce treatment-related morbidity, as follows:

(1) HPV-associated: This type represents most cases and is commonly observed in younger women with slow progression from an HSIL to a basaloid or warty invasive cancer exhibiting block-type immunoreactivity to p16 immunostaining and positive HPV-ISH.

(2) HPV-independent (TP_{53} mutant): This entity is observed in postmenopausal patients with a high propensity for recurrence and a poor outcome. It usually arises from differentiated vulvar intraepithelial neoplasia.

(3) HPV-independent (wild-type TP_{53}): Verrucous squamous cell carcinoma is frequently associated with a wild-type p53 expression pattern [36].

10. Hereditary Cancer Syndrome of the Female Genetic Tract

Early onset cancers raise the possibility of inherited mutations. Familial cancer syndromes are caused by mutations in tumor suppressors or DNA mismatch repair genes. For instance, *BRCA1/2* are involved in hereditary breast and ovarian cancer syndromes. *APC* in familial adenomatous polyposis syndrome. and *MLH1*, *MSH2*, *MSH6* and *PMS2* in hereditary nonpolyposis colorectal cancer syndrome (Lynch syndrome) [37–49]. Furthermore, Table 1 (Ref. [38,40–47]) summarizes the hereditary gene associations.

11. Conclusions

As the treatment of advanced or recurrent cancers with conventional regimens is becoming challenging, novel and highly specific therapeutic targets must be developed for the better detection and identification of gynecological cancers. The molecular mechanisms of human cancers have been investigated over the years through an exponential increase in genomic and proteomic data collection. In gynecologic oncology, studies dealing with prognostic indicators have aimed to identify subsets of patients with a high risk of recurrence. Hence, analyzing the prognostic factors might be beneficial for segregating the extent and effectiveness of the surgical approach.

The current review highlights the importance of targeted detection in clinical settings, including prognostic and diagnostic purposes and personalized medicine. Therefore, molecular signatures and the genomic profiling insight are beneficial for treatment planning for common gynecological cancers and therapeutic purposes.

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Ethics Approval and Consent to Participate

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Conflict of Interest

The author declares no conflict of interest.

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