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Editorial

Advancements in Gynecologic Pathology: A Molecular, Digital, and Biobanking Perspective

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The landscape of women's health is constantly evolving. In the field of gynecologic pathology, the cornerstone of accurate diagnosis and treatment planning has long been histopathology, the microscopic examination of tissues. By precisely defining tumor type, grade, and invasion depth, histopathology guides critical decisions that impact a woman's course of treatment and overall prognosis. However, despite its established role, histopathology faces limitations in early cancer detection, managing the variability seen in tissue samples, and adapting to the growing use of minimally invasive surgical techniques.

Recent years have witnessed a remarkable evolution fueled by advancements in molecular pathology, digital pathology, and biobanking. These transformative technologies have not only revolutionized our understanding of disease processes but have also paved the way for personalized diagnostics and therapeutics.

1. Molecular Pathology Unveils the Molecular Landscape

Molecular pathology has revolutionized our understanding of gynecologic diseases [1]. Techniques like next-generation sequencing (NGS) enable the identification of actionable mutations for targeted therapies.

Endometrial cancer (EC) classification has traditionally relied on a type I/type II system, but this approach falls short in capturing the full molecular heterogeneity of the disease. The advent of molecular characterization has revolutionized our understanding of EC, identifying four distinct subgroups with unique genetic profiles through analysis of tumor DNA.

This shift towards molecular characterization extends beyond mere classification. By pinpointing specific mutations, such as those in the gene which encodes the catalytic subunit of DNA polymerase epsilon (*POLE* gene), we can gain valuable prognostic information. *POLE* mutations often correlate with favorable outcomes despite aggressive histological features. This newfound knowledge can directly impact treatment decisions, with certain molecular markers demonstrating responsiveness to immunotherapy.

While powerful, molecular characterization faces challenges. Techniques, such as whole-genome sequencing, seem ideal but are cost-prohibitive and have limited availability in routine clinical practice.

The future of EC classification likely lies in integrating traditional methods with robust molecular data. This synergistic approach will empower clinicians to create a more nuanced picture of each patient's cancer, ultimately leading to more accurate risk stratification and personalized treatment strategies [2,3].

Epithelial ovarian cancer (EOC) is a complex disease with various types. Breast cancer genes (*BRCA*) mutations are prevalent in high-grade serous carcinomas (HGSOC) and influence treatment decisions. Traditionally, *BRCA* testing analyzed blood (germline DNA). Currently, Next Generation Sequencing (NGS) allows testing on tumor formalin-fixed and paraffin embedded (FFPE). While NGS offers advantages, it presents challenges due to mixed cell populations in tumors and complex *BRCA* gene variations. However, NGS-based tumor *BRCA* testing can identify somatic mutations and assess poly (ADP-ribose) polymerase inhibitors (PARPi) therapy potential. Studies support the reliability of tumor *BRCA* testing, and although some propose it for Hereditary Breast and Ovarian Cancer (HBOC) diagnosis, proper validation is essential [4].

BRCA mutations are more common in high-grade serous ovarian cancer (HGSC), but National Comprehensive Cancer Network (NCCN) guidelines advise testing all EOC patients to identify hereditary risk. Some societies recommend a more targeted approach for HGSC/non-mucinous tumors due to cost-effectiveness. *BRCA* testing can identify variants of uncertain significance (VUS) which complicate treatment decisions. Researchers are working to refine VUS interpretation for better risk assessment and targeted therapies in EOC [5].

If PARPi have revolutionized treatment for EOC patients with *BRCA* mutations, a subset of EOCs without *BRCA* mutations might also benefit from PARP therapy. One potential indicator is *BRCA1* gene methylation, a process where a chemical group silences the gene. Studies suggest *BRCA1* methylation might predict a good response to PARP inhibitors, but results have been inconsistent due to different testing methods. This inconsistency highlights the need for standardized testing methods. Pyrosequencing,

a highly quantitative technique, appears promising for accurately measuring *BRCA1* methylation levels in FFPE tumor samples. Further research is crucial to validate pyrosequencing as a reliable method for *BRCA1* methylation testing. If successful, it could pave the way for using *BRCA1* methylation as a biomarker to identify EOC patients who might benefit from PARP inhibitor therapy [6].

However, *BRCA* mutations only represent one cause of homologous recombination deficiency (HRD). Other genetic alterations and epigenetic factors can also contribute to a deficient HRD state. This emphasizes the need for comprehensive HRD testing beyond just *BRCA* mutation analysis. Several assays have been developed to assess HRD status, including analysis of genomic scars from homologous recombination events (Loss of Heterozygosity and Translesion Synthesis), functional assays measuring DNA repair capacity, and mutation analysis of other HRD-related genes [7].

While *BRCA* mutations are a significant indicator of HRD, they are not sufficient to definitively determine a patient's HRD status. Further studies are essential to fully understand the complex interplay between *BRCA* mutations, HRD, and response to PARPi therapy in EOC patients. Implementing comprehensive HRD testing strategies will ensure optimal treatment selection and improved clinical outcomes for this patient population [8].

EOC remains a deadly foe, with most cases diagnosed at late stages. PARPi have transformed treatment for *BRCA*-mutated EOC, but new options are urgently needed for other subtypes. The culprit for many EOCs is the *TP53* gene, which controls critical tumor-suppressing functions. Mutations in *TP53* disrupt these controls, making tumors more aggressive. The sheer number and variety of *TP53* mutations pose a challenge for developing one-size-fits-all drugs.

Identifying null mutations with immunohistochemistry could be a game-changer. It might allow clinicians to predict tumor aggressiveness and tailor treatments accordingly. This approach, if validated, could pave the way for more effective therapies and improved outcomes for EOC patients [9].

While traditional therapies have been the mainstay of treatment, limitations exist managing variability in gynecologic cancers. This has spurred the exploration of more personalized treatment options. One particularly exciting area is immunotherapy, which uses the body's own immune system to fight cancer. Immune checkpoint inhibitors (ICIs) such as pembrolizumab and atezolizumab have shown success in various cancers, but their effectiveness in gynecologic cancers is limited. Researchers are focusing on understanding the tumor microenvironment and how it suppresses the immune system to improve immunotherapy outcome. Combining molecular pathology with tumor immune microenvironment (TIME) studies offers a promising approach for gynecologic cancers. Molecular pathology identifies targets for immunotherapy, while TIME analysis reveals the immune landscape of the tumor. This knowledge allows tailoring immunotherapy for each patient and developing strategies to overcome resistance. This synergy holds the key to personalized and effective immunotherapy in gynecologic malignancies [10].

Gynecologic cancers are especially challenging due to their immunosuppressive environment, making immunotherapy a particularly promising avenue for treatment. Programmed Cell Death Protein 1 (PD-1) is a protein that helps prevent T cells from attacking healthy cells. Drugs that block PD-1, similar to pembrolizumab, can boost the immune system's attack on cancer cells. Interestingly, PD-1 is also found on Natural Killer (NK) cells, suggesting that blocking this receptor could improve their anti-tumor activity. Studies have shown that ovarian tumors have a high number of PD-1 + NK cells.

Clinical trials are currently underway to improve immunotherapy for gynecologic cancers, including combinations with traditional treatments. For example, atezolizumab combined with paclitaxel is used for some advanced breast cancers, while pembrolizumab is used for specific types of endometrial cancer.

Researchers are aiming to improve immunotherapy for gynecologic cancers by understanding the immune system's role in these tumors and identifying the best treatment strategies for individual patients. This includes exploring the reasons behind treatment failures. This knowledge will be crucial for developing new immunotherapies and optimizing combination treatments for personalized cancer care [11].

2. Digital Pathology Augments Diagnostic Accuracy and Collaboration

Digital pathology has transcended traditional microscopy-based diagnostics by digitizing histopathologic slides and enabling remote viewing, analysis, and sharing of pathologic specimens. Leveraging image analysis algorithms and machine learning, digital pathology offers enhanced diagnostic accuracy, reproducibility, and efficiency [12]. Whole slide imaging (WSI) is a key component, enabling quantitative analysis of tissue samples [13]. Artificial intelligence (AI) has emerged as a valuable tool in digital pathology, with algorithms suggesting diagnoses for pathologist review [14].

Despite its advantages, challenges remain. These include initial costs, data security concerns, regulations, integrating it with existing workflows, potential resistance to change, validating AI algorithms, and optimizing its use with other diagnostic techniques. Additionally, specific challenges exist in gynecologic diagnosis due to unique sample types, complex interpretations, and the need for collaboration across specialties.

Digital pathology has the potential to improve gynecologic pathology practice. However, careful consideration of

its cost-effectiveness is essential for successful implementation. More research is needed to understand the long-term impact of digital pathology on patient outcomes and healthcare costs, especially within the unique economic landscape of women's healthcare.

3. Biobanking Enables Translational Research and Precision Medicine

Biobanking plays a pivotal role in synergy with molecular pathology and digital pathology by providing a repository of well-annotated tissue specimens and biomaterials for research purposes. By systematically collecting and preserving diverse biospecimens, including tissues, blood, and bodily fluids, biobanks facilitate translational research endeavors aimed at deciphering disease mechanisms, identifying therapeutic targets, and validating diagnostic biomarkers [15]. Biobanked gynecologic tissues are essential for validating novel molecular assays and exploring disease heterogeneity

4. Conclusions

The convergence of molecular pathology, digital pathology, and biobanking heralds a new era in gynecologic, pathology, characterized by unparalleled insights into disease pathogenesis, refined diagnostic algorithms, and personalized therapeutic strategies. As we navigate this era of precision medicine, collaborative efforts among pathologists, clinicians, researchers, and policymakers are paramount to harnessing the full potential of these transformative technologies and translating scientific discoveries into tangible improvements in patient care and outcomes.

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All work was conceived and completed by VGV.

Ethics Approval and Consent to Participate

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