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Genomic Profiling of Primary Vaginal Tumors: Molecular Landscape, Clinical Significance, and Future Directions

A. Mohamed Sikkander[1*], Sangeeta R. Mishra[2]

[1] Professor, Department of Chemistry, GKM College of Engineering and Technology, Chennai 600063, India
[2] Associate Professor, Department of Electronics & Telecommunication, Thakur College of Engineering, Mumbai, India.

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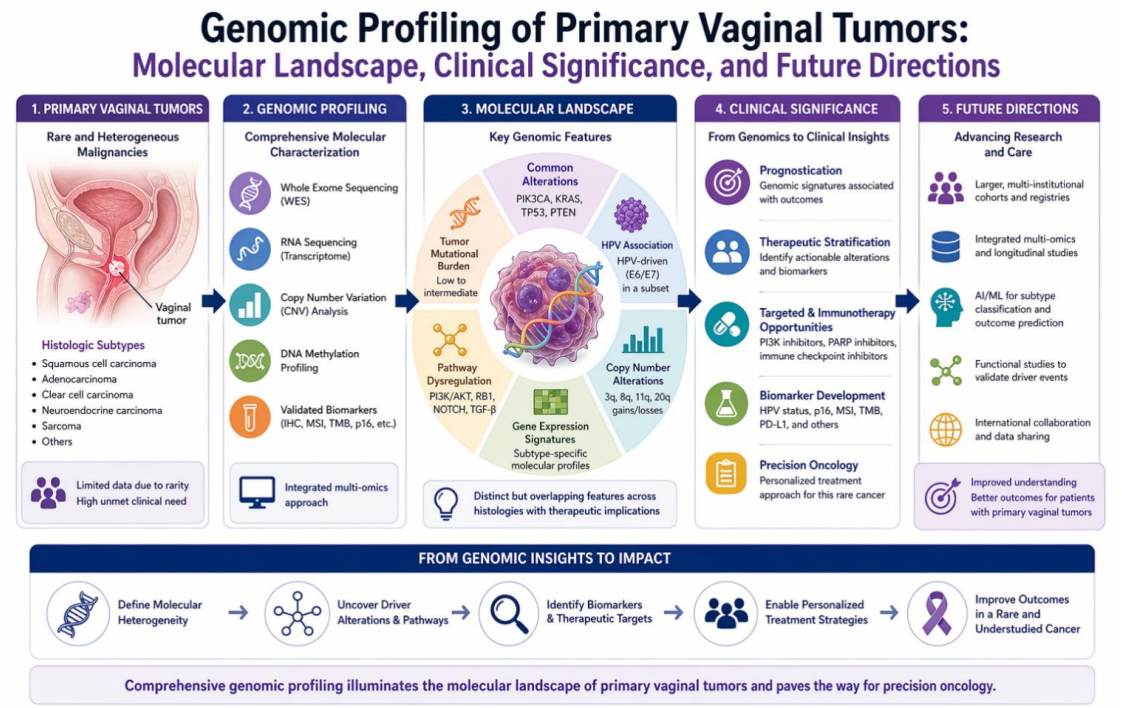
Abstract: Squamous cell carcinoma (SCC) is the most common histological subtype of primary vaginal cancer, a rare gynaecologic disease that accounts for fewer than 2% of female genital tract cancers. Because it is uncommon, therapeutic approaches are frequently generalised from vulvar and cervical malignancies, which restricts individualised treatment plans. Recent advancements in multi-omics and next-generation sequencing (NGS) technologies have made it possible to profile the genomes of primary vaginal tumours, revealing their molecular heterogeneity and finding useful mutations. The genomic landscape of primary vaginal tumours is reviewed in this study, with an emphasis on important genetic changes, molecular markers linked to HPV, and clinically significant pathways.

To find recurring mutations, copy number variations, and pathway-level disruptions, a methodical research approach was used by analysing recent genomic publications, cancer genome archives, and clinical sequencing reports. To show the frequency of mutations like TP53, PIK3CA, PTEN, CDKN2A, KRAS, and changes in EGFR and TERT, data were collated. Different molecular characteristics, such as viral-driven oncogenesis vs genomic instability and p53 disruption, are revealed by comparing the profiles of HPV-positive and HPV-negative tumours. Prognostic stratification, immunotherapy biomarkers, and targeted therapeutics are all considered in regard to the clinical consequences of genetic profiling.Challenges such as small cohort sizes, tumor heterogeneity, and limited clinical trial evidence remain barriers to translation. Future perspectives emphasize integrated transcriptomics, liquid biopsy monitoring, and AI-driven precision oncology. Genomic profiling offers a transformative approach for improving diagnosis, prognostic prediction, and biomarker-guided therapy in vaginal cancer.

Keywords: Vaginal cancer, genomic profiling, HPV-associated carcinoma, next-generation sequencing, PIK3CA, TP53, actionable mutations, precision oncology.

Graphical Abstract



***Corresponding Author**
A. Mohamed Sikkander*
E-mail: ams240868@gmail.com

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1. Introduction

In gynaecologic oncology, primary vaginal cancer is one of the rarest cancers; squamous cell carcinoma (SCC) accounts for about 80–90% of cases, with adenocarcinoma, melanoma, and sarcoma following. Depending on the location and stage of the tumour, clinical management usually involves radiation, chemoradiation, and surgical resection. However, there are few reliable randomised clinical studies for vaginal cancer because of its low incidence, and treatment plans frequently resemble those for cervical cancer. The distinct biology of vaginal tumours might not be reflected in this extrapolation-based method.

By making it possible to identify the molecular changes that cause carcinogenesis, the growing use of genomic profiling has revolutionised cancer research. Researchers can find point mutations, gene fusions, copy number variations, and structural rearrangements using NGS-based sequencing technologies. Understanding carcinogenesis, differentiating HPV-driven tumours from HPV-independent malignancies, and finding clinically useful biomarkers all depend on this genetic data.

Vaginal SCC is significantly influenced by the human papillomavirus (HPV), particularly HPV16 and HPV18. Tumours that are positive for HPV usually show oncogenic viral integration, which causes the viral proteins E6 and E7 to dysregulate tumour suppressor pathways such p53 and Rb. On the other hand, alternative pathways characterised by TP53 mutations, genomic instability, and carcinogen-driven molecular changes may result in the development of HPV-negative tumours. Because HPV-positive tumours frequently respond better to radiotherapy and have better survival rates than HPV-negative tumours, this differentiation is therapeutically significant.

Compared to other gynaecologic cancers as ovarian or cervical cancer, there is still less genomic profiling available for vaginal cancer. However, new research has started to detect recurrent molecular modifications, such as changes in PI3K/AKT/mTOR signalling and mutations in TP53, PIK3CA, PTEN, CDKN2A, FAT1, and NOTCH1. These results imply that vaginal tumours have molecular similarities to cervical and head-and-neck squamous malignancies, which are often linked to HPV.

With an emphasis on molecular subtypes, frequently mutated genes, pathway-level disruptions, and translational significance for precision oncology, this study reviews current developments in genomic profiling of primary vaginal tumours. This work attempts to offer a structured overview of the mutational landscape of vaginal cancer by tabulating genomic data from published publications. It also highlights the clinical potential of molecular stratification in directing targeted therapy and enhancing patient outcomes.

2. Research Methodology

2.1 Study Design

This study summarizes the mutational landscape of primary vaginal tumours using an approach based on systematic reviews and comparative genomic dataset evaluation. Large-scale genomic datasets are scarce due to the rarity of vaginal cancer; hence evidence was obtained from case series, smaller cohort sequencing studies, and publically accessible cancer genome platforms.

2.2 Data Sources and Study Selection

The genetic profiling of primary vaginal tumours reported in peer-reviewed literature was examined. The included studies were published between 2015 and 2025, which corresponds with the fast growth of NGS. Whole-exome sequencing (WES), targeted NGS panels, whole-genome sequencing (WGS), RNA sequencing, and comparative genomic hybridization (CGH) were all used to extract data from reports. In order to guarantee that only clinically pertinent and genomically useful data were examined, the inclusion criteria for choosing studies and patient cases in this review were established.

First, only those who had a primary vaginal cancer diagnosis were included. This criterion proved crucial for separating metastatic lesions from other gynecologic cancers, such vulvar or cervical cancer, which may resemble vaginal tumours but have quite different molecular features and treatment consequences. Histopathological analysis and clinical records were used to confirm the diagnosis. Second, research was only considered if tumour tissue—such as biopsy or surgical specimens was subjected to genetic profiling.

Because tissue-based sequencing offers direct insight into molecular changes unique to tumours, such as somatic mutations and pathway dysregulation, it was given priority. Third, the chosen papers have to offer genomic information at the mutation or route level, such as findings from whole-exome sequencing, next-generation sequencing (NGS), targeted gene panels, or molecular pathway analysis. This made it possible for the study to provide useful information on oncogenic drivers, actionable genetic changes, or biomarker signals related to precision oncology.

Lastly, papers that described the histological subtype (e.g., squamous cell carcinoma, adenocarcinoma, melanoma, sarcoma) or reported HPV status were given preference for inclusion. The recording of HPV infection aids in the interpretation of mutation patterns and tumour behavior because it is a significant factor in the pathophysiology of several gynecologic malignancies. Similarly, different vaginal cancer subtypes may have varied genetic profiles, prognostic outcomes, and treatment responses, making histological classification crucial. When taken as a whole, these standards guaranteed that the included studies were methodologically sound, physiologically significant, and appropriate for assessing molecular changes and specific therapy options in vaginal cancer.

In order to preserve the scientific validity and dependability of the genetic evidence presented in this review, the exclusion criteria were set. First, studies that reported tumours that were mislabeled as primary vaginal cancer but were found to be metastatic lesions originating from the cervix, vulva, or other anatomical sites were discarded. This differentiation was crucial because, whereas metastatic gynaecologic tumours may have similar clinical characteristics, their molecular fingerprints, tumour microenvironment, and response to treatment differ significantly. Incorporating such examples may result in inaccurate interpretations of pathway enrichment, mutation frequencies, and biomarker relevance unique to actual vaginal cancer.

Second, studies that did not disclose molecular outcomes—that is, that did not offer gene expression profiles, pathway changes, mutation findings, or clinically significant genomic interpretations—were eliminated. Studies without molecular results

were deemed inadequate for meaningful analysis because the main goal of this review was to assess genetic changes and their role in directing precision oncology therapies. Therefore, reports without genetic data that just discussed clinical presentation, imaging results, histology, or treatment outcomes were excluded.

Third, articles with incomplete genomic datasets were not included. These included studies with incomplete sequencing findings, lacking mutation lists, missing variant annotations, or missing important genomic factors including copy number variation status, tumour mutational load, or pathway-level interpretation. Incomplete datasets make it harder to compare studies and make trustworthy inferences about therapeutic targets or actionable mutations. Furthermore, research that lacked bioinformatics validation, had unclear sequencing methods, or had poor sample quality were deemed inadequate. In general, the purpose of these exclusion criteria was to reduce bias, guarantee diagnostic precision, and preserve uniformity in genetic reporting. The review's capacity to offer a thorough assessment of molecular drivers and precision medicine potential in primary vaginal cancer was increased by eliminating studies with incorrectly categorized tumour origins, missing molecular evidence, or insufficient genomic findings.

2.3 Data Extraction Parameters

To guarantee a thorough assessment of genetic changes and biomarker relevance in primary vaginal cancer, the extracted data from qualified research were methodically gathered. Initially, the histological subtype of the tumour was recorded, encompassing key classifications such squamous cell carcinoma, adenocarcinoma, melanoma, sarcoma, and other uncommon variations. Because several subtypes exhibit unique genetic patterns, biological aggressiveness, and therapeutic responses, histological categorization was crucial.

Second, whenever the HPV association status was recorded, it was extracted. In addition to influencing mutation distribution, carcinogenic pathway activation, and clinical outcome, HPV positivity or negativity offers important etiological knowledge. While HPV-negative tumours may have different molecular causes, HPV-related vaginal malignancies often entail viral oncogene-driven carcinogenesis. Each study's sequencing technique, such as targeted next-generation sequencing (NGS) panels, whole-exome sequencing (WES), and whole-genome sequencing (WGS), was also documented. This variable was crucial since different platforms have different levels of genome coverage, which can impact the identification of uncommon variants, copy number changes, and structural changes.

The main altered genes found in tumour samples, such as changes in TP53, PIK3CA, PTEN, KRAS, CDKN2A, or other oncogenes and tumour suppressors, were among the important genomic discoveries that were meticulously gathered. In order to facilitate comparison study between cohorts and case series, the mutation frequency of each gene was extracted where available. Furthermore, disturbances in the PI3K/AKT/mTOR pathway, MAPK signalling, cell cycle regulation, DNA repair processes, and immune evasion pathways were reported as pathway-level changes. Beyond single-gene alterations, pathway mapping made it possible to understand more extensive carcinogenic processes.

Finding actionable molecular targets such as mutations or amplifications connected to FDA-approved treatments or experimental targeted agents—helped prioritise clinically meaningful discoveries. This includes changes that might be affected by immune checkpoint inhibitors, PI3K inhibitors, or treatments that target the DNA damage response.

Additionally, when biomarkers such as PD-L1 expression, microsatellite instability (MSI) status, and tumour mutational burden (TMB) were reported, their relevance was noted. Immunotherapy decisions are increasingly influenced by these immune-related indicators, particularly in uncommon tumours where there are few standardised therapeutic alternatives. When taken as a whole, these extracted factors guaranteed that the dataset included translational biomarkers and genetic drivers pertinent to precision oncology-based treatment of vaginal cancer.

2.4 Comparative Framework and Tabulation Strategy

In order to identify the key genetic drivers of vaginal cancer, the results of mutational profiling were methodically examined and categorized. Based on their functional relevance in tumour biology, the identified variations were divided into three major mutational categories. Tumour suppressor gene changes, including mutations or deletions in important regulators including TP53, CDKN2A, and RB1, made up the first category. These genes are crucial for maintaining genomic integrity, apoptosis, and cell-cycle checkpoints. Because TP53 alterations are frequently linked to aggressive tumour behavior, medication resistance, and a poor prognosis in a variety of gynaecologic malignancies, they were especially important. Similarly, loss of RB1 and CDKN2A causes dysregulation of the G1/S checkpoint, which leads to unchecked proliferation.

Oncogenic signalling mutations, which trigger growth-promoting pathways and aid in the development of malignancy, were included in the second group. Changes in PIK3CA, PTEN, KRAS, and EGFR were included in this category. These proteins are involved in important intracellular signalling cascades that regulate cell survival, metabolism, and proliferation. The PI3K/AKT/mTOR pathway was found to be activated by mutations in PIK3CA and loss-of-function alterations in PTEN, indicating possible susceptibility to pathway-specific inhibitors. While EGFR changes revealed potential susceptibility to targeted tyrosine kinase inhibitors in specific situations, KRAS mutations, though less common, indicated abnormal MAPK signalling.

Mutations impacting DNA repair and genomic stability, such as those in BRCA1/2, ATM, and TERT, were included in the third group. Defects in homologous recombination repair processes can increase genomic instability and may predict responsiveness to PARP inhibitors or platinum-based treatments, making these changes therapeutically significant. Because TERT changes are linked to telomere maintenance, cellular immortality, and tumour growth, they were noted.

Mutation datasets were tabulated and sorted by HPV-positive and HPV-negative tumour status to improve comparative interpretation. This made it possible to assess variations in the frequency of mutations and carcinogenic pathways impacted by viral carcinogenesis. Cell-cycle dysregulation was more frequently linked to HPV-positive tumours, while TP53 mutations and genomic instability-related changes were more common in HPV-negative tumours.

To find dominant dysregulated networks, a pathway-based analysis was conducted in addition to gene-level classification. PI3K/AKT/mTOR signalling, NOTCH signalling, and cell-cycle

regulation were among the major pathways that were identified. These pathways supported the practical applicability of precision oncology techniques and targeted therapy approaches in vaginal cancer.

3. Results and Data Tabulation

3.1 Genomic Alterations in Primary Vaginal Tumors

Together, the genomic profile studies suggest that cell cycle, DNA repair, and growth signalling pathways are frequently altered in primary vaginal malignancies. PI3K/AKT/mTOR signalling is the most often implicated pathway, mostly due to PTEN loss and PIK3CA mutations. Additionally prevalent is tumour suppressor disruption, particularly TP53 mutations in HPV-negative individuals. Moreover, genes associated to the NOTCH pathway and chromatin remodelling appear to be often changed, indicating dysregulation related to differentiation and epigenetics in **Table 1**.

Table 1. Commonly reported mutated genes in primary vaginal tumors across published genomic profiling studies, highlighting gene function, mutation type, clinical relevance, and associated oncogenic pathways.

Gene	Functional Role	Mutation Type	Clinical Relevance	Associated Pathway
TP53	Tumor suppressor	Missense/frameshift	Poor prognosis marker	DNA damage response
PIK3CA	Oncogene	Activating mutation	Targetable pathway	PI3K/AKT/mTOR
PTEN	Tumor suppressor	Deletion/mutation	PI3K activation	PI3K/AKT/mTOR
CDKN2A	Cell cycle inhibitor	Loss/inactivation	Predicts aggressive disease	Cell cycle
RB1	Tumor suppressor	Loss	HPV pathway interaction	Cell cycle
NOTCH1	Differentiation signaling	Mutation	Potential target	NOTCH pathway
FAT1	Tumor suppressor-like	Loss mutation	Linked to invasion	WNT/Cell adhesion
EGFR	Growth receptor	Amplification	Targetable in some cases	RTK signaling
KRAS	Oncogene	Activating mutation	Therapy resistance marker	MAPK pathway
TERT	Telomerase activation	Promoter mutation	Immortality mechanism	Telomere maintenance

3.2 HPV-Positive vs HPV-Negative Tumor Profiles

Because the viral E6 protein effectively deactivates p53, HPV-positive tumours exhibit less TP53 mutations. Rather, these tumours frequently exhibit immune-related pathway changes including PIK3CA mutations. Higher TP53 mutation frequencies and more chromosomal instability in HPV-negative tumours suggest distinct carcinogenic pathways in **Table 2**.

Table 2. Comparative genomic features of HPV-positive and HPV-negative primary vaginal tumors, summarizing dominant molecular mechanisms, mutation frequency trends, immune-related signatures, therapeutic response, and prognostic outcomes.

Feature	HPV-Positive Vaginal Tumors	HPV-Negative Vaginal Tumors
Dominant driver mechanism	Viral integration (E6/E7)	Genomic instability
TP53 mutation frequency	Low	High
RB pathway disruption	Viral E7 mediated	RB1 deletion/mutation
PIK3CA mutation	Moderate–high	Moderate
PTEN loss	Moderate	High
Immune activation signatures	High	Variable/low
TMB	Moderate	Higher
Response to radiation	Generally favorable	Less favorable
Prognosis	Better	Worse

3.3 Actionable Targets and Therapeutic Opportunities

Targeted treatments for other malignancies may be beneficial for vaginal cancer, according to genomic profiling. For PIK3CA-mutant tumours, PI3K inhibitors may be investigated. EGFR amplification indicates potential sensitivity to EGFR inhibitors. Immune checkpoint drugs may be effective against tumours with elevated TMB or MSI-like signatures in **Table 3**.

Table 3. Actionable genomic alterations identified in primary vaginal cancer and their potential targeted therapy options, including drug examples, therapy class, and current level of supporting clinical evidence.

Alteration	Targeted Therapy Option	Therapy Class	Clinical Evidence Level
PIK3CA mutation	Alpelisib (off-label potential)	PI3K inhibitor	Moderate
PTEN loss	AKT inhibitors	Signal inhibitors	Emerging
EGFR amplification	Erlotinib, Gefitinib	EGFR-TKI	Limited
PD-L1 expression	Pembrolizumab, Nivolumab	Checkpoint inhibitors	Moderate
MSI-H/dMMR	Pembrolizumab	Tumor-agnostic	Strong
High TMB	Checkpoint inhibitors	Immunotherapy	Moderate
NOTCH pathway alterations	Gamma-secretase inhibitors	Experimental	Low
KRAS mutation	KRAS inhibitors (G12C)	Targeted therapy	Rare occurrence
DNA repair defects	PARP inhibitors	Synthetic lethality	Emerging

3.4 Pathway-Level Disruption Patterns

According to a route-based perspective, cell-cycle dysregulation and changes to the NOTCH pathway follow the dominance of the PI3K pathway. This gives precision oncology trials a logical foundation in **Table 4**.

Table 4. Major dysregulated molecular pathways in primary vaginal tumors revealed through genomic profiling studies, including representative key genes and translational clinical significance.

Pathway	Key Genes Involved	Clinical Significance
PI3K/AKT/mTOR	PIK3CA, PTEN, AKT1	Growth and survival signaling
Cell-cycle control	TP53, CDKN2A, RB1	Tumor progression, poor prognosis
MAPK signaling	KRAS, BRAF	Resistance mechanisms
NOTCH signaling	NOTCH1, DLL3	Differentiation and invasion
DNA repair pathways	ATM, BRCA1/2	Treatment sensitivity
Telomere maintenance	TERT	Immortality and recurrence

4. Discussion

Similar to other squamous cancers, especially cervical and head-and-neck cancers, the genomic landscape of primary vaginal tumours exhibits molecular heterogeneity. The most constant genetic trait is changes in the PI3K pathway, indicating that PI3K/AKT/mTOR inhibitors would be a feasible targeted strategy. However, because to a small number of patients, clinical trial data on vaginal cancer are still scarce.

Viral-driven carcinogenesis, in which E6/E7 proteins inhibit p53 and Rb tumour suppressor pathways without necessitating significant TP53 gene alterations, is the hallmark of the HPV-associated molecular subtype. This is in line with the finding that TP53 mutations are less common in HPV-positive tumours. HPV-negative tumours, on the other hand, rely on traditional carcinogenesis processes such as genomic instability, CDKN2A loss, and direct TP53 mutation. These tumours typically show decreased therapeutic sensitivity and inferior clinical outcomes.

The potential role of immunotherapy is another significant translational result. Potential targets for PD-1/PD-L1 checkpoint inhibition are HPV-positive tumours, which may show enhanced immune infiltration as a result of viral antigen expression. Furthermore, neoantigens produced by tumours with high TMB may enhance the response to immunotherapy. Pembrolizumab's application in MSI-H tumours offers a tumor-agnostic approach that may be used in uncommon cases of vaginal cancer. The creation of basket trials, in which women with vaginal cancer can be enrolled based on actionable mutations rather than tumour site, is also aided by genomic profiling. For instance, EGFR-amplified tumours may benefit from EGFR-targeted drugs, whereas a patient with a PIK3CA mutation may be eligible for PI3K inhibitor studies. Because traditional vaginal cancer trials are challenging to run due to low incidence, these trial designs are crucial.

A number of obstacles still exist despite advancements. A single biopsy may not adequately capture the genetic complexity of vaginal tumours due to intra-tumoral heterogeneity. Furthermore, substantial clinical cohorts have yet to verify many genetic discoveries. Translation into routine clinical decision-making is further hampered by the absence of standardised sequencing panels and reference mutation databases unique to vaginal cancer.

All things considered, genomic profiling is altering our knowledge of the biology of vaginal cancer and is anticipated to enhance precision treatment approaches through biomarker-based categorization.

5. Future Perspectives

The creation of multicenter genetic databases must be a top priority for future vaginal cancer genomics research in order to overcome the primary shortcoming of the current evidence, which is primarily based on small cohorts and isolated case reports. Subtype-specific mutation mapping, the identification of uncommon but useful molecular targets, and statistical power would all be enhanced by large-scale collaborative registries incorporating hospitals, cancer centers, and multinational consortia. To ensure that genomic results are comparable across institutions, standardised sequencing procedures and unified reporting standards will be crucial.

Integrating multi-omics techniques including transcriptomics, proteomics, epigenomics, and metabolomics may offer a more thorough understanding of tumour biology in addition to increasing sample size. Transcriptomic and proteome profiling can identify dysregulated gene expression networks, post-translational modifications, and signalling linkages that contribute to tumour microenvironment control, immune evasion, and therapeutic resistance, whereas genomic sequencing can identify driver mutations. These methods may also aid in the discovery of new biomarkers that indicate how well immunotherapy or targeted therapies will work.

Another crucial direction is the expanding use of liquid biopsy technology, namely circulating tumour DNA (ctDNA) analysis. ctDNA monitoring provides a minimally intrusive method for tracking new resistance mutations in real time, evaluating residual disease, and detecting recurrence early. This lessens reliance on repeated tissue samples, which can be challenging in cases of vaginal cancer because of anatomical difficulties and tissue scarcity. Dynamic treatment modification based on changing tumour genetics may also be supported by liquid biopsy.

Furthermore, it is anticipated that machine learning and artificial intelligence (AI) would be crucial to the interpretation of high-dimensional genomic datasets. In order to forecast therapy response patterns, classify patients into risk categories, and find hidden biomarker signatures that conventional analysis might miss, AI-driven models can incorporate genetic, clinical, and imaging data. Precision oncology decision-making could be improved by these technologies, particularly in uncommon cancers where physician experience is scarce.

From the standpoint of clinical trials, by permitting enrolment based on molecular changes rather than tumour site, basket studies and tumor-agnostic medication approvals will probably speed up patient access to targeted medicines. For uncommon malignancies like vaginal carcinoma, where traditional randomised trials are challenging to carry out, this approach is very beneficial.

Lastly, research on immune microenvironment regulation and HPV-specific therapeutic vaccines is still very promising, particularly for HPV-driven tumours. Immune checkpoint pathways combined with viral oncogenes may enhance long-lasting responses. In general, the most effective future course for enhancing survival and quality of life for patients with vaginal cancer is genomics-guided and immune-informed approaches.

6. Conclusion

A very useful method for comprehending the molecular processes behind this uncommon and aggressive cancer is the genomic profiling of primary vaginal tumours. Due to the rarity of vaginal cancer, conventional treatment approaches have mostly been modified from cervical and vulvar cancer procedures. But more and more genomic research shows that vaginal tumours have unique molecular characteristics that can be used in precision oncology. Consistent patterns of oncogenic mutations and pathway-level dysregulation that contribute to tumour development, progression, and treatment resistance have been identified through profiling utilizing next-generation sequencing (NGS), whole-exome sequencing (WES), and related technologies.

The common disruption of the PI3K/AKT/mTOR signalling pathway, which is frequently caused by activating mutations in PIK3CA and loss-of-function changes in PTEN, is a significant result across several research. This route controls vital cellular functions like angiogenesis, metabolism, proliferation, and survival; when it is hyperactivated, tumour growth and treatment resistance are encouraged. Vaginal malignancies not only activate the PI3K pathway but also significantly disturb cell-cycle control, especially through changes in TP53, CDKN2A, and RB1. In particular, the TP53 mutation is closely linked to aggressive tumour behavior, genomic instability, and decreased response to traditional treatments. Similar to this, defects in CDKN2A and RB1 impair checkpoint regulation, permitting unchecked cell proliferation and malignant transformation.

The biological distinctions between HPV-positive and HPV-negative vaginal tumours are further highlighted by comparative genomic research. Viral oncogene-mediated inactivation of tumour suppressor pathways, specifically the functional suppression of p53 and RB-related processes, is frequently the cause of HPV-positive cases. On the other hand, HPV-negative tumours have more genomic instability and a larger prevalence of direct TP53

mutations, which may account for their generally worse clinical outcomes and more rapid disease development. The significance of HPV stratification in molecular interpretation and clinical decision-making is highlighted by these variations.

Finding genetic changes that are clinically actionable has significant therapeutic implications. Opportunities for tailored therapy approaches, such as PI3K inhibitors, EGFR-directed medicines, and drugs that target DNA damage response pathways, are suggested by mutations such PIK3CA activation, EGFR amplification, and abnormalities in the DNA repair pathway. Furthermore, immune-related indicators such higher tumour mutational burden (TMB), PD-L1 expression, and microsatellite instability (MSI) in certain situations suggest that immune checkpoint inhibitors may be beneficial. When these genetic changes are methodically documented, they show repeatable patterns that can direct the selection of individualized treatments and bolster the case for enrolling individuals with vaginal cancer in basket trials focused on common molecular targets rather than tumour site.

The clinical application of genomic profiling is now limited by a number of issues, despite these encouraging advancements. Due to the rarity of vaginal cancer, biomarker reporting is uneven, study cohorts are small, and sequencing uniformity is restricted. Furthermore, therapy recommendations are mainly extrapolative because few clinical trials have explicitly validated targeted medicines in populations with vaginal cancer. Expanded patient registries, standardised genomic methods, and multicenter partnerships will be necessary for future advancements. It may be possible to follow resistance mutations in real time and enhance early recurrence identification by integrating multi-omics platforms with liquid biopsy-based monitoring utilizing circulating tumour DNA (ctDNA).

In conclusion, by moving the profession away from generalized therapeutic approaches and toward molecularly guided personalized oncology, genomic profiling is quickly changing the management of vaginal cancer and providing fresh hope for better results in this uncommon cancer.

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