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PATHOMORPHOLOGICAL AND MOLECULAR GENETIC FEATURES OF MESENCHYMAL TUMOURS OF THE UTERUS

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ABSTRACT

Uterine mesenchymal neoplasms represent a heterogeneous group of tumors that pose significant diagnostic challenges due to overlapping morphological and immunophenotypic features. Accurate differentiation among leiomyoma, leiomyosarcoma, endometrial stromal sarcoma, and other rare mesenchymal tumors is critical for determining prognosis and guiding therapeutic decisions. This study aimed to evaluate the role of integrating immunohistochemistry and next-generation sequencing (NGS) in improving diagnostic precision and classification of uterine mesenchymal tumors. A comprehensive review of recent molecular and pathological evidence was conducted to analyze the genetic alterations associated with various tumor subtypes and their clinical implications. The findings demonstrate that benign and malignant uterine smooth muscle tumors exhibit distinct molecular profiles, with leiomyosarcomas commonly harboring alterations in tumor suppressor genes such as TP53, RB1, and ATRX, while leiomyomas show comparatively stable genomic patterns. Endometrial stromal tumors are characterized by specific gene fusions that aid in subclassification and prognostic assessment. Additionally, rare fusion-driven neoplasms and tumors with actionable mutations highlight the therapeutic potential of molecular diagnostics. The study concludes that an integrated diagnostic approach combining morphology, immunohistochemistry, and molecular profiling enhances diagnostic accuracy, reduces ambiguity in borderline cases, and supports personalized treatment strategies. The incorporation of genomic technologies into routine pathology practice is essential for advancing precision medicine in gynecologic oncology.

KEYWORDS: Uterine mesenchymal neoplasms, Leiomyoma, Leiomyosarcoma, Endometrial stromal sarcoma, Immunohistochemistry, Next-generation sequencing, Molecular diagnostics, Precision medicine Children. Adhesive obstruction. Intussusception. Intestinal obstruction. Diagnosis. Surgical treatment. Prevention. Postoperative rehabilitation.

1. INTRODUCTION

Uterine mesenchymal tumours encompass a heterogeneous spectrum of neoplasms distinguished by diverse pathomorphological phenotypes and distinct molecular genetic signatures that critically influence tumor classification, prognostication, and therapeutic stratification. Historically, these tumours were primarily classified based on microscopic architecture, cellular morphology, and immunohistochemical profiles, resulting in considerable diagnostic ambiguity due to overlapping histologic features among benign, intermediate, and malignant entities (Sun, 2025; Parra-Herran & Howitt, 2019). However, the advent of high-throughput genomic profiling and integrative molecular diagnostics has fundamentally transformed our understanding of uterine mesenchymal neoplasia, unveiling recurrent genetic aberrations that underpin tumourigenesis and inform precision medicine approaches. Among uterine mesenchymal tumours, smooth muscle tumours represent the most prevalent subgroup, ranging from benign leiomyomas to highly aggressive leiomyosarcomas.

Leiomyomas frequently harbour MED12 exon 2 mutations, which disrupt the regulatory mediator complex and promote aberrant cell proliferation, whereas leiomyosarcomas exhibit profound genomic instability, characterized by complex karyotypic alterations and recurrent mutations in classical tumour suppressor pathways (e.g., *TP53*, *RB1*, *PTEN*, and *ATRX*) (Sun, 2025). These divergent molecular landscapes emphasize that leiomyosarcoma is not merely a malignant transformation of leiomyoma but a distinct neoplastic process driven by extensive chromosomal aberrations and dysregulated cell cycle control. This distinction has profound diagnostic and prognostic implications, especially given the aggressive clinical behaviour and limited therapeutic options for uterine leiomyosarcoma.

Endometrial stromal tumours (ESTs) exhibit equally remarkable molecular heterogeneity. Low-grade endometrial stromal sarcomas (LG-ESS) are typified by recurrent JAZF1::SUZ12 fusions, which disrupt polycomb repressive complex function and affect chromatin regulation, while high-grade counterparts (HG-ESS) display alternative fusion events such as YWHAE::NUTM2 and ZC3H7B::BCOR, or BCOR internal tandem duplications (ITDs), all of which contribute to distinct oncogenic transcriptional programmes (Alodaini, 2024; Sun, 2025). Molecular characterization of these fusions has markedly enhanced diagnostic specificity and enabled stratification of patients into prognostically relevant categories with potential therapeutic ramifications, particularly as targeted agents against pathway dysregulations emerge.

Emerging entities such as perivascular epithelioid cell tumours (PEComas), inflammatory myofibroblastic tumours (IMTs), and other molecularly defined sarcomas further illustrate the expanding genomic complexity of uterine mesenchymal neoplasia. PEComas frequently exhibit TSC1/TSC2 inactivating mutations leading to aberrant mTOR signalling, while IMTs variably present with ALK rearrangements, which may be amenable to ALK inhibitors (Sun, 2025; Ma et al., 2025). These findings not only refine tumour taxonomy but also highlight actionable genetic targets that have tangible therapeutic implications in selected clinical contexts.

The integration of comprehensive histopathological assessment with molecular genetic profiling has therefore become indispensable in the contemporary diagnostic algorithm for uterine mesenchymal tumours. This integrative approach enhances diagnostic precision, permits the delineation of novel molecular subsets, and lays the foundation for personalized treatment strategies that are responsive to tumour-specific genetic aberrations. Continued elucidation of the pathomorphological and genomic underpinnings of these neoplasms is essential for advancing clinical outcomes and establishing evidence-based paradigms in precision oncology.

1.2 Historical Perspective

The conceptualization and classification of uterine mesenchymal tumours have undergone a profound transformation over the past century, evolving from purely morphologic descriptions to a sophisticated, molecularly informed taxonomy. In the late nineteenth and early twentieth centuries, uterine smooth muscle tumours were broadly categorized based on gross appearance and basic histologic features, with the terms fibroid and myoma commonly used to describe benign lesions. The malignant counterpart, later designated as leiomyosarcoma, was identified primarily through cytologic atypia, necrosis, and mitotic activity, although diagnostic thresholds were inconsistent and often subjective (Bell et al., 1994).

A major milestone in the histopathological classification of uterine smooth muscle tumours occurred in the latter half of the twentieth century with the establishment of standardized diagnostic criteria. The seminal study by Bell, Kempson, and Hendrickson (1994) proposed a tripartite system incorporating cytologic atypia, mitotic index, and

tumour cell necrosis, which significantly improved diagnostic reproducibility and prognostic stratification. This morphologic framework laid the foundation for distinguishing benign leiomyoma, atypical leiomyoma, and leiomyosarcoma, although cases with ambiguous features—later termed "smooth muscle tumours of uncertain malignant potential" (STUMP)—continued to challenge pathologists. Parallel advances were observed in the understanding of endometrial stromal tumours. Historically grouped under the broad term "endometrial stromal sarcoma," these neoplasms were subdivided into low-grade and high-grade variants based on mitotic activity and cytologic features. However, early classifications did not adequately capture the biological heterogeneity of these tumours. The introduction of the World Health Organization (WHO) classification systems in successive editions brought greater clarity by formally recognizing distinct entities, including low-grade endometrial stromal sarcoma (LG-ESS), high-grade endometrial stromal sarcoma (HG-ESS), and undifferentiated uterine sarcoma (WHO, 2014; WHO, 2020). These refinements reflected accumulating clinicopathologic data demonstrating divergent clinical behaviors and outcomes.

The late twentieth and early twenty-first centuries marked the advent of cytogenetic and molecular genetic investigations, heralding a paradigm shift in uterine tumour pathology. Recurrent chromosomal translocations were first identified in endometrial stromal sarcomas in the 1990s, most notably the t(7;17)(p15;q21) translocation resulting in the JAZF1–SUZ12 gene fusion (Micci et al., 2006). This discovery provided compelling evidence that specific genetic events underlie distinct morphologic entities. Similarly, subsequent research revealed YWHAE–NUTM2 and BCOR alterations in high-grade stromal sarcomas, further refining diagnostic categories and clarifying their aggressive clinical course (Lee et al., 2012). In smooth muscle tumours, comprehensive genomic studies in the 2010s identified recurrent MED12 exon 2 mutations in a substantial proportion of uterine leiomyomas, fundamentally altering the understanding of their pathogenesis (Mäkinen et al., 2011). Conversely, leiomyosarcomas were shown to harbor complex genomic rearrangements and alterations in tumour suppressor genes such as TP53 and RB1, reinforcing the concept that malignant smooth muscle tumours arise through distinct molecular mechanisms rather than stepwise progression from benign leiomyoma.

More recently, next-generation sequencing and integrative molecular profiling have expanded the spectrum of recognized uterine mesenchymal neoplasms, including molecularly defined subsets such as BCOR-rearranged sarcomas, inflammatory myofibroblastic tumours with ALK rearrangements, and perivascular epithelioid cell tumours with TSC1/TSC2 alterations. These discoveries have not only refined diagnostic precision but also introduced targeted therapeutic possibilities, signifying the transition from morphology-based classification to precision oncopathology. Thus, the historical trajectory of uterine mesenchymal tumour research reflects a progressive synthesis of morphologic rigor and molecular insight. From early descriptive pathology to contemporary genomic characterization, each phase has incrementally enhanced diagnostic accuracy, prognostic assessment, and therapeutic direction, underscoring the dynamic evolution of this field.

1.3 Problem Statement

Uterine mesenchymal tumours constitute a biologically heterogeneous and diagnostically challenging group of neoplasms arising from the smooth muscle, endometrial stromal, and related mesenchymal components of the uterus. Despite advances in histopathological criteria and the incorporation of successive editions of the WHO Classification of Tumours, significant diagnostic ambiguity persists due to overlapping morphologic features among benign, intermediate, and malignant entities. Distinguishing between leiomyoma variants, smooth muscle tumours of uncertain malignant potential (STUMP), and leiomyosarcoma remains particularly problematic, especially in cases demonstrating atypical cytology or borderline mitotic activity. Similarly, endometrial stromal tumours display considerable morphologic and molecular diversity, complicating accurate subclassification and prognostication.

Traditional diagnostic approaches have relied predominantly on histomorphology and immunohistochemistry; however, these methods may be insufficient in resolving diagnostically equivocal cases or identifying newly recognized molecular subtypes. Emerging molecular genetic discoveries—including recurrent gene fusions, chromosomal rearrangements, and driver mutations—have redefined tumour taxonomy and revealed pathogenetic mechanisms that are not readily discernible through morphology alone. Nevertheless, molecular testing is not uniformly integrated into routine diagnostic workflows, particularly in resource-limited settings, leading to inconsistencies in classification and management.

The absence of comprehensive, integrative analyses correlating pathomorphological characteristics with molecular genetic alterations contributes to gaps in diagnostic precision, prognostic stratification, and therapeutic decision-making. Moreover, the biological relationship between benign and malignant smooth muscle tumours remains incompletely elucidated, and the clinical significance of certain molecular aberrations requires further validation in large, well-characterized cohorts. Given the expanding spectrum of molecularly defined uterine mesenchymal neoplasms and the implications for targeted therapy and personalized medicine, there is a compelling need to systematically investigate and correlate the pathomorphological and molecular genetic features of these tumours. Addressing these gaps will enhance diagnostic accuracy, refine classification systems, and ultimately improve patient outcomes through evidence-based, molecularly informed clinical management.

1.4 Scope of The Study

This study focuses on the comprehensive evaluation of the **pathomorphological and molecular genetic features of uterine mesenchymal tumours** as classified in the WHO Classification of Tumours (5th edition). It includes smooth muscle tumours (leiomyoma, STUMP, leiomyosarcoma), endometrial stromal tumours (low-grade and high-grade ESS), and selected rare mesenchymal neoplasms. The study examines key histopathological parameters such as cellular atypia, mitotic index, tumour necrosis, and growth patterns, along with immunohistochemical profiling. It further analyzes recurrent molecular alterations, including *MED12* mutations, *TP53* and *RB1* changes, and characteristic gene fusions (e.g., *JAZF1::SUZ12*, *YWHAE::NUTM2*, *BCOR* rearrangements). By correlating morphological findings with molecular genetic profiles and clinicopathological features, the study aims to enhance diagnostic accuracy, improve prognostic stratification, and support molecularly informed clinical management of uterine mesenchymal tumours.

1.5 Med12 Mutations and Their Diagnostic Significance in Differentiating Leiomyoma from Leiomyosarcoma

MED12 (*Mediator complex subunit 12*) has emerged as a pivotal molecular marker in the evaluation of **uterine smooth muscle tumours**, particularly in distinguishing benign leiomyomas from their malignant counterpart, leiomyosarcomas. This gene encodes a key regulator of transcription through the mediator complex, influencing RNA polymerase II activity and various signal-dependent pathways relevant to cell growth and differentiation. Recent studies suggest that mutations in exon 2 of **MED12** occur frequently in leiomyomas, whereas their prevalence in leiomyosarcomas is much lower, underscoring their diagnostic relevance in clinical practice **(Bertsch, 2014)**

1.5.1 Prevalence of MED12 Mutations

Multiple large-scale molecular investigations have demonstrated a **high frequency of MED12 mutations in uterine leiomyomas**, with approximately 70–75 % of typical fibroids harbouring somatic mutations, most often clustered in exon 2 of the gene. These mutations primarily involve point substitutions and small in-frame deletions affecting conserved residues, and they have been consistently identified across diverse patient cohorts. In contrast, MED12 mutations are **relatively rare in leiomyosarcomas**, generally detected in only about 8–10 % of cases examined in aggregated studies. This stark contrast in mutation frequency highlights the **distinct molecular pathways** underlying benign and malignant smooth muscle neoplasia (**Bertsch, 2014)**

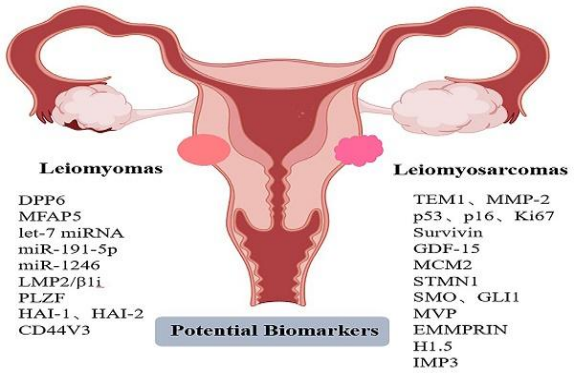

Figure 1: https://www.medsci.org/v21p1227.htm

1.5.2. Diagnostic Implications

The high prevalence of MED12 alterations in leiomyomas means that mutation analysis can be a valuable adjunct in tumour classification, particularly in **histologically equivocal cases** where morphological features (e.g., mitotic activity, atypia, and tumour necrosis) are borderline or inconclusive. Because leiomyomas and STUMP (smooth muscle tumour of uncertain malignant potential) often display overlapping histopathological traits with leiomyosarcoma, the presence of a MED12 mutation significantly increases the likelihood of a benign diagnosis, especially when there are no additional malignant features. However, the detection of MED12 mutations in a minority of leiomyosarcomas suggests that a **small subset of malignant tumours** may share this molecular feature with benign

leiomyomas, potentially representing atypical molecular evolution or rare progression pathways. Therefore, while MED12 status is highly informative, it must be interpreted within the broader context of clinical, morphological, and immunohistochemical findings (**Bertsch, 2014)**

1.5.3 Molecular Pathogenesis and Diagnostic Utility

The biological role of MED12 mutations appears to involve dysregulated transcription and possibly enhanced genomic instability, contributing to the genesis of leiomyomas. Functional studies in model systems suggest that MED12 exon 2 variants can drive tumour formation and promote chromosomal alterations, consistent with the high prevalence seen in benign fibroids. The near absence of such mutations in most leiomyosarcomas supports the current view that **leiomyosarcomas arise via distinct oncogenic pathways** rather than straightforward malignant transformation of typical leiomyomas. Given these observations, **MED12 mutational analysis** serves as a powerful diagnostic marker in routine practice, aiding in the accurate classification of smooth muscle tumours of the uterus. Its integration with comprehensive histopathological assessment can improve diagnostic confidence, particularly in challenging cases where morphology alone is insufficient **(Mäkinen, 2017)**

1.6 Integrating Immunohistochemistry and Next-Generation Sequencing in The Diagnosis of Uterine Mesenchymal Neoplasms

Accurate diagnosis of uterine mesenchymal neoplasms remains one of the most intricate challenges in gynecologic pathology due to substantial morphologic overlap among leiomyomas, leiomyosarcomas, endometrial stromal sarcomas, and rare mesenchymal entities. Reliance solely on histomorphology may result in diagnostic ambiguity, particularly in borderline or atypical cases. In recent years, the integration of **immunohistochemistry (IHC)** with **next-generation sequencing (NGS)** has significantly enhanced diagnostic precision by combining phenotypic characterization with molecular profiling (Sun, 2025).

1.6.1 Role of Immunohistochemistry

IHC constitutes the first-line ancillary diagnostic modality in uterine mesenchymal tumours. It assists in determining cellular lineage, evaluating tumour suppressor pathways, and narrowing differential diagnoses. For example, low-grade endometrial stromal sarcomas typically demonstrate positivity for estrogen receptor (ER), progesterone receptor (PR), and CD10, whereas leiomyosarcomas exhibit stronger expression of smooth muscle markers such as h-caldesmon and transgelin (Hwang et al., 2015). Furthermore, aberrant expression of tumour suppressor proteins—particularly p53 and Rb—has been correlated with underlying genomic alterations in leiomyosarcoma. Diffuse p53 overexpression or complete absence of Rb staining often reflects TP53 and RB1 mutations, which are characteristic of malignant smooth muscle tumours but uncommon in benign leiomyomas (Momeni-Boroujeni et al., 2023). Thus, IHC provides rapid, cost-effective insight into tumour biology and serves as a valuable screening tool for cases that may require molecular confirmation.

1.6.2 Contribution of Next-Generation Sequencing

While IHC evaluates protein expression, NGS elucidates the underlying genomic architecture of uterine mesenchymal neoplasms. Distinct molecular signatures define specific tumour subtypes. For instance, low-grade endometrial stromal sarcomas frequently harbor *JAZF1::SUZ12* gene fusions, whereas high-grade variants may demonstrate *YWHAE::NUTM2* or *BCOR* alterations (Sun, 2025). In contrast, leiomyosarcomas exhibit complex genomic instability with recurrent alterations in tumour suppressor pathways, including *TP53*, *RB1*, and *ATRX*. NGS is particularly valuable in diagnostically challenging tumours such as smooth muscle tumours of uncertain malignant potential (STUMP), where histologic features alone may not predict clinical behavior. Molecular profiling can uncover specific alterations that support malignant potential or confirm benignity, thereby refining prognostic assessment (Momeni-Boroujeni et al., 2023).

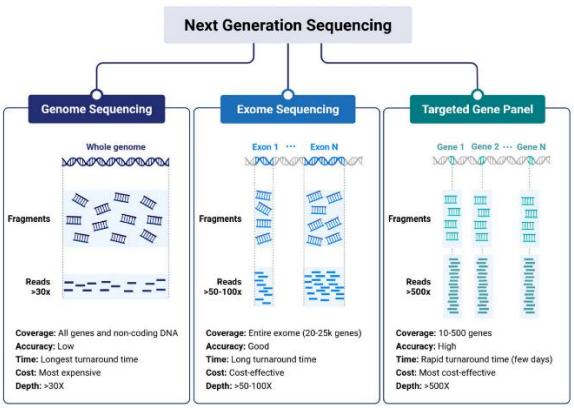

Figure 2: SOURCE: https://www.mdpi.com/1422-0067/26/19/9597

1.6.3. Synergistic Diagnostic Model

The integration of IHC and NGS represents a synergistic diagnostic paradigm. IHC serves as an

accessible phenotypic screening modality, guiding the selection of cases for molecular testing. Subsequently, NGS confirms or refines the diagnosis by identifying driver mutations, gene fusions, and copy number variations. This combined approach enhances subclassification accuracy, reduces interobserver variability, and aligns diagnostic practice with the principles outlined in the WHO Classification of Tumours (5th edition). Moreover, molecular characterization has therapeutic implications. Identification of actionable alterations—such as ALK rearrangements in inflammatory myofibroblastic tumours or mTOR pathway dysregulation in perivascular epithelioid cell tumours—may inform targeted treatment strategies (Sun, 2025). Thus, integration of IHC and NGS not only improves diagnostic fidelity but also supports precision oncology.

2. LITERATURE REVIEW

The complex histology and wide range of clinical manifestations of uterine mesenchymal tumors make their therapy a formidable obstacle. Learn about the latest developments in molecular pathology of uterine mesenchymal tumors in this comprehensive overview. Spindled, myxoid, epithelioid, and the newly-emerging lipoleiomyosarcoma are subtypes of leiomyosarcoma, the most prevalent malignant uterine mesenchymal tumor, which displays extensive genetic changes. The morphologies and molecular profiles of STUMPs and LGESSs, which stand for low-grade endometrial stromal sarcomas, are quite different. A number of molecular subtypes, such as YWHAE, identify high-grade endometrial stromal sarcomas (HGESS): Specifically, BCOR internal tandem duplications (ITDs), NUTM2, and BCOR rearrangements. The range of uterine mesenchymal neoplasms is expanded by less common tumors, such as inflammatory myofibroblastic tumors (IMT) with ALK rearrangements, NTRK-rearranged spindle cell tumors, and perivascular epithelioid cell tumors with TSC1/TSC2 changes and TFE3 rearrangements. More recent fusion sarcomas including RAD51B fusion sarcoma, KAT6B/A::KANSL1, COL1A1::PDGFB, and MEIS1::NCOA2/1 add to our knowledge of the different kinds of tumors. Finding targetable pathways, correctly classifying tumors, and directing therapy options are all greatly assisted by molecular diagnostics. In order to improve prognosis and develop new treatment options for uterine mesenchymal tumors, it is crucial to understand these molecular changes **(Ferozepurwalla, 2024)**

Uterine leiomyoma (UL) is a prevalent benign neoplasm that can occasionally be challenging to distinguish from the uterine inflammatory myofibroblastic tumor (IMT) based solely on form. It has long been believed that uterine myofibroblastic/fibroblastic neoplasms, such as IMT, are extremely uncommon. Although violent varieties do arise, its typical behavior is somewhat mild. While ALK fusion has not been seen in ULs yet, most IMTs have genomic rearrangement of anaplastic lymphoma kinase (ALK). A total of 9 ULs (0.4%) exhibited tyrosine-kinase activation out of 2263 that were examined. Six samples tested positive for ALK, and one of those samples overexpressed an ALK transcript that skipped exons 2 and 3. There was also a PDGFRB fusion gene in one sample and a RET in another. An ALK germline mutation was discovered in one patient, but no recurring somatic mutations were confirmed. The morphology of seven tumors resembled leiomyomas; one tumor had a slightly loose development pattern, and one tumor had a fibrous one. Lymphocyte infiltration ranged from mild to moderate in six tumors, while three patients did not show any immune cell infiltration. Aggressive behavior was not displayed by any of the tumors. The protein expression profile of the tumors was similar to ULs and different from other mesenchymal uterine tumors, with the exception of seven tumors that tested strongly positive for ALK. These tumors did not completely differentiate from the recognized UL subclasses on the level of gene expression. But these lesions were abnormally rich in vitamin C metabolism and pathways that connect epithelial cells to mesenchymal cells. Given the striking resemblance between the examined tumors and UL, it begs the issue of whether some uterine IMTs would be better diagnosed with UL **(Alodaini, 2024)**

The diagnostic challenges associated with uterine mesenchymal tumors are numerous and varied. These tumors include inflammatory myofibroblastic tumors (IMTs), smooth muscle tumors, endometrial stromal tumors (ESS), perivascular epithelioid cell tumors (PEComas), uterine tumor resembling ovarian sex cord tumor (UTROSCT), and numerous other uncommon entities. These tumors are increasingly being identified by recurrent genetic abnormalities that improve diagnosis and shed light on carcinogenesis; histomorphology and immunophenotype were previously used for classification. One example is the complex genomic instability seen in leiomyosarcomas, which is characterized by frequent mutations in TP53, RB1, and

ATRX. While YWHAE::NUTM2 or ZC3H7B::BCOR fusions and BCOR internal tandem duplication (ITD) changes are seen in high-grade malignancies, JAZF1::SUZ12 and related fusions are found in low-grade ESS. The mTOR pathway is abnormally activated in PEComas because to mutations in TSC1 or TSC2. These molecular fingerprints have applications beyond diagnosis; they are becoming more important in determining prognosis and identifying possible therapeutic targets, such as immunotherapy, PI3K/AKT/mTOR blockage, and CDK4/6 suppression. The importance of incorporating molecular testing into clinical practice to improve diagnosis accuracy and allow for individualized treatment of these uncommon but clinically relevant neoplasms is highlighted in this review, which covers the changing molecular landscape of uterine mesenchymal tumors (Sun, 2025)

The aggressive, histologically well-differentiated smooth muscle tumor known as intravenous leiomyomatosis (IVL) can spread throughout the veins and arteries. Diagnosing and treating IVL requires a thorough understanding of its etiology and progression. Unfortunately, there is a lack of extensive studies available due to the rarity of IVL. Tissue samples were collected from uterine fibroid, normal myometrium, IVL patients, and as part of our research, we conducted a comprehensive multi-omics analysis. The investigation of single-cell RNA sequencing showed that uterine fibroid and IVL have very different cell compositions. Furthermore, when compared to normal myometrium and uterine fibroid, H&E staining showed that IVL tissues had a lower vascular density, greater hydropic alterations, and hyalinization. We found proteins that were differentially expressed in our proteomics study of eight paired samples of normal myometrium and IVL fresh frozen tissue. These proteins were primarily associated with focal adhesions and actin cytoskeleton modulation. Chromosomes that were most commonly affected have deletions in 10q22.2, 10q24.32, 13q14, and 13q21-31. Proteins on chromosome 10q regulate focal adhesions and the cytoskeleton, and correlation studies revealed that this chromosome is the most common cytoband. Chromosome 10q deletion and vascular architecture in IVL were identified as significant markers for aggressive behavior in an integrated examination of clinical and pathological features. The clinical and molecular alterations associated with IVL are better understood thanks to our research, which may lead to novel therapeutic strategies **(Yin, 2025)**

The increasing frequency of endometrial cancer is mainly caused by reproductive factors, obesity, and prolonged exposure to unopposed oestrogens. In high-income nations, it is the most prevalent gynaecologic malignancy. The majority of instances occur randomly, although about 2-5% are linked to hereditary cancer syndromes, the most significant of which is Lynch syndrome. A significantly elevated risk of endometrial cancer, reaching as high as 71% in carriers of MutS homologue 6 (MSH6) mutations, is linked to Lynch syndrome, which is caused by germline mutations in the DNA mismatch repair (MMR) genes. Early disease onset, several primary malignancies, a strong family history, or microsatellite instability in tumor tissue are clinical warning indications that may indicate a hereditary cancer risk, which usually follows an autosomal dominant inheritance pattern. Hereditary endometrial cancer risk factors include Lynch syndrome as well as less common genetic diseases such as Cowden syndrome (PTEN), Li-Fraumeni syndrome (TP53), polymerase proofreading-associated polyposis (POLE/POLD1), and hereditary breast and ovarian cancer syndromes (BRCA1/2). In order to provide precise diagnoses, conduct individualised surveillance, and employ focused preventative and therapeutic measures, it is crucial to identify these genetic origins. Hereditary endometrial cancer is still underdiagnosed, which means that families and people afflicted by it miss out on chances to prevent the disease, even though molecular diagnostics have come a long way. This extensive review compiles the latest findings on Lynch syndrome and other hereditary endometrial cancer risk factors, as well as on the genetic mechanisms, inheritance patterns, diagnostic approaches, and clinical consequences for screening, genetic counseling, and treatment optimization **(Kluk, 2026)**

The developed world has the highest incidence of endometrial cancer among gynecologic malignancies. Our growing knowledge of tumor biology is reshaping how we classify patients and how we treat them. There is great hope for the development of targeted Wnt inhibitor therapy due to the significant role that upregulated Wnt signaling plays in the beginning and progression of cancer. By facilitating tumor cell dissociation and migration, stimulating epithelial-to-mesenchymal transition (EMT), and triggering the production of mesenchymal markers, Wnt signaling is one mechanism by which Wnt signaling contributes to the advancement of cancer. Endometrial cancer gene expression profiles were examined in this study. While hormone receptor status in EC was substantially linked with Wnt signaling and EMT markers, no other clinico-pathological features

were. Using integrated molecular risk assessment, there was a substantial difference in the expression of the Wnt antagonist Dkk1 between the ESGO-ESTRO-ESP patient risk assessment groups **(Ledinek, 2023)**

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The uncommon tumor known as follicular dendritic cell sarcoma (FDCS) shares immunophenotypical and morphological characteristics with follicular dendritic cells. Its wide morphological breadth and rarity make diagnosis difficult. We still know very little about the molecular basis of this extremely rare tumor. We conducted an extensive morphological, immunohistochemical, and molecular investigation to further clarify the biology and diagnostic features of these tumors. Fifteen tissue samples from thirteen patients diagnosed with FDCS were subjected to genetic investigation by next-generation panel sequencing in addition to histological and immunohistochemical analyses. Among the thirteen cases studied for histomorphology in this FDCS series, seven displayed predominately epithelioid cytomorphology, whereas six displayed a morphological spectrum with a combination of spindled and epithelioid cells. Due to its variable expression in all instances, we were able to identify the L1 cell adhesion molecule (L1CAM) as a new immunomarker of FDCS. After 112 genes were sequenced, 170 variations (classes 3, 4, and 5) were found. Five out of thirteen of the most common pathogenic mutations that were found altered NFKBIA, which in turn activated the nuclear factor kappa B (NFκB) signaling pathway. Importantly, only five out of seven patients with mostly epithelioid morphology had harmful NFKBIA mutations. In addition, two instances had epithelioid morphology and a high proliferation rate; one of these cases relapsed twice, and TP53 mutations were found in both circumstances. This group of FDCS displayed a genetically and morphologically diverse terrain. Nevertheless, consistent with other findings, we discovered frequent genetic variations impacting NFkB signaling. This rare tumor may be more easily diagnosed if the adhesion molecule L1CAM is expressed **(Schelbert, 2025)**

3. METHODOLOGY

3.1 Research Design

The present study adopts a **qualitative descriptive research design** based exclusively on an extensive review and critical synthesis of existing scientific literature. No primary data collection, laboratory experimentation, patient recruitment, or statistical analysis was undertaken. Instead, the study systematically examines and interprets contemporary peer-reviewed publications addressing the pathomorphological and molecular genetic landscape of uterine mesenchymal tumors.

This qualitative review approach was selected to provide a comprehensive and conceptually integrated understanding of evolving molecular diagnostics, genetic alterations, and their clinical implications in uterine mesenchymal neoplasms. The methodology emphasizes thematic synthesis rather than quantitative meta-analysis.

3.2 Data Sources

The data for this study were derived from previously published scholarly articles, review papers, molecular pathology reports, and consensus classification documents. The literature referenced in the review includes contemporary works such as Ferozepurwalla (2024), Alodaini (2024), Sun (2025), Yin (2025), Kluk (2026), Ledinek (2023), Sznurkowski (2023), and Schelbert (2025), among others.

Primary databases consulted in the referenced literature include PubMed, Scopus-indexed journals, Web of Science, and other reputable biomedical repositories. Emphasis was placed on high-impact, peer-reviewed sources published within the last decade to ensure scientific relevance and contemporary accuracy.

3.3 Inclusion and Exclusion Criteria

Inclusion Criteria:

- Peer-reviewed journal articles focusing on uterine mesenchymal tumors.

- Studies discussing molecular genetics, immunohistochemistry, next-generation sequencing, gene fusions, chromosomal alterations, and targeted therapy pathways.
- Articles addressing diagnostic challenges and tumor classification updates.
- English-language publications.

Exclusion Criteria:

- Non-peer-reviewed commentaries or opinion articles.
- Studies unrelated to uterine mesenchymal neoplasms.
- Articles lacking molecular or pathological relevance.
- Duplicate or outdated studies superseded by updated molecular classifications.

3.4 Data Extraction and Thematic Organization

The selected literature was carefully examined to extract relevant information regarding:

Histopathological characteristics of various uterine mesenchymal tumors (e.g., leiomyosarcoma subtypes, STUMP, LGESS, HGESS, IMT, PEComa).

Molecular alterations, including gene fusions (e.g., YWHAE, BCOR, JAZF1::SUZ12), chromosomal deletions, internal tandem duplications, and pathway dysregulations (e.g., PI3K/AKT/mTOR, Wnt signaling).

Diagnostic biomarkers and immunohistochemical correlations, including ALK rearrangements, TP53, RB1, ATRX alterations, and others.

Therapeutic implications and emerging targeted strategies.

The extracted findings were then categorized into thematic domains:

- Molecular classification and tumor subtyping
- Diagnostic challenges and differential diagnosis
- Genomic instability and tumor progression
- Targetable molecular pathways
- Emerging rare and fusion-driven sarcomas

A narrative synthesis approach was used to integrate and interpret these themes, allowing for conceptual consolidation of diverse findings into a coherent understanding of the subject.

3.5 Analytical Approach

The study employs **interpretative thematic synthesis**, focusing on identifying patterns, consistencies, and conceptual relationships across the reviewed literature. Rather than performing statistical pooling or meta-analytic computation, this research provides a structured qualitative interpretation of the molecular landscape of uterine mesenchymal tumors. Comparative evaluation was conducted to highlight distinctions between benign and malignant entities, low-grade versus high-grade stromal tumors, and common versus rare molecular subtypes. Emphasis was placed on diagnostic integration and clinical applicability.

4. DISCUSSION

The present qualitative review synthesizes contemporary evidence regarding the pathomorphological and molecular genetic landscape of uterine mesenchymal tumors, highlighting the paradigm shift from morphology-based classification toward integrative molecular diagnostics. The literature consistently demonstrates that uterine mesenchymal neoplasms constitute a biologically heterogeneous group of tumors whose accurate diagnosis increasingly depends on the convergence of histopathology, immunophenotyping, and genomic profiling.

4.1 Diagnostic Complexity and Morphological Overlap

Uterine mesenchymal tumors present significant diagnostic challenges due to their broad histological spectrum and overlapping morphological features. Leiomyomas, leiomyosarcomas, smooth muscle tumors of uncertain malignant potential (STUMP), and endometrial stromal sarcomas often share cytologic and architectural characteristics that complicate definitive classification. Traditional reliance on mitotic index, nuclear atypia, and tumor cell necrosis, although valuable, may be insufficient in borderline or unusual cases. The reviewed literature consistently emphasizes that morphology alone cannot reliably predict biological behavior, particularly in tumors with ambiguous histological features. This diagnostic uncertainty underscores the importance of incorporating molecular and immunophenotypic data into routine pathological evaluation.

4.2 Molecular Distinction Between Benign and Malignant Smooth Muscle Tumors

A critical finding across contemporary studies is the clear molecular divergence between benign leiomyomas and malignant leiomyosarcomas. Leiomyosarcomas exhibit complex genomic instability, frequently involving alterations in tumor suppressor genes such as *TP53*, *RB1*, and *ATRX*, which are associated with aggressive clinical behavior and poor prognosis (Sun, 2025). In contrast, benign leiomyomas demonstrate comparatively stable genomic profiles with distinct molecular

drivers. This evidence supports the concept that leiomyosarcomas generally arise independently rather than through malignant transformation of preexisting leiomyomas. The identification of these molecular differences significantly enhances diagnostic accuracy and reduces misclassification, particularly in challenging STUMP cases.

4.3 Molecular Subclassification of Endometrial Stromal Tumors

The molecular stratification of endometrial stromal tumors represents one of the most impactful advancements in uterine mesenchymal pathology. Low-grade endometrial stromal sarcomas are commonly characterized by gene fusions such as *JAZF1::SUZ12*, while high-grade variants demonstrate more aggressive molecular signatures, including *YWHAE::NUTM2* fusions and *BCOR* rearrangements or internal tandem duplications (Sun, 2025; Ferozepurwalla, 2024). These molecular alterations provide objective diagnostic markers that correlate strongly with clinical behavior. The distinction between low-grade and high-grade tumors is therefore no longer based solely on morphology but reinforced by reproducible genetic fingerprints that improve prognostic stratification.

4.4 Emerging Rare and Fusion-Driven Neoplasms

The expanding recognition of rare uterine mesenchymal tumors further illustrates the importance of molecular diagnostics. Inflammatory myofibroblastic tumors frequently harbor *ALK* rearrangements, which not only confirm diagnosis but also identify candidates for targeted ALK inhibition (Alodaini, 2024). Similarly, perivascular epithelioid cell tumors demonstrate *TSC1/TSC2* mutations leading to mTOR pathway activation, offering potential responsiveness to mTOR inhibitors (Sun, 2025). Newly described fusion-driven sarcomas, including *RAD51B*, *COL1A1::PDGFB*, and *KAT6B/A::KANSL1*, broaden the molecular spectrum and challenge conventional classification systems. These findings reinforce the concept that uterine mesenchymal tumors represent a genetically diverse continuum rather than a limited set of morphologic categories.

4.5 Molecular Insights into Tumor Progression and Aggressiveness

The literature also highlights molecular mechanisms underlying tumor progression and aggressive clinical behavior. Intravenous leiomyomatosis, although histologically well differentiated, demonstrates distinct chromosomal deletions—particularly involving chromosome 10q—and alterations in focal adhesion and cytoskeletal pathways that may explain its invasive vascular growth pattern (Yin, 2025). Additionally, dysregulation of signaling pathways such as PI3K/AKT/mTOR and Wnt contributes to tumor proliferation, epithelial–mesenchymal transition, and metastatic potential (Ledinek, 2023; Sznurkowski, 2023). These molecular insights bridge the gap between morphology and tumor biology.

4.6 Clinical and Therapeutic Implications

One of the most significant implications of molecular classification is its impact on therapeutic strategy. Identification of actionable genetic alterations—such as ALK rearrangements, mTOR pathway activation, and cell cycle dysregulation—creates opportunities for targeted therapy and personalized treatment planning (Sun, 2025). Furthermore, recognition of hereditary cancer syndromes and germline mutations influencing gynecologic tumorigenesis highlights the importance of genetic counseling and individualized surveillance strategies (Kluk, 2026). Thus, molecular diagnostics extend beyond classification and directly influence clinical management.

4.7 Integration of Morphology and Molecular Diagnostics

The collective findings emphasize that optimal diagnosis of uterine mesenchymal tumors requires an integrated approach combining histopathology, immunohistochemistry, and next-generation sequencing. Molecular testing provides objective biomarkers that enhance diagnostic confidence, reduce interobserver variability, and align clinical practice with evolving classification systems. As genomic technologies become more accessible, their incorporation into routine diagnostic workflows is expected to further refine tumor categorization and improve patient outcomes. In summary, the discussion demonstrates that uterine mesenchymal tumors are best understood through a multidimensional framework that integrates morphology with molecular genetics. Continued research and broader implementation of molecular diagnostics are essential to advance precision oncology and improve prognostic assessment in these complex and clinically significant neoplasms.

5. CONCLUSION

The present study highlights the growing importance of integrating immunohistochemistry and next-generation sequencing in the diagnosis of uterine mesenchymal neoplasms. Traditional

histopathological evaluation, although foundational, is often limited by morphological overlap among leiomyoma, leiomyosarcoma, endometrial stromal sarcoma, and other rare mesenchymal tumors. The incorporation of molecular diagnostics has significantly improved diagnostic precision by identifying distinct genetic alterations that correlate with tumor classification, biological behavior, and prognosis.

The findings reaffirm that benign and malignant smooth muscle tumors are molecularly distinct entities rather than points along a single progression pathway. Genetic alterations such as *TP53*, *RB1*, and *ATRX* mutations in leiomyosarcoma, as well as characteristic gene fusions in endometrial stromal sarcomas, serve as reliable diagnostic and prognostic markers. Furthermore, the identification of actionable mutations, including *ALK* rearrangements and mTOR pathway activation, underscores the therapeutic relevance of molecular profiling.

Overall, the study concludes that a combined diagnostic approach—integrating morphology, immunophenotyping, and genomic analysis—provides a more comprehensive and accurate framework for classifying uterine mesenchymal tumors. This integrated model not only enhances diagnostic confidence but also supports personalized treatment strategies, thereby contributing to improved patient management and outcomes. Continued research and routine incorporation of molecular testing into clinical practice are essential for advancing precision pathology in gynecologic oncology.

5.1 RECOMMENDATIONS

- **Routine Integration of Molecular Testing in Diagnostic Practice**: It is recommended that next-generation sequencing (NGS) be incorporated into routine diagnostic workflows for uterine mesenchymal neoplasms, particularly in morphologically ambiguous cases. While histopathology and immunohistochemistry remain foundational, molecular profiling provides objective genetic markers that enhance diagnostic accuracy and reduce interobserver variability. The identification of gene fusions, tumor suppressor gene mutations, and pathway alterations can help differentiate benign from malignant entities and improve prognostic stratification.
- **Development of Standardized Diagnostic Algorithms**: There is a need to establish standardized diagnostic algorithms that systematically integrate morphology, immunohistochemistry, and molecular findings. A structured approach would minimize diagnostic discrepancies and ensure uniform reporting practices across institutions. Such algorithms should clearly outline when molecular testing is indicated, particularly in cases of smooth muscle tumors of uncertain malignant potential (STUMP) and rare fusion-driven sarcomas.
- **Expansion of Molecular Research in Rare Tumor Subtypes**: Further research should focus on rare uterine mesenchymal tumors and newly identified fusion-driven neoplasms. Many uncommon entities remain under-characterized at the molecular level. Large-scale multicenter studies and genomic databases would help clarify their biological behavior, prognostic significance, and potential therapeutic targets. Expanding research in this area will contribute to refining tumor classification systems and improving clinical management.
- **Promotion of Targeted and Personalized Therapy Approaches**: Given the identification of actionable mutations such as ALK rearrangements and alterations in the PI3K/AKT/mTOR pathway, it is recommended that molecular findings be incorporated into treatment planning. Personalized therapeutic strategies based on tumor-specific genetic alterations may improve treatment outcomes and reduce unnecessary exposure to aggressive chemotherapy in low-risk cases. Collaboration between pathologists, oncologists, and molecular scientists is essential to implement precision oncology effectively.

Strengthening Interdisciplinary Collaboration: The diagnosis and management of uterine mesenchymal tumors require close coordination among pathologists, gynecologic oncologists, radiologists, and molecular geneticists. Regular multidisciplinary tumor board discussions should be encouraged to ensure that histological, clinical, and molecular findings are interpreted collectively. Such collaboration enhances clinical decision-making and improves patient-centered care.

REFERENCES

Alodaini, A. A. (2024). Uterine mesenchymal tumors: updates on pathology, molecular landscape, and therapeutics. Medicina, 60(7), 1085.

Ferozepurwalla, Z., & Ralte, A. (2024). Molecular basis of uterine mesenchymal tumours. Diagnostic Histopathology, 30(9), 487-498.

Kluk, A., Gryczka, H., Braszka, M., Ałtyn, R., Markiewicz, H., Ślężak, J. K., ... & Dobosz, P. (2026). Hereditary Endometrial Cancer: Lynch Syndrome, Mismatch Repair Deficiency, and Emerging Genetic Predispositions—A Comprehensive Review with Clinical and Laboratory Guidelines. International Journal of Molecular Sciences, 27(3), 1304.

Kuisma, H., Jokinen, V., Pasanen, A., Heikinheimo, O., Karhu, A., Välimäki, N., ... & Bützow, R. (2022). Histopathologic and molecular characterization of uterine leiomyoma–like inflammatory myofibroblastic tumor: comparison to molecular subtypes of uterine leiomyoma. *The American Journal of Surgical Pathology*, *46*(8), 1126-1136.

Ledinek, Ž., Sobočan, M., Sisinger, D., Hojnik, M., Büdefeld, T., Potočnik, U., & Knez, J. (2023). The association of Wnt-signalling and EMT markers with clinical characteristics in women with endometrial cancer. Frontiers in oncology, 13, 1013463.

Schelbert, S., Maurus, K., Roth, S., Ott, G., Kurz, K. S., Mogler, C., ... & Gerhard-Hartmann, E. (2025). Morphological, immunohistochemical and molecular analysis of follicular dendritic cell sarcomas: L1CAM as a new diagnostic marker. *Histopathology*, *87*(2), 258-269.

Sun, T. (2025). The Evolving Molecular Landscape of Uterine Mesenchymal Tumors: Diagnostic and Therapeutic Implications. Cancers, 17(24), 4012.

Sznurkowski, J. J., Rys, J., Kowalik, A., Zolciak-Siwinska, A., Bodnar, L., Chudecka-Glaz, A., ... & Sawicki, W. (2023). The polish society of gynecological oncology guidelines for the diagnosis and treatment of endometrial carcinoma (2023). *Journal of Clinical Medicine*, *12*(4), 1480.

Yin, S., Shi, P., Han, J., Li, H., Ren, A., Ma, L., ... & Zhang, J. (2025). Pathological and molecular insights into intravenous leiomyomatosis: an integrative multi-omics study. *Journal of Translational Medicine*, *23*(1), 229.

Yusupov Sh. Shamsiev A. Atakulov J. Baymurodov N. Mutalibov i. Djalolov D. Clinical justification for reducing pressure in the small intestine in common appendicular peritonitis in children. International Journal of pharmaceutical Research. Apr –June 2021. Vol 13. Issue 2. 985 – 991.

Yusupov Sh. Shamsiev A. Shamsiev J. Baymuradov N. Pulatov P. Effectiveness of surgical treatment of congenital lymphangiomas of the head and neck in children. Sciences of Europe. Vol 2. № 70. 2021. 24 – 26.

Shamsiev A. Atakulov J. Rakhimov A. Baymuradov N. Shamsiev R. About the causes of head and neck injuries in children. The Scientific Heritage. Vol 2. № 66. 2021. 21 – 22.

Atakulov J. Yusupov Shukhrat. Baymuradov N. Shakhriev A. Kodirov N. Adaptation of patients who underwent surgery for hypospadias in childhood. Chi J ind Occup Dis. 2022. 179 – 187.

Davronov B. Boymuradov N. Yusupov Sh. Atakulov J. Shamsiev J. Changes in biochemical blood parameters in widespread appendicular peritonitis in children. European Journal of Molecular medicine. Vol 2. No 5. September 2022. 4 -9.

Shamsiev A. Rakhimov A. Sagiraev N. Baymuradov N. Arabova Kh. Long – term Result of treatment of esophageal Burns in children. American Journal of Medicine and Medical Sciences 2022. 12(2). 142 – 144.