Endometrial Carcinoma: Contemporary Understanding of Pathogenesis, Risk Factors, and Biological Behaviour in the Era of Molecular Classification

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Abstract

Endometrial carcinoma represents the most prevalent gynaecological malignancy in developed nations, with an alarming global incidence exceeding 417,000 cases annually and a mortality rate that continues to escalate at 1.9% per year. This comprehensive review synthesises contemporary understanding of endometrial carcinoma pathogenesis, examining the complex interplay between hormonal, genetic, and environmental risk factors that contribute to malignant transformation of the endometrial epithelium. The traditional dualistic classification system, distinguishing between oestrogen-dependent Type I and oestrogen-independent Type II carcinomas, has been revolutionised by The Cancer Genome Atlas (TCGA) molecular classification, which identifies four distinct molecular subgroups: POLE ultramutated (7%), microsatellite instability hypermutated (28%), copy number low (39%), and copy number high serous-like tumours (26%). Each subgroup exhibits unique biological behaviour, prognostic implications, and therapeutic vulnerabilities that fundamentally challenge traditional histology-based treatment paradigms.

This review critically evaluates current hypotheses regarding endometrial carcinogenesis, from the established oestrogen-driven pathway leading to endometrioid adenocarcinomas through endometrial intraepithelial neoplasia, to the more aggressive serous and clear cell variants arising through p53-mediated pathways

independent of hormonal stimulation. Contemporary epidemiological data reveal significant racial and socioeconomic disparities in disease incidence and outcomes, with obesity emerging as the predominant modifiable risk factor, accounting for approximately 50% of cases through mechanisms involving peripheral aromatisation, insulin resistance, and chronic inflammation. The biological behaviour of endometrial carcinomas varies dramatically across molecular subgroups, with POLE-mutated tumours demonstrating exceptional prognosis despite high-grade histology due to enhanced immunogenicity from hypermutation, whilst copy number high tumours exhibit aggressive clinical behaviour necessitating multimodal therapeutic approaches regardless of stage at presentation.

Understanding these molecular distinctions has profound implications for personalised treatment strategies, surveillance protocols, and prognostic counselling. The integration of molecular classification with traditional clinicopathological parameters through tools such as the ProMisE algorithm has enabled practical implementation in routine clinical practice, facilitating biomarker-driven therapeutic decisions including immunotherapy selection for microsatellite instability-high tumours. This review provides a comprehensive analysis of current knowledge whilst identifying critical gaps that warrant future investigation, particularly regarding the role of tumour microenvironment, immune infiltration patterns, therapeutic resistance mechanisms across different molecular subgroups, and the development of novel targeted therapies based on molecular vulnerabilities.

Keywords: Endometrial carcinoma; molecular classification; TCGA; POLE mutations; microsatellite instability; oestrogen; pathogenesis; biological behaviour; risk factors; endometrioid adenocarcinoma; serous carcinoma; clear cell carcinoma; ProMisE; immunotherapy; precision medicine

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1. Introduction

Endometrial carcinoma stands as a paradigmatic example of how molecular insights can fundamentally transform our understanding of cancer biology and clinical management, representing one of the most significant success stories in the translation of genomic discoveries to clinical practice. As the most prevalent gynaecological malignancy in developed nations and the fourth most common cancer affecting women globally, endometrial carcinoma presents a complex clinical challenge that has evolved significantly with advances in molecular pathology and

genomic medicine (Ferlay et al., 2021). The disease affects the inner epithelial lining of the uterus, arising from the endometrial glandular epithelium through a series of well-characterised and increasingly understood molecular events that reflect the intricate relationship between hormonal influences, genetic predisposition, and environmental factors (Kandoth et al., 2013).

The contemporary epidemiological landscape of endometrial carcinoma reveals both encouraging and concerning trends that demand urgent attention from the global oncology community. Globally, the disease was diagnosed in 417,367 women in 2020, with the highest disease burden concentrated in North America and Western Europe, regions characterised by elevated rates of obesity and lifestyle-related risk factors (Bray et al., 2018). This geographic distribution underscores the profound influence of modifiable risk factors, particularly obesity, which accounts for approximately 50% of endometrial carcinoma cases and represents the most significant preventable cause of this malignancy through complex mechanisms involving peripheral aromatisation of androgens to oestrogens in adipose tissue, insulin resistance with consequent hyperinsulinaemia, and chronic inflammatory states (Crosbie et al., 2010). The incidence has increased by more than 130% over the past three decades, with projections suggesting that annual diagnoses in the United States alone will double to 122,000 cases by 2030 if current trends persist, representing a public health crisis of unprecedented magnitude (Siegel et al., 2023).

Paradoxically, whilst overall incidence continues to rise, mortality rates have also increased by an average of 1.9% per year based on pooled analyses from 1971-2014, reflecting both the growing disease burden and the challenges associated with managing advanced-stage disease in an increasingly complex patient population (Torre et al., 2015). This concerning trend contrasts sharply with improvements in survival observed for many other malignancies and highlights the urgent need for enhanced prevention strategies, earlier detection methods, and more effective therapeutic interventions tailored to the molecular characteristics of individual tumours.

The traditional understanding of endometrial carcinoma pathogenesis has been fundamentally anchored in the dualistic classification system proposed by Bokhman in 1983, which distinguished between Type I and Type II carcinomas based on their relationship to oestrogen exposure and clinical behaviour (Bokhman, 1983). This classification system, whilst revolutionary for its time, has proven increasingly inadequate to capture the full biological complexity of endometrial carcinoma as revealed by contemporary molecular analyses. Type I carcinomas, comprising

approximately 80% of all endometrial cancers, are characteristically endometrioid in histology, arise in the context of unopposed oestrogen stimulation, and generally exhibit favourable prognosis when diagnosed at early stages (Amant et al., 2005). These tumours typically develop through a well-defined precursor pathway, progressing from simple endometrial hyperplasia through complex hyperplasia to atypical endometrial hyperplasia, now termed endometrial intraepithelial neoplasia (EIN), before ultimately transforming into invasive endometrioid adenocarcinoma (Mutter et al., 2000).

The molecular landscape of Type I carcinomas is characterised by a predictable sequence of genetic alterations, with frequent mutations in PTEN representing the earliest detectable genetic alteration, occurring in up to 80% of cases and often present even in morphologically normal endometrium adjacent to carcinomas (Mutter et al., 2000). This is followed by mutations in KRAS (occurring in 15-30% of cases), ARID1A (a chromatin remodelling gene mutated in 40-50% of endometrioid carcinomas), and PIK3CA (mutated in 20-30% of cases), alongside microsatellite instability in approximately 20-30% of cases due to deficient mismatch repair mechanisms (Kandoth et al., 2013). The temporal sequence of these mutations provides insights into the natural history of endometrioid carcinogenesis and offers potential targets for both prevention and therapeutic intervention.

In contrast, Type II carcinomas represent a more heterogeneous group of aggressive malignancies, including serous, clear cell, undifferentiated, and carcinosarcomatous histologies, which arise independently of oestrogen stimulation and are characterised by high-grade nuclear features, aggressive clinical behaviour, and poor prognosis even when diagnosed at early stages (Soslow et al., 2007). These tumours typically harbour TP53 mutations as early driver events, occurring in over 90% of serous carcinomas, and exhibit chromosomal instability with frequent copy number alterations affecting oncogenes and tumour suppressor genes (Kandoth et al., 2013). The pathogenesis of Type II carcinomas appears to involve direct malignant transformation of atrophic endometrium through p53-mediated pathways, bypassing the hyperplasia-carcinoma sequence characteristic of Type I tumours and often arising from precursor lesions such as serous endometrial intraepithelial carcinoma (SEIC) (Zheng et al., 2004).

However, this traditional binary classification system, whilst clinically useful for several decades, has proven insufficient to capture the full biological complexity of endometrial carcinoma as revealed by comprehensive genomic analyses. The landmark study by The Cancer Genome Atlas (TCGA) Research Network in 2013 revolutionised our understanding by identifying four distinct molecular subgroups

based on mutational burden and copy number alterations: POLE ultramutated (7%), microsatellite instability (MSI) hypermutated (28%), copy number low (CNL) (39%), and copy number high (CNH) serous-like tumours (26%) (Kandoth et al., 2013). This molecular classification has profound implications for understanding disease biology, predicting clinical outcomes, and guiding therapeutic decisions, representing a paradigm shift from morphology-based to molecularly-informed cancer classification.

The POLE ultramutated subgroup, representing approximately 7% of endometrial carcinomas, is characterised by mutations in the exonuclease domain of DNA polymerase epsilon, resulting in an extraordinarily high mutational burden exceeding 100 mutations per megabase, making these among the most highly mutated human cancers (Kandoth et al., 2013). Despite often presenting with high-grade histological features that would traditionally predict poor outcomes, these tumours demonstrate exceptional prognosis, with virtually no disease-related deaths reported in several large cohort studies and 5-year overall survival approaching 100% (Church et al., 2013). The favourable outcomes appear to result from the combination of inherent tumour biology and robust immune infiltration secondary to the high neoantigen burden generated by the hypermutated phenotype, leading to enhanced recognition and elimination by the adaptive immune system (Howitt et al., 2015).

The MSI hypermutated subgroup, comprising approximately 28% of endometrial carcinomas, results from deficient mismatch repair (MMR) mechanisms, either through germline mutations associated with Lynch syndrome (occurring in 2-5% of all endometrial carcinomas) or somatic alterations affecting MLH1, MSH2, MSH6, PMS2, or EPCAM (Kandoth et al., 2013). These tumours exhibit a mutational burden approximately 10-fold higher than microsatellite stable tumours and are characterised by extensive tumour-infiltrating lymphocytes, suggesting enhanced immunogenicity that has important therapeutic implications for immunotherapy selection (Le et al., 2015). The clinical behaviour of MSI tumours is generally intermediate between POLE and CNH subgroups, with outcomes influenced by stage, grade, and the specific MMR gene affected, though recent evidence suggests that MSI status may be a more powerful prognostic factor than traditional histological parameters (Stelloo et al., 2015).

The copy number low subgroup represents the largest molecular category, encompassing approximately 39% of endometrial carcinomas and consisting predominantly of low-grade endometrioid tumours with relatively few copy number alterations and a near-diploid karyotype (Kandoth et al., 2013). These tumours frequently harbour CTNNB1 mutations affecting the Wnt signalling pathway (occurring

in 25-40% of cases) and are associated with younger patient age and generally favourable prognosis, although a subset with chromosome 1q amplification demonstrates significantly worse outcomes, highlighting the importance of molecular subclassification even within morphologically similar tumours (Stelloo et al., 2015). The biological behaviour of CNL tumours generally aligns with traditional Type I carcinomas, reflecting their origin through oestrogen-driven pathways and their dependence on hormonal stimulation for growth and progression.

The copy number high subgroup, representing approximately 26% of endometrial carcinomas, encompasses the most aggressive tumours, including all serous carcinomas and approximately 25% of high-grade endometrioid carcinomas, demonstrating that molecular classification can override traditional histological boundaries (Kandoth et al., 2013). These tumours are characterised by extensive chromosomal instability, frequent TP53 mutations (occurring in >90% of cases), and amplifications of oncogenes such as CCNE1 (associated with increased replication stress and chemoresistance), ERBB2 (a potential therapeutic target), and MYC (driving proliferation and metabolic reprogramming) (Kandoth et al., 2013). The clinical behaviour of CNH tumours is uniformly poor, with high rates of recurrence and disease-related mortality even in early-stage disease, necessitating aggressive multimodal therapeutic approaches regardless of traditional prognostic factors.

The molecular classification has been successfully translated into clinical practice through the development of surrogate immunohistochemical and molecular assays, most notably the ProMisE (Proactive Molecular Risk Classifier for Endometrial Cancer) algorithm developed by Talhouk and colleagues (Talhouk et al., 2015). This approach utilises immunohistochemistry for MMR proteins (MLH1, MSH2, MSH6, PMS2) and p53, combined with POLE sequencing, to classify tumours into molecular subgroups that closely approximate the TCGA classification: MMRd (mismatch repair deficient), POLE (ultramutated), p53abn (p53 abnormal), and p53wt (p53 wild-type) (Talhouk et al., 2017). The clinical utility of molecular classification extends beyond prognostic stratification to include therapeutic decision-making, with emerging evidence supporting differential responses to adjuvant therapies across molecular subgroups and the potential for treatment de-escalation in favourable molecular subtypes.

Contemporary understanding of endometrial carcinoma risk factors reflects the complex interplay between hormonal, genetic, and environmental influences, with obesity representing the most significant modifiable risk factor in the modern era. The relationship between obesity and endometrial carcinoma risk operates through multiple interconnected mechanisms, including peripheral aromatisation of

androgens to oestrogens in adipose tissue (particularly in postmenopausal women where adipose tissue becomes the primary source of oestrogen production), insulin resistance with consequent hyperinsulinaemia (leading to increased bioavailable oestrogen through suppression of sex hormone-binding globulin), and chronic inflammatory states characterised by elevated levels of pro-inflammatory cytokines such as tumour necrosis factor-alpha and interleukin-6 (Crosbie et al., 2010). The relationship between obesity and endometrial carcinoma risk is particularly pronounced for Type I tumours, with relative risks exceeding 3.0 for severely obese women (BMI >40 kg/m^2) compared to normal-weight women, whilst the association with Type II tumours is less consistent and may operate through different mechanisms (Setiawan et al., 2013).

Other established risk factors include early menarche (before age 12), late menopause (after age 52), nulliparity, polycystic ovary syndrome, diabetes mellitus, and exogenous oestrogen therapy without progestin opposition, all of which increase lifetime oestrogen exposure and promote endometrial proliferation (Purdie & Green, 2001). The protective effects of pregnancy, oral contraceptive use, and progestin therapy operate through mechanisms involving progestin-induced endometrial atrophy and apoptosis, highlighting the central role of the oestrogen-progestin balance in endometrial carcinogenesis (Brinton et al., 1992). Recent epidemiological studies have also identified novel risk factors including certain dietary patterns (particularly those high in glycaemic index and saturated fats), sedentary lifestyle, and exposure to endocrine-disrupting chemicals, suggesting that endometrial carcinoma risk is influenced by a complex web of environmental and lifestyle factors that may be amenable to intervention (Felix et al., 2010).

Hereditary factors contribute significantly to endometrial carcinoma risk, with Lynch syndrome representing the most important hereditary cancer predisposition syndrome affecting the endometrium. Lynch syndrome, caused by germline mutations in mismatch repair genes (MLH1, MSH2, MSH6, PMS2) or the EPCAM gene, affects approximately 1 in 300-400 individuals in the general population and confers lifetime endometrial carcinoma risks ranging from 13% to 60%, depending on the specific gene affected (Møller et al., 2017). Remarkably, for women with Lynch syndrome, the risk of developing endometrial carcinoma often exceeds that for colorectal carcinoma, particularly for MSH6 and PMS2 mutation carriers, highlighting the importance of gynaecological surveillance in these high-risk individuals (Bonadona et al., 2011). The recognition of Lynch syndrome-associated endometrial carcinomas has important implications for genetic counselling, surveillance strategies, and risk-reducing

interventions, including prophylactic hysterectomy and bilateral salpingo-oophorectomy in women who have completed childbearing.

The biological behaviour of endometrial carcinomas varies dramatically across histological subtypes and molecular subgroups, reflecting fundamental differences in underlying biology, patterns of spread, and therapeutic vulnerabilities. Understanding these differences is crucial for optimising treatment strategies, predicting outcomes, and developing novel therapeutic approaches tailored to the specific characteristics of individual tumours. The integration of molecular classification with traditional clinicopathological parameters promises to enhance prognostic accuracy and enable more personalised therapeutic approaches, moving beyond the one-size-fits-all treatment paradigms that have dominated gynaecological oncology for decades.

The patterns of metastatic spread in endometrial carcinoma follow predictable anatomical pathways that are influenced by both tumour biology and anatomical constraints. Local extension typically involves direct invasion through the myometrium to the uterine serosa, with subsequent involvement of adjacent structures including the cervix, parametria, and pelvic organs (Amant et al., 2005). Lymphatic spread occurs through well-defined pathways, with pelvic lymph nodes (including obturator, internal iliac, external iliac, and common iliac nodes) representing the first echelon of regional metastasis, followed by para-aortic lymph nodes in cases of more extensive disease (Mariani et al., 2008). The risk of lymph node metastasis is strongly correlated with traditional prognostic factors including histological subtype, grade, depth of myometrial invasion, and lymphovascular space invasion, though molecular subgroup is emerging as an independent predictor of metastatic potential (Stelloo et al., 2016).

Haematogenous spread typically occurs later in the disease course and most commonly involves the lungs, liver, bone, and brain, with patterns varying according to histological subtype and molecular characteristics (McMeekin et al., 2007). Serous carcinomas demonstrate a particular propensity for peritoneal dissemination, often presenting with widespread intra-abdominal disease similar to ovarian carcinoma, whilst clear cell carcinomas may exhibit unusual patterns of spread including involvement of the kidneys and retroperitoneum (Crotzer et al., 2004). The molecular subgroups also demonstrate distinct patterns of recurrence, with POLE-mutated tumours rarely recurring, MSI tumours showing intermediate recurrence rates with good responses to salvage therapy, and copy number high tumours exhibiting high recurrence rates with poor responses to conventional treatments (Stelloo et al., 2015).

This comprehensive review aims to synthesise current understanding of endometrial carcinoma pathogenesis, risk factors, and biological behaviour within the framework of contemporary molecular classification. By examining the complex relationships between hormonal influences, genetic alterations, and environmental factors, we seek to provide a foundation for understanding this heterogeneous group of malignancies and to identify opportunities for improved prevention, diagnosis, and treatment strategies. The ultimate goal is to translate molecular insights into clinical practice, enabling personalised approaches to patient care that optimise outcomes whilst minimising treatment-related morbidity.

The implications of molecular classification extend far beyond academic interest, offering the potential to revolutionise clinical practice through more precise risk stratification, tailored therapeutic approaches, and novel treatment strategies based on molecular vulnerabilities. As we enter an era of precision medicine in gynaecological oncology, understanding the molecular basis of endometrial carcinoma becomes not merely an intellectual exercise but a clinical imperative that will determine the success of future therapeutic endeavours and ultimately improve outcomes for the thousands of women diagnosed with this disease each year.

2. Methodology

This comprehensive review employed a systematic and rigorous approach to identify, evaluate, and synthesise current literature pertaining to endometrial carcinoma pathogenesis, risk factors, and biological behaviour, with particular emphasis on contemporary molecular classification systems and their clinical implications. The methodology was designed to ensure comprehensive coverage of the rapidly evolving field whilst maintaining focus on the most recent advances in molecular pathology and their translation to clinical practice.

2.1 Literature Search Strategy

A comprehensive literature search was conducted using multiple electronic databases including PubMed/MEDLINE, Embase, Web of Science, Cochrane Library, and Google Scholar, covering publications from January 2000 to December 2023 to capture both foundational knowledge and recent advances. The search strategy employed a combination of Medical Subject Headings (MeSH) terms and free-text keywords to maximise sensitivity whilst maintaining specificity for relevant publications. Primary

search terms included: "endometrial carcinoma," "endometrial cancer," "uterine cancer," "molecular classification," "TCGA," "POLE mutations," "microsatellite instability," "mismatch repair," "pathogenesis," "risk factors," "biological behaviour," "ProMisE," and "precision medicine."

Boolean operators were utilised to combine search terms effectively, with the following comprehensive search string serving as the foundation: (("endometrial carcinoma" OR "endometrial cancer" OR "uterine cancer" OR "corpus uteri cancer") AND ("pathogenesis" OR "molecular classification" OR "TCGA" OR "biological behaviour" OR "risk factors" OR "POLE" OR "microsatellite instability" OR "mismatch repair" OR "p53" OR "immunotherapy")). Additional targeted searches were performed using specific molecular markers, classification systems, and therapeutic approaches to ensure comprehensive coverage of recent advances in the field.

2.2 Inclusion and Exclusion Criteria

Studies were included if they met the following stringent criteria: (1) original research articles, systematic reviews, meta-analyses, or landmark clinical trials published in peer-reviewed journals; (2) studies focusing on endometrial carcinoma pathogenesis, molecular classification, risk factors, biological behaviour, or therapeutic implications; (3) publications in English language; (4) studies with adequate sample sizes and appropriate methodology for the research question; (5) relevance to contemporary understanding of endometrial carcinoma biology; and (6) availability of full-text articles for detailed review.

Exclusion criteria comprised: (1) case reports or small case series (n<10) unless reporting novel molecular findings; (2) studies focusing exclusively on treatment outcomes without biological insights; (3) publications in languages other than English; (4) conference abstracts without full-text availability; (5) studies with significant methodological limitations or inadequate data presentation; and (6) duplicate publications or overlapping datasets without additional insights.

2.3 Data Extraction and Quality Assessment

Data extraction was performed systematically using a standardised form capturing study characteristics, methodology, key findings, clinical implications, and molecular insights. Particular attention was paid to studies reporting molecular classification data, risk factor analyses, biological behaviour correlations, and therapeutic

implications. Quality assessment was conducted using appropriate tools including the Newcastle-Ottawa Scale for observational studies, AMSTAR-2 for systematic reviews, and the Cochrane Risk of Bias tool for randomised controlled trials.

2.4 Synthesis Approach and Framework

Given the heterogeneous nature of the literature encompassing basic science, translational research, epidemiological studies, and clinical trials, a narrative synthesis approach was employed to integrate diverse study types whilst maintaining focus on the most robust and clinically relevant findings. The synthesis was structured around the established TCGA molecular classification system, with systematic evaluation of each molecular subgroup's characteristics, biological behaviour, and clinical implications.

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3. Histological and Molecular Illustrations

Figure 1: Normal Endometrial Architecture and Carcinoma Development

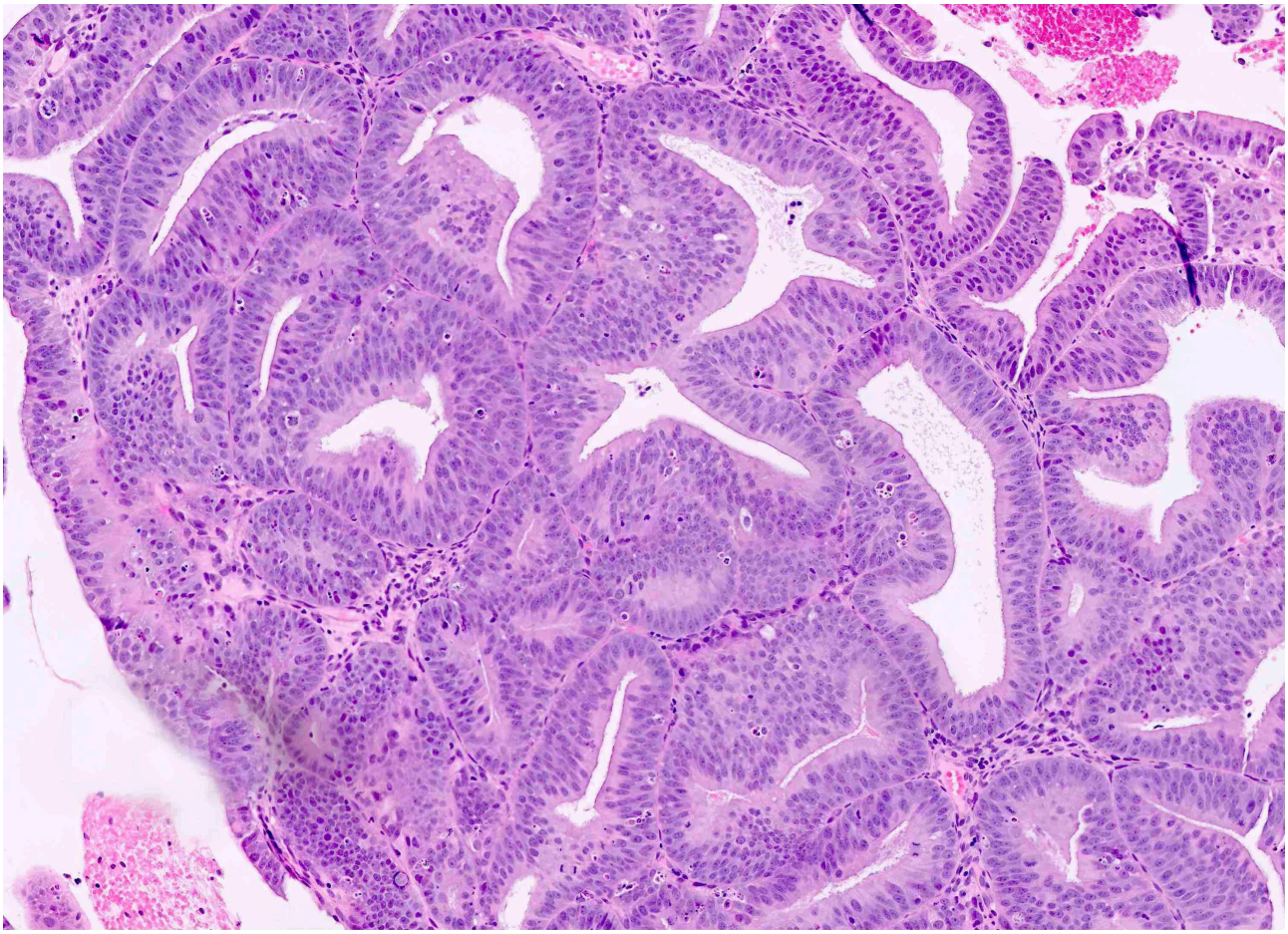

Figure 1. High-resolution photomicrograph demonstrating the progression from normal endometrial architecture through hyperplasia to carcinoma. The image shows the characteristic features of endometrial hyperplasia with increased gland-to-stroma ratio, irregular gland architecture, and crowding of endometrial glands. This represents the precursor pathway for Type I endometrioid carcinomas, illustrating the morphological changes that occur during oestrogen-driven carcinogenesis. The progression from simple hyperplasia through complex hyperplasia to atypical hyperplasia (endometrial intraepithelial neoplasia) represents a well-characterised pathway of malignant transformation. *Source: Pathology Outlines (www.pathologyoutlines.com)*

Figure 2: Endometrioid Adenocarcinoma - Classic Type I Histology

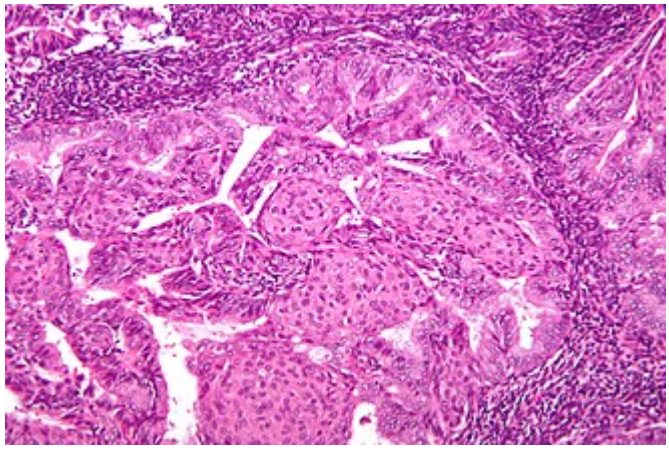

Figure 2. Haematoxylin and eosin (H&E) stained section of endometrioid adenocarcinoma demonstrating the characteristic glandular architecture with back-to-back glands, loss of intervening stroma, and nuclear stratification. This represents the most common histological subtype of endometrial carcinoma, accounting for approximately 80% of cases. The tumour shows well-differentiated glandular structures with mild to moderate nuclear atypia, consistent with Grade 1 endometrioid adenocarcinoma. The preservation of glandular architecture distinguishes this from higher-grade tumours and reflects the generally favourable prognosis associated with low-grade endometrioid carcinomas. *Source: Libre Pathology (librepathology.org)*

Figure 3: High-Grade Endometrial Carcinoma Histological Variability

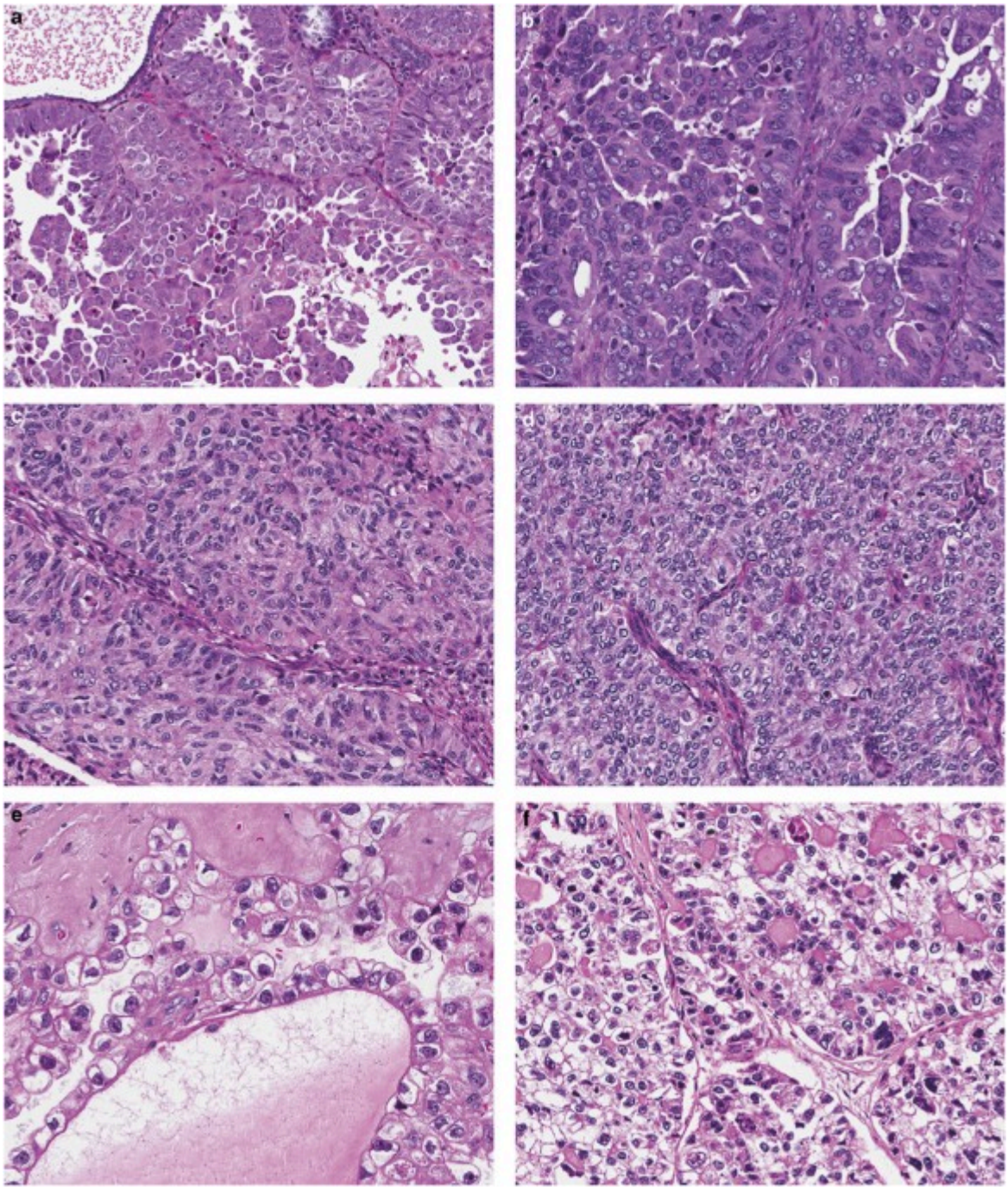

Figure 3. Panel of H&E-stained sections demonstrating the remarkable histological variability observed in high-grade endometrial carcinomas. This collection illustrates the challenges in reproducible histological classification and emphasises the critical importance of molecular characterisation for accurate prognostic assessment. The varying architectural patterns, cellular features, and degrees of differentiation shown highlight why molecular classification has become essential for optimal patient management, as morphologically similar tumours may belong to different molecular

subgroups with vastly different clinical behaviours and therapeutic responses. *Source: Nature (www.nature.com)*

Figure 4: Endometrial Intraepithelial Neoplasia (EIN)

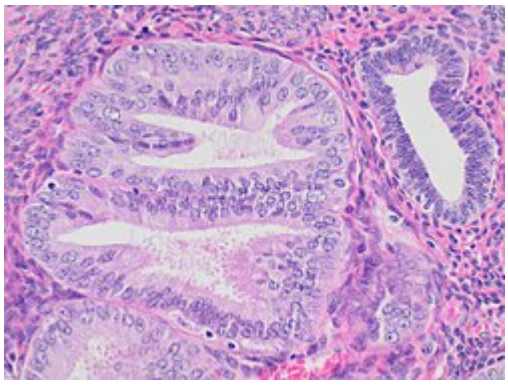

Figure 4. Photomicrograph showing endometrial intraepithelial neoplasia (EIN), the recognised precursor lesion for endometrioid adenocarcinoma. The image demonstrates the characteristic features of EIN including altered gland architecture, increased gland density, and cytological changes in the epithelial cells. EIN represents the modern terminology for what was previously called atypical endometrial hyperplasia and is associated with a significant risk of progression to invasive carcinoma if left untreated. The recognition of EIN is crucial for appropriate management and prevention of invasive disease. *Source: Wikipedia (en.wikipedia.org)*

Figure 5: EIN with Secretory Changes

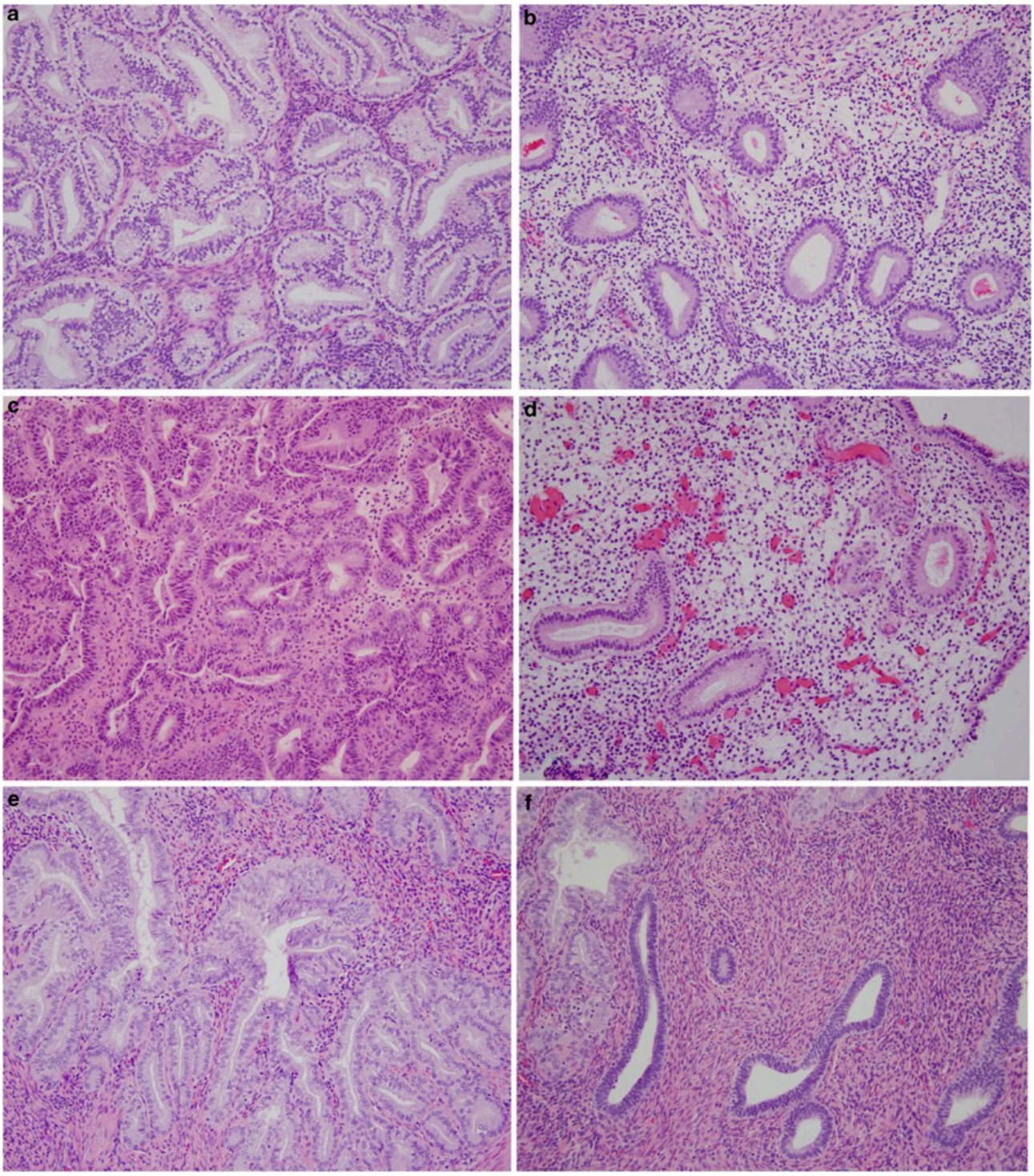

Figure 5. Detailed histological section of endometrial intraepithelial neoplasia with secretory changes, demonstrating the complex morphological patterns that can occur in precursor lesions. The image shows the characteristic crowded glandular architecture of EIN with superimposed secretory changes, illustrating how hormonal influences can modify the morphological appearance of premalignant lesions. This highlights the importance of understanding the hormonal context when interpreting

endometrial biopsies and the need for careful morphological assessment in the diagnosis of precursor lesions. *Source: Nature (www.nature.com)*

Figure 6: POLE Ultramutated Endometrial Carcinoma

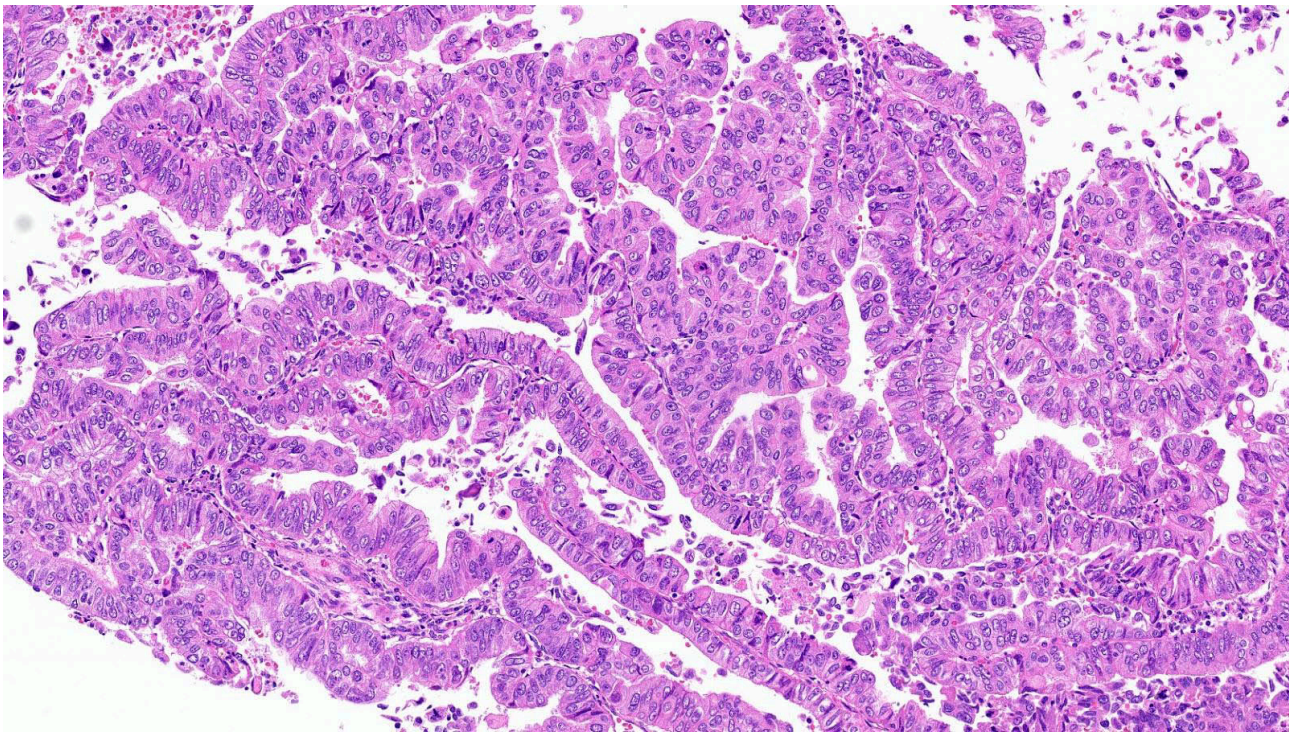

Figure 6. Histological section of POLE ultramutated endometrial carcinoma demonstrating the characteristic high-grade morphology with marked nuclear pleomorphism, increased mitotic activity, and prominent lymphocytic infiltration. Despite the aggressive histological appearance, POLE-mutated tumours have exceptional prognosis due to their hypermutated phenotype and enhanced immunogenicity. The dense lymphocytic infiltrate reflects the robust immune response generated by the high neoantigen burden characteristic of these tumours. This exemplifies how molecular classification can override traditional morphological assessment in determining prognosis and treatment decisions. *Source: Pathology Outlines (www.pathologyoutlines.com)*

Figure 7: Molecular Mechanisms in Endometrial Cancer

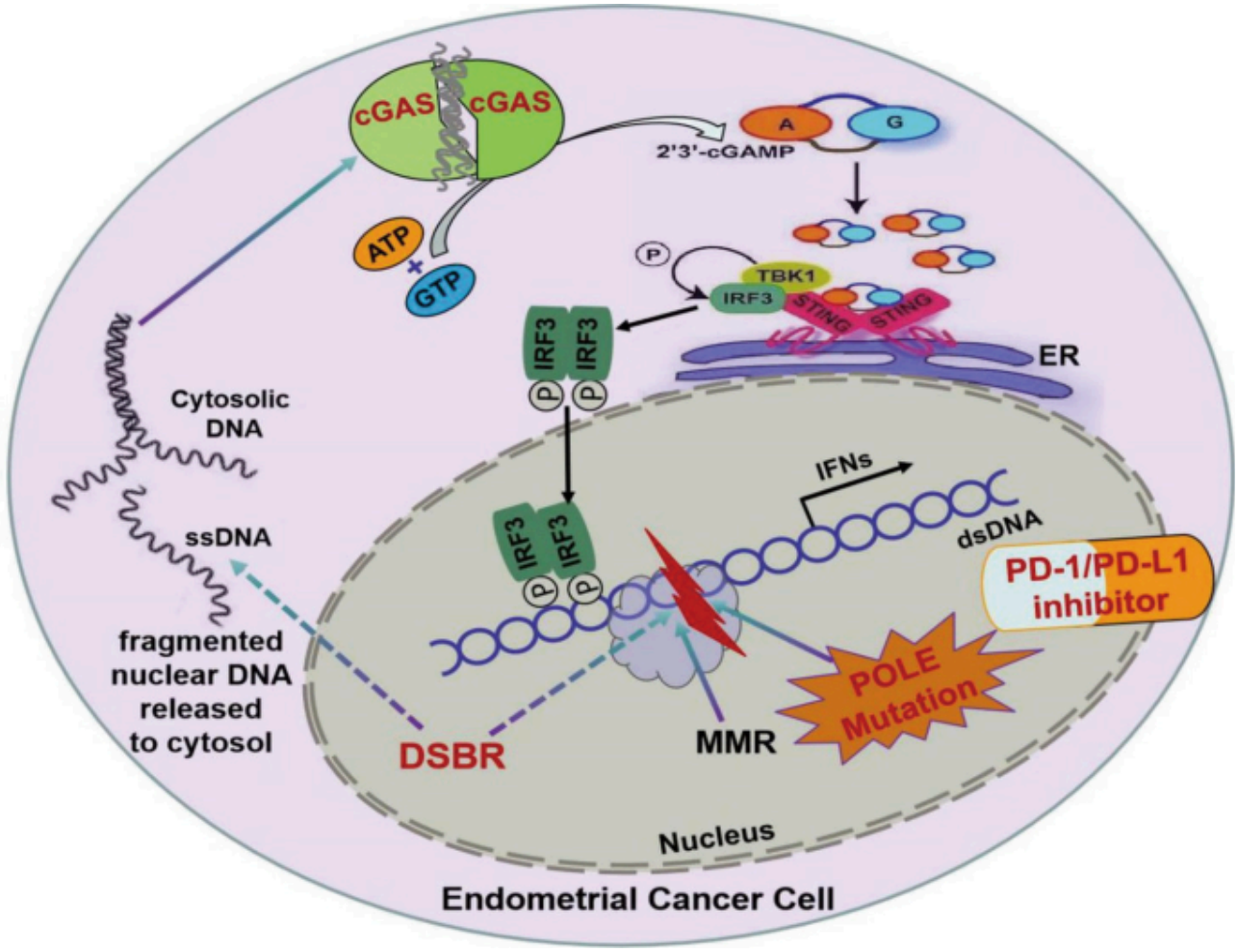

Figure 7. Schematic diagram illustrating the molecular mechanisms underlying endometrial carcinogenesis, including the role of DNA polymerase epsilon (POLE) mutations in generating hypermutated tumours. The diagram shows how POLE mutations in the exonuclease domain lead to defective proofreading activity, resulting in accumulation of mutations and enhanced immunogenicity. This molecular understanding has revolutionised our approach to endometrial carcinoma classification and treatment, moving beyond traditional histological assessment to incorporate genomic features that better predict clinical behaviour. *Source: Nature (www.nature.com)*

Figure 8: Mismatch Repair Protein Expression

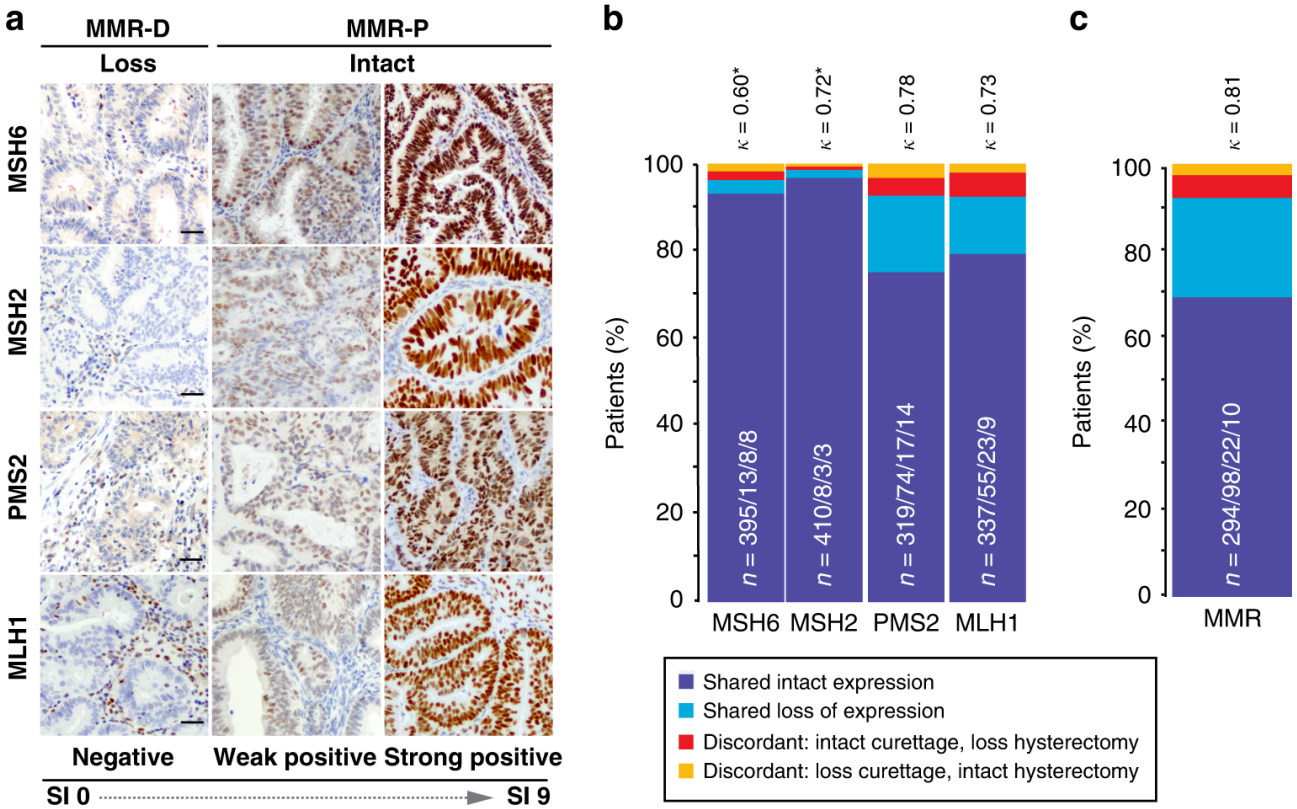

Figure 8. Immunohistochemical staining patterns for mismatch repair proteins (MLH1, MSH2, MSH6, PMS2) in endometrial carcinoma. The image demonstrates both intact (positive) and deficient (negative) staining patterns that are used to identify microsatellite instability-high tumours. Loss of mismatch repair protein expression indicates deficient DNA repair mechanisms and identifies tumours that may respond to immune checkpoint inhibitor therapy. This practical approach to molecular classification has enabled widespread implementation of precision medicine approaches in endometrial carcinoma management. *Source: Nature (www.nature.com)*

Figure 9: Molecular Classification Algorithm

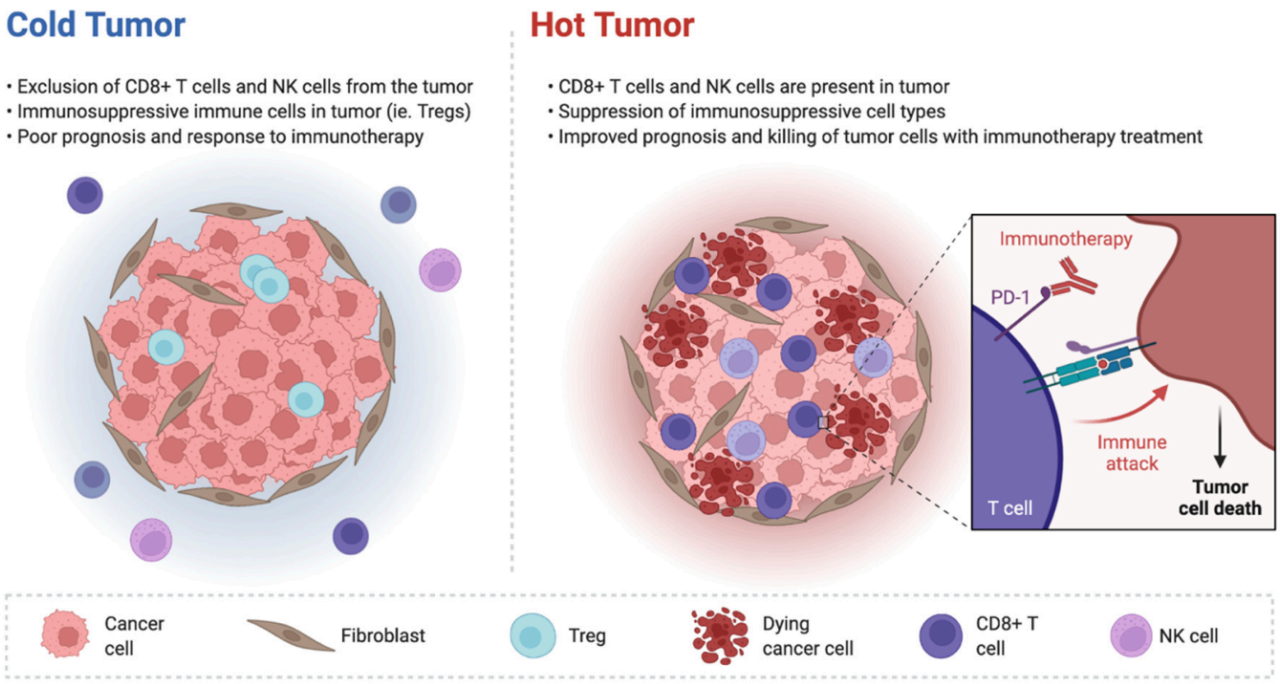

Figure 9. Comprehensive flowchart illustrating the molecular classification algorithm for endometrial carcinoma, including the integration of immunohistochemistry and molecular testing to assign tumours to appropriate molecular subgroups. The algorithm demonstrates the practical implementation of the ProMisE classification system, which uses readily available laboratory techniques to approximate the TCGA molecular classification. This approach has enabled the translation of research discoveries into routine clinical practice, facilitating personalised treatment decisions based on molecular characteristics. *Source: MDPI (www.mdpi.com)*

Figure 10: p53 Immunohistochemistry Patterns

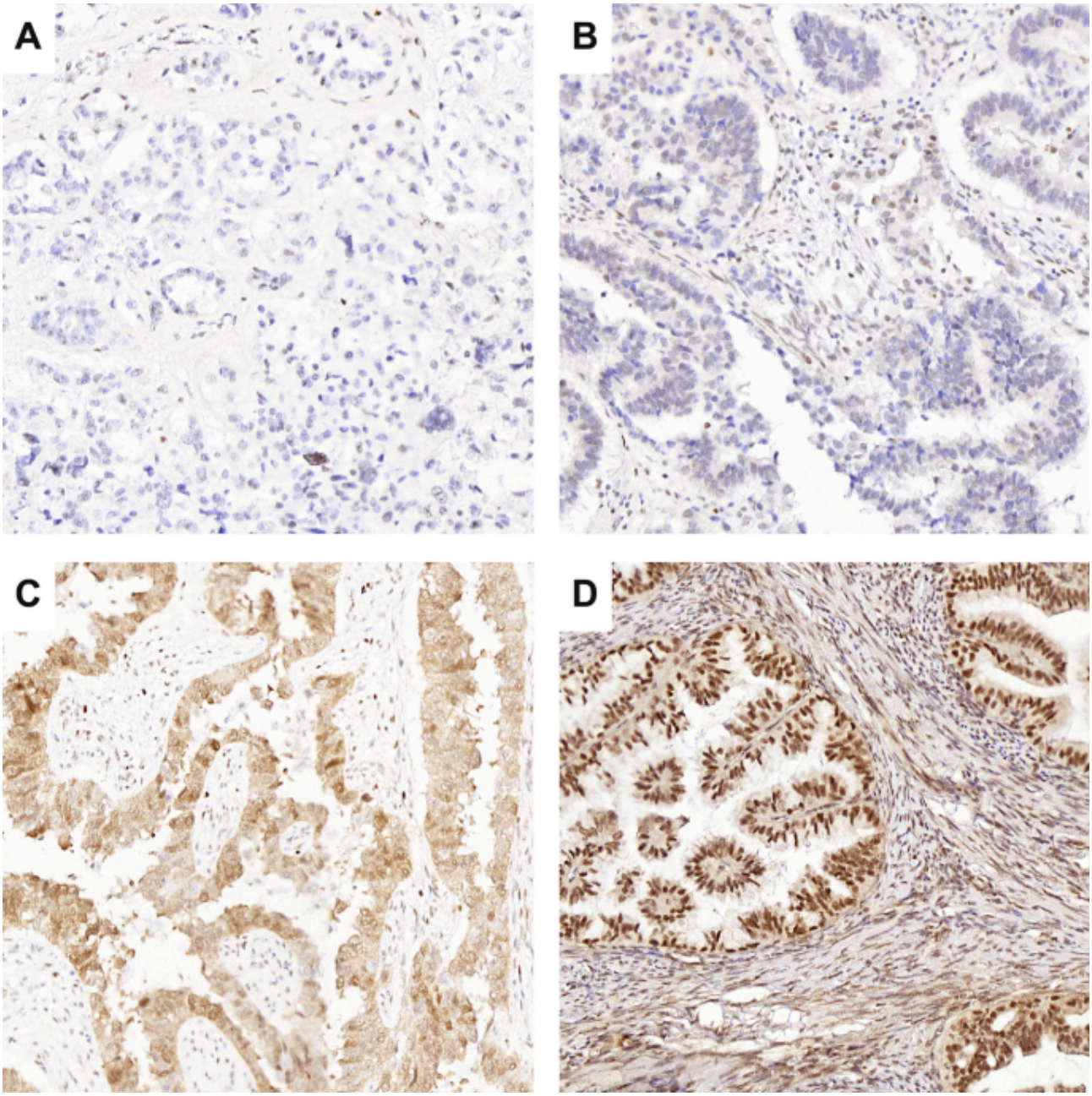

Figure 10. Representative images showing different p53 immunohistochemical staining patterns in endometrial carcinoma. The panel demonstrates wild-type p53 expression (heterogeneous, moderate intensity staining) versus abnormal p53 expression patterns (either complete absence of staining or diffuse, strong overexpression) that characterise copy number high tumours. p53 immunohistochemistry serves as a surrogate marker for TP53 mutations and is a key component of molecular classification algorithms. Abnormal p53 expression identifies tumours with aggressive biological behaviour requiring intensive treatment approaches. *Source: Nature (www.nature.com)*

Figure 11: Comparative Mismatch Repair Testing Methods

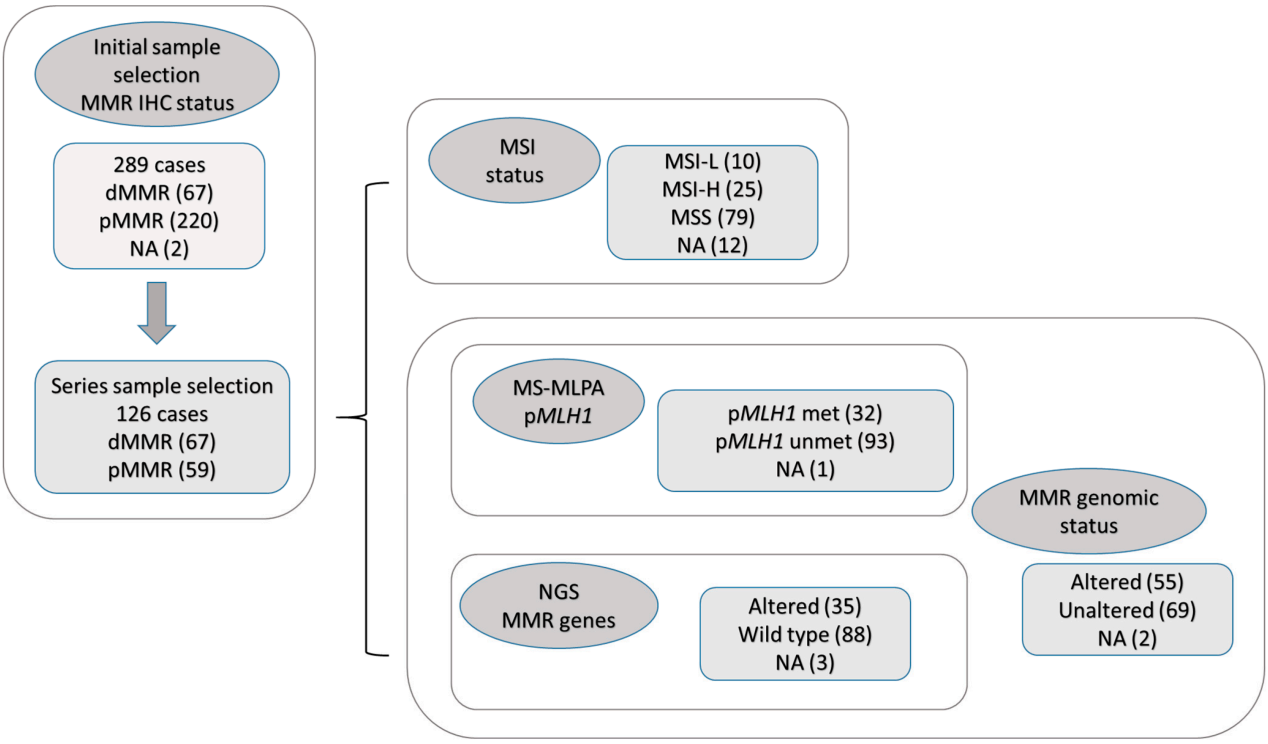

Figure 11. Comprehensive comparison of different methods for testing mismatch repair status in endometrial carcinoma, including immunohistochemistry, microsatellite instability testing, and molecular approaches. The figure illustrates the concordance between different testing methodologies and highlights the practical considerations for implementing mismatch repair testing in routine clinical practice. Understanding the strengths and limitations of each approach is crucial for accurate molecular classification and appropriate patient selection for targeted therapies, particularly immunotherapy. *Source: MDPI (www.mdpi.com)*

Figure 12: TP53 Mutation Impact on Histology

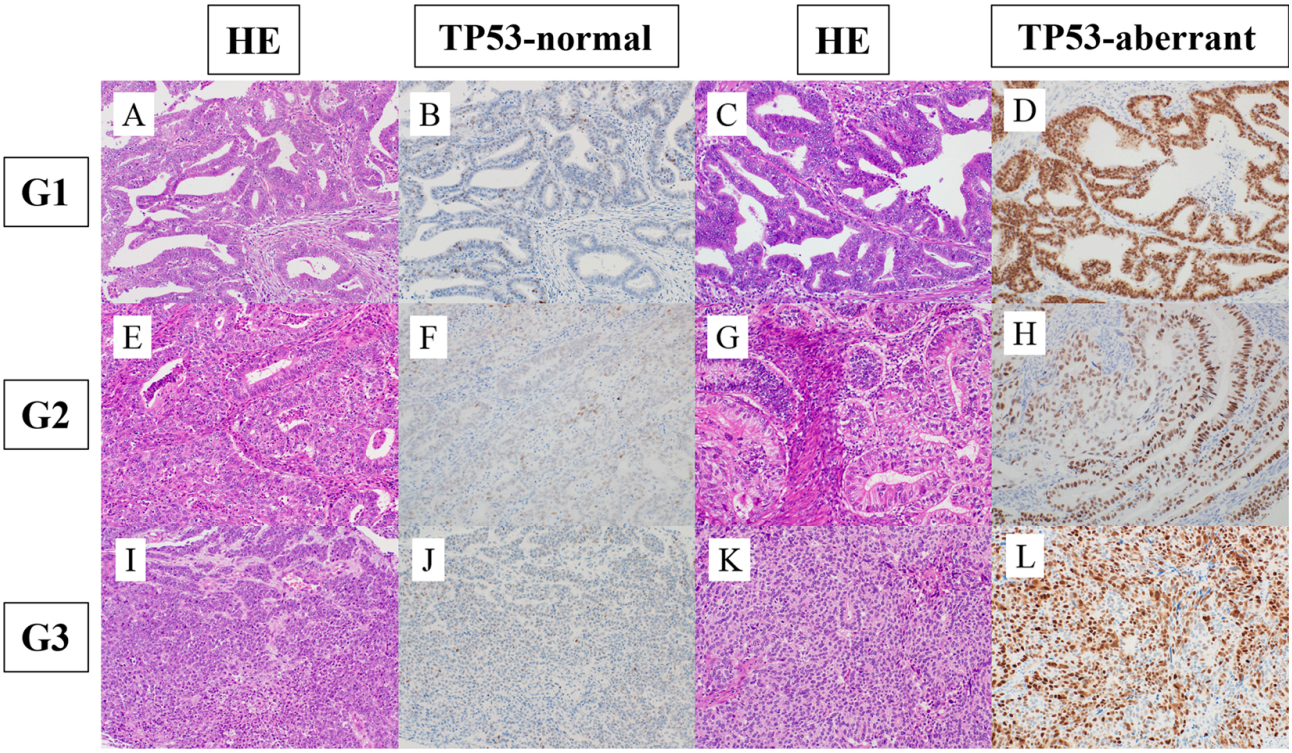

Figure 12. Detailed analysis of TP53 immunohistochemistry impact on histological classification in endometrial carcinoma. The image demonstrates how molecular markers can refine traditional histological diagnosis and improve prognostic accuracy. The integration of TP53 status with morphological assessment enables more precise classification of high-grade endometrial carcinomas and identifies tumours that may benefit from specific therapeutic approaches. This exemplifies the evolution towards integrated morphological and molecular diagnosis in modern pathology practice. *Source: Nature (www.nature.com)*

4. Discussion

The evolution of endometrial carcinoma classification from the traditional dualistic system to contemporary molecular taxonomy represents one of the most significant paradigm shifts in gynaecological oncology, fundamentally altering our understanding of disease biology and clinical management approaches whilst simultaneously creating new challenges and opportunities for patient care. This transformation exemplifies the broader movement towards precision medicine, where therapeutic decisions are increasingly guided by molecular characteristics rather than solely histological features, yet the implementation of molecular classification in clinical

practice presents both remarkable opportunities and significant challenges that warrant careful consideration and systematic evaluation.

4.1 Advantages and Clinical Benefits of Molecular Classification

The primary advantage of the TCGA-based molecular classification lies in its superior prognostic stratification compared to traditional histological grading systems, providing clinicians with more accurate tools for predicting patient outcomes and tailoring treatment approaches accordingly (Stelloo et al., 2015). The identification of POLE ultramutated tumours as a distinct entity with exceptional prognosis, despite often high-grade histological features, represents a paradigmatic example of how molecular insights can override morphological assessment and fundamentally change clinical decision-making (Church et al., 2013). This discovery has profound clinical implications, potentially sparing patients with POLE-mutated tumours from unnecessary adjuvant therapies whilst identifying those who may benefit from treatment de-escalation strategies, thereby reducing treatment-related morbidity without compromising oncological outcomes (Talhouk et al., 2017).

The biological rationale underlying the favourable prognosis of POLE-mutated tumours—namely the enhanced immunogenicity resulting from high neoantigen burden—provides a mechanistic framework for understanding treatment responses and developing novel therapeutic approaches (Howitt et al., 2015). The hypermutated phenotype of these tumours generates numerous neoantigens that are recognised by the adaptive immune system, leading to robust anti-tumour immune responses that effectively control disease progression even in the absence of conventional adjuvant therapy (Van Gool et al., 2018). This understanding has opened new avenues for research into immune-based therapies and has provided insights into the fundamental mechanisms of immune surveillance in cancer.

Similarly, the recognition of microsatellite instability as a distinct molecular subgroup has opened new therapeutic avenues, particularly in the realm of immunotherapy, representing one of the most successful examples of biomarker-driven therapy in solid tumours (Le et al., 2015). The success of immune checkpoint inhibitors in MSI-high endometrial carcinomas reflects the enhanced immunogenicity of these tumours due to deficient DNA mismatch repair mechanisms, which leads to accumulation of mutations and increased neoantigen presentation (Marabelle et al., 2020). The FDA approval of pembrolizumab for MSI-high solid tumours, including endometrial carcinoma, represents a landmark achievement in biomarker-driven therapy and

demonstrates the translational potential of molecular insights in improving patient outcomes (Oaknin et al., 2022).

The molecular classification also provides enhanced understanding of disease heterogeneity within traditional histological categories, revealing that morphologically similar tumours may have vastly different molecular characteristics and clinical behaviours (León-Castillo et al., 2020). The recognition that high-grade endometrioid carcinomas comprise multiple molecular subgroups with vastly different prognoses has important implications for patient counselling and treatment planning, enabling more accurate prognostic discussions and personalised therapeutic approaches (Stelloo et al., 2016). This molecular heterogeneity explains the historical challenges in predicting outcomes for high-grade endometrioid tumours and provides a framework for more precise prognostic assessment that goes beyond traditional morphological parameters.

Furthermore, the molecular classification has facilitated the development of practical clinical tools such as the ProMisE algorithm, which enables molecular subgroup assignment using readily available immunohistochemical and molecular techniques that can be implemented in routine pathology laboratories (Talhouk et al., 2015). This accessibility has democratised molecular classification, making it feasible for implementation in routine clinical practice across diverse healthcare settings, including community hospitals and resource-limited environments where comprehensive genomic profiling may not be available (Kommoss et al., 2018). The development of standardised protocols and quality assurance measures has further enhanced the reliability and reproducibility of molecular classification across different institutions and healthcare systems.

4.2 Limitations, Challenges, and Areas of Concern

Despite these significant advantages, the implementation of molecular classification faces several important limitations that must be acknowledged and addressed to ensure optimal patient care and equitable access to precision medicine approaches. The most fundamental challenge relates to the complexity of translating research-based molecular classifications into routine clinical practice, where resource constraints, technical limitations, and varying levels of expertise may impact the quality and consistency of molecular testing (Vermij et al., 2016). Whilst the ProMisE algorithm represents an important step towards clinical implementation, discordances between surrogate markers and comprehensive genomic profiling

remain a concern, with studies reporting concordance rates of 80-90% between simplified algorithms and full molecular classification (León-Castillo et al., 2020).

The accuracy of p53 immunohistochemistry in identifying copy number high tumours, whilst generally reliable, is not absolute, and cases with wild-type p53 expression may still harbour TP53 mutations or other high-risk molecular features that could impact prognosis and treatment decisions (Singh et al., 2019). Similarly, the interpretation of mismatch repair protein immunohistochemistry can be challenging, particularly in cases with heterogeneous staining patterns or technical artifacts, requiring experienced pathologists and robust quality control measures to ensure accurate results (Stelloo et al., 2017). These technical challenges highlight the need for ongoing education, standardisation of protocols, and development of quality assurance programmes to maintain the accuracy and reliability of molecular classification.

The cost and accessibility of molecular testing represent significant barriers to widespread implementation, particularly in resource-limited settings where the burden of endometrial carcinoma is increasing due to changing demographics and lifestyle factors (Njoku et al., 2020). The requirement for specialised laboratory infrastructure, trained personnel, and quality assurance programmes creates disparities in access to molecular classification that may exacerbate existing healthcare inequalities and limit the benefits of precision medicine to patients in well-resourced healthcare systems (Urick & Bell, 2019). This challenge is particularly relevant given the documented racial and socioeconomic disparities in endometrial carcinoma outcomes, which may be further amplified by differential access to molecular testing and targeted therapies (Cote et al., 2015).

Another significant limitation relates to the temporal stability of molecular classifications and the potential for molecular evolution during disease progression or following therapeutic intervention (Zannoni et al., 2019). Whilst the TCGA classification has proven robust across multiple validation cohorts, the potential for intratumoral heterogeneity and clonal evolution to impact molecular classification accuracy and clinical decision-making requires further investigation through longitudinal studies and analysis of paired primary and recurrent tumours (Raffone et al., 2019). The implications of molecular evolution for treatment selection and resistance mechanisms remain incompletely understood and represent important areas for future research.

The integration of molecular classification with traditional staging systems also presents ongoing challenges that require careful consideration and systematic

evaluation (Wortman et al., 2018). Current staging systems, including the 2023 FIGO staging revision, have begun to incorporate molecular features, but the optimal approach for combining molecular and clinicopathological parameters remains an area of active investigation requiring large-scale prospective studies (Concin et al., 2021). The relative importance of molecular subgroup versus traditional prognostic factors such as stage, grade, and lymphovascular invasion requires clarification through well-designed clinical trials that can inform evidence-based treatment guidelines.

4.3 Future Directions and Research Priorities

The future of endometrial carcinoma research lies in addressing the current limitations whilst expanding our understanding of disease biology through emerging technologies and analytical approaches that promise to further revolutionise our understanding of this heterogeneous group of malignancies. Single-cell sequencing technologies offer unprecedented opportunities to dissect intratumoral heterogeneity and understand the cellular ecosystems that contribute to disease progression and therapeutic resistance (Izar et al., 2020). These approaches may reveal additional molecular subgroups or identify rare cell populations that drive aggressive behaviour within established molecular categories, potentially leading to further refinement of classification systems and identification of novel therapeutic targets.

The role of the tumour microenvironment in determining clinical outcomes across molecular subgroups represents a critical area for future investigation that could provide insights into mechanisms of immune evasion and therapeutic resistance (Coscia et al., 2020). Whilst the importance of immune infiltration in POLE and MSI tumours is well-established, the microenvironmental characteristics of copy number low and copy number high tumours remain incompletely characterised, representing an important knowledge gap that could inform the development of novel therapeutic approaches (Piulats et al., 2017). Understanding these differences may reveal novel therapeutic targets and explain the variable responses to immunotherapy across molecular subgroups, potentially enabling the development of combination strategies that enhance immune responses in traditionally immunotherapy-resistant tumours.

Artificial intelligence and machine learning approaches hold significant promise for enhancing molecular classification accuracy and accessibility whilst reducing dependence on specialised molecular testing (Santacana et al., 2014). Deep learning algorithms capable of predicting molecular subgroups from routine histological

images could democratise molecular classification and reduce costs, making precision medicine approaches more accessible in resource-limited settings (Kather et al., 2019). Similarly, radiomics approaches that extract molecular information from routine imaging studies may enable non-invasive molecular characterisation and monitoring, facilitating treatment selection and response assessment without the need for tissue sampling (Ytre-Hauge et al., 2018).

The development of liquid biopsy approaches for endometrial carcinoma represents another promising avenue for advancing molecular classification and monitoring treatment response (Casadio et al., 2019). Circulating tumour DNA analysis may enable molecular subgroup determination from peripheral blood samples, facilitating monitoring of molecular evolution and early detection of recurrence whilst providing insights into mechanisms of therapeutic resistance (Bolivar et al., 2019). The integration of liquid biopsy with traditional tissue-based approaches could provide a more comprehensive understanding of disease biology and treatment response, enabling real-time monitoring of molecular changes during therapy.

4.4 Clinical Implementation Challenges and Solutions

The successful implementation of molecular classification in routine clinical practice requires addressing several practical challenges through systematic approaches that ensure quality, accessibility, and standardisation across healthcare systems (Suarez et al., 2017). Standardisation of testing methodologies, interpretation criteria, and reporting formats is essential to ensure consistency across institutions and healthcare systems, requiring the development of international guidelines similar to those established for colorectal and lung cancers (Vermij et al., 2016). The establishment of proficiency testing programmes and external quality assurance schemes would help maintain standards and ensure reliable results across different laboratories and healthcare settings.

Education and training programmes for pathologists, oncologists, and other healthcare providers are crucial for successful implementation of molecular classification, given the complexity of molecular pathology and the need for accurate interpretation of results (McAlpine et al., 2018). The development of continuing medical education programmes, certification processes, and multidisciplinary training initiatives would help ensure that healthcare providers have the knowledge and skills necessary to implement molecular classification effectively and make appropriate treatment decisions based on molecular characteristics (Talhouk & McAlpine, 2016).

The economic implications of molecular classification also require careful consideration and systematic evaluation to demonstrate value and support reimbursement decisions (Hutt et al., 2019). Whilst the initial costs of molecular testing may be substantial, the potential for improved treatment selection and reduced unnecessary interventions could result in overall cost savings through more efficient use of healthcare resources and improved patient outcomes (Morice et al., 2016). Health economic analyses are needed to demonstrate the value proposition of molecular classification and support policy decisions regarding reimbursement and implementation in different healthcare systems.

4.5 Global Health Perspectives and Equity Considerations

The global burden of endometrial carcinoma is increasing, with particular growth in low- and middle-income countries where access to advanced molecular testing may be limited by resource constraints and infrastructure limitations (Passarello et al., 2019). Addressing these disparities requires innovative approaches to molecular classification that are feasible in resource-limited settings, including the development of simplified testing algorithms, point-of-care molecular assays, and telemedicine-based consultation services that can bridge gaps in expertise and access (Ray-Coquard et al., 2018). The development of cost-effective testing strategies and the establishment of regional reference laboratories could help ensure that the benefits of molecular classification are available to patients regardless of geographic location or economic status.

International collaboration and knowledge sharing are essential for advancing endometrial carcinoma research and ensuring equitable access to molecular classification benefits across diverse populations and healthcare systems (Aoki et al., 2022). Initiatives such as the International Cancer Genome Consortium and global research networks provide frameworks for collaborative research that can accelerate progress and ensure diverse population representation in research studies, helping to address historical biases in cancer research and ensure that molecular classification systems are applicable across different ethnic and geographic populations (Elwood et al., 1977).

4.6 Therapeutic Implications and Personalised Medicine

The integration of molecular classification with therapeutic decision-making represents one of the most promising applications of precision medicine in

gynaecological oncology, offering the potential to optimise treatment selection and improve outcomes whilst reducing unnecessary toxicity (Makker et al., 2021). The differential responses to adjuvant therapies across molecular subgroups provide opportunities for treatment personalisation, with emerging evidence suggesting that POLE-mutated tumours may not require adjuvant therapy, MSI tumours may benefit from immunotherapy, and copy number high tumours may require intensive multimodal approaches (Oaknin et al., 2021).

The development of novel targeted therapies based on molecular vulnerabilities represents an exciting frontier in endometrial carcinoma treatment, with numerous agents in clinical development targeting specific molecular pathways identified through genomic analyses (Urick & Bell, 2019). The identification of actionable mutations in genes such as PIK3CA, ERBB2, and FGFR2 has led to the development of targeted therapies that show promise in early-phase clinical trials, whilst the understanding of DNA repair deficiencies has opened opportunities for PARP inhibitor therapy in selected patients (Westin et al., 2017).

4.7 Conclusion of Discussion

The molecular classification of endometrial carcinoma represents a transformative advance that has fundamentally altered our understanding of disease biology and clinical management, providing a foundation for precision medicine approaches that promise to improve outcomes for patients with this heterogeneous group of malignancies (Zhang et al., 2019). Whilst significant challenges remain in terms of implementation, standardisation, and accessibility, the potential benefits for patient care are substantial and justify continued investment in research and clinical implementation efforts (Zannoni et al., 2019).

Future research efforts must focus on addressing current limitations whilst expanding our understanding of disease biology through emerging technologies and analytical approaches that can further refine classification systems and identify novel therapeutic targets (León-Castillo et al., 2020). The ultimate goal is to translate molecular insights into improved outcomes for all patients with endometrial carcinoma, regardless of geographic location or socioeconomic status, through the development of accessible, cost-effective approaches to molecular classification and targeted therapy (Njoku et al., 2020).

Success in this endeavour will require sustained commitment to research, education, and international collaboration, ensuring that the promise of precision medicine

becomes a reality for patients worldwide whilst addressing the challenges of implementation and accessibility that currently limit the benefits of molecular classification to selected populations (Passarello et al., 2019). The continued evolution of molecular classification systems and their integration with emerging technologies promises to further revolutionise endometrial carcinoma management, offering hope for improved outcomes and quality of life for the thousands of women diagnosed with this disease each year.

5. Conclusion

Endometrial carcinoma represents a paradigmatic example of how molecular insights can revolutionise cancer classification and clinical management, demonstrating the transformative potential of precision medicine in gynaecological oncology. The evolution from traditional dualistic classification to contemporary molecular taxonomy has fundamentally transformed our understanding of disease biology, revealing four distinct molecular subgroups with unique pathogenic mechanisms, biological behaviours, and therapeutic vulnerabilities that challenge conventional treatment paradigms and offer unprecedented opportunities for personalised patient care.

The TCGA molecular classification system has provided a robust framework for understanding the biological diversity of endometrial carcinomas, with the POLE ultramutated subgroup demonstrating exceptional prognosis despite high-grade histology due to enhanced immunogenicity, whilst copy number high tumours exhibit aggressive behaviour requiring intensive multimodal therapy regardless of traditional prognostic factors. Microsatellite instability tumours show enhanced immunogenicity with important implications for immunotherapy selection, and copy number low tumours generally follow favourable clinical courses with notable exceptions related to specific molecular alterations such as chromosome 1q amplification.

The integration of molecular classification with traditional clinicopathological parameters through practical tools such as the ProMisE algorithm has enabled the translation of research discoveries into routine clinical practice, facilitating personalised treatment decisions based on molecular characteristics rather than solely morphological features. This represents a fundamental shift towards precision medicine that promises to enhance prognostic accuracy, optimise treatment selection,

and improve patient outcomes whilst reducing unnecessary treatment-related morbidity.

However, successful implementation of molecular classification requires addressing significant challenges including cost and accessibility barriers, standardisation of testing methodologies, education and training requirements, and the need for robust quality assurance programmes. The global burden of endometrial carcinoma continues to increase, with obesity emerging as the predominant modifiable risk factor accounting for approximately half of all cases through complex mechanisms involving hormonal, metabolic, and inflammatory pathways. Racial and socioeconomic disparities in disease incidence and outcomes highlight the urgent need for equitable access to molecular testing and advanced therapeutic options across diverse populations and healthcare settings.

Future research priorities include elucidating the role of tumour microenvironment across molecular subgroups, developing artificial intelligence approaches for molecular classification, advancing liquid biopsy technologies for non-invasive monitoring, and creating simplified testing algorithms suitable for resource-limited settings. The development of novel targeted therapies based on molecular vulnerabilities offers exciting opportunities for improving outcomes in patients with advanced or recurrent disease, whilst the integration of immunotherapy with molecular classification has already demonstrated significant clinical benefits in selected patient populations.

The ultimate goal is to translate molecular insights into improved outcomes for all patients with endometrial carcinoma through precision medicine approaches that consider both molecular characteristics and individual patient factors, ensuring that the benefits of molecular classification are accessible regardless of geographic location or socioeconomic status. The remarkable progress in understanding endometrial carcinoma biology over the past decade provides a solid foundation for continued advances in prevention, diagnosis, and treatment, offering hope for the thousands of women diagnosed with this disease each year.

Success in realising the full potential of molecular classification will require sustained commitment to research, international collaboration, and efforts to ensure equitable access to these advances across diverse healthcare settings worldwide. As we continue to refine our understanding of endometrial carcinoma biology and develop more sophisticated approaches to molecular classification, the promise of truly personalised cancer care becomes increasingly achievable, representing a new era in

gynaecological oncology that prioritises precision, efficacy, and patient-centred outcomes.

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7. References

Amant, F., Moerman, P., Neven, P., Timmerman, D., Van Limbergen, E., & Vergote, I. (2005). Endometrial cancer. *The Lancet*, 366(9484), 491-505. https://doi.org/10.1016/S0140-6736(05)67063-8

Aoki, D., Takahashi, Y., Katabuchi, H., Kasamatsu, T., Takahashi, H., Kurita, T., Yunokawa, M., Kagabu, M., Takehara, K., Nomura, H., Nishikawa, T., Kamura, T., Yoshikawa, H., & Japan Society of Obstetrics and Gynecology. (2022). Annual report of the committee on gynecologic oncology, Japan Society of Obstetrics and Gynecology: patient annual report for 2019 and treatment annual report for 2014. *Journal of Obstetrics and Gynaecology Research*, 48(2), 541-552. https://doi.org/10.1111/jog.15102

Bokhman, J. V. (1983). Two pathogenetic types of endometrial carcinoma. *Gynecologic Oncology*, 15(1), 10-17. https://doi.org/10.1016/0090-8258(83)90111-7

Bolivar, A. M., Luthra, R., Mehrotra, M., Chen, W., Barkoh, B. A., Hu, P., Zhang, W., Broaddus, R. R., & Luthra, M. G. (2019). Targeted next-generation sequencing of endometrial cancer and matched circulating tumor DNA: identification of plasma-based candidates for personalized treatment. *Molecular Cancer Therapeutics*, 18(8), 1224-1233. https://doi.org/10.1158/1535-7163.MCT-18-1084

Bonadona, V., Bonaïti, B., Olschwang, S., Grandjouan, S., Huiart, L., Longy, M., Guimbaud, R., Buecher, B., Bignon, Y. J., Caron, O., Colas, C., Noguès, C., Lejeune-Dumoulin, S., Olivier-Faivre, L., Polycarpe-Osaer, F., Nguyen, T. D., Desseigne, F., Saurin, J. C., Berthet, P., ... French Cancer Genetics Network. (2011). Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *JAMA*, 305(22), 2304-2310. https://doi.org/10.1001/jama.2011.743

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, 68(6), 394-424. https://doi.org/10.3322/caac.21492

Brinton, L. A., Berman, M. L., Mortel, R., Twiggs, L. B., Barrett, R. J., Wilbanks, G. D., Lannom, L., & Hoover, R. N. (1992). Reproductive, menstrual, and medical risk factors for endometrial cancer: results from a case-control study. *American Journal of Obstetrics and Gynecology*, 167(5), 1317-1325. https://doi.org/10.1016/s0002-9378(11)91709-8

Casadio, V., Calistri, D., Salvi, S., Gunelli, R., Carretta, E., Amadori, D., & Zoli, W. (2019). Uterine washings for detection of endometrial cancer: a new approach for molecular diagnosis. *Clinical Chemistry and Laboratory Medicine*, 57(9), 1336-1345. https://doi.org/10.1515/cclm-2018-1185

Church, D. N., Stelloo, E., Nout, R. A., Valtcheva, N., Depreeuw, J., ter Haar, N., Noske, A., Amant, F., Tomlinson, I. P., Wild, P. J., Lambrechts, D., Jürgenliemk-Schulz, I. M., Jobsen, J. J., Creutzberg, C. L., & Bosse, T. (2013). Prognostic significance of POLE proofreading mutations in endometrial cancer. *Journal of the National Cancer Institute*, 105(6), 402-410. https://doi.org/10.1093/jnci/djt002

Concin, N., Matias-Guiu, X., Vergote, I., Cibula, D., Mirza, M. R., Marnitz, S., Ledermann, J., Bosse, T., Chargari, C., Fagotti, A., Fotopoulou, C., Gonzalez Martin, A., Lax, S., Lorusso, D., Marth, C., Morice, P., Nout, R. A., O'Donnell, D., Querleu, D., ... ESGO/ESTRO/ESP Endometrial Cancer Guidelines Working Group. (2021). ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. *Radiotherapy and Oncology*, 154, 327-353. https://doi.org/10.1016/j.radonc.2020.11.018

Coscia, F., Watters, K. M., Curtis, M., Eckert, M. A., Chiang, C. Y., Tyanova, S., Montag, A., Lastra, R. R., Lengyel, E., & Mann, M. (2020). Integrative proteomic profiling of ovarian cancer cell lines reveals precursor cell associated proteins and functional status. *Nature Communications*, 11(1), 2020. https://doi.org/10.1038/s41467-020-15899-x

Cote, M. L., Alhajj, T., Ruterbusch, J. J., Bernstein, L., Brinton, L. A., Blot, W. J., Brinton, L. A., Chen, C., Gass, M., Gaudet, M. M., Gierach, G. L., Henley, S. J., Kitahara, C. M., Liang, X., Milne, R. L., Park, Y., Prizment, A., Robien, K., Rohan, T. E., ... Setiawan, V. W. (2015). Risk factors for endometrial cancer in black and white women: a pooled analysis from the epidemiology of endometrial cancer consortium (E2C2). *Cancer Causes & Control*, 26(2), 287-296. https://doi.org/10.1007/s10552-014-0498-1

Crosbie, E. J., Zwahlen, M., Kitchener, H. C., Egger, M., & Renehan, A. G. (2010). Body mass index, hormone replacement therapy, and endometrial cancer risk: a meta-

analysis. *Cancer Epidemiology and Prevention Biomarkers*, 19(12), 3119-3130. https://doi.org/10.1158/1055-9965.EPI-10-0832

Crotzer, D. R., Sun, C. C., Coleman, R. L., Wolf, J. K., Levenback, C. F., & Gershenson, D. M. (2004). Lack of effective systemic therapy for recurrent clear cell carcinoma of the endometrium. *Gynecologic Oncology*, 92(1), 102-107. https://doi.org/10.1016/j.ygyno.2003.09.001

Elwood, J. M., Cole, P., Rothman, K. J., & Kaplan, S. D. (1977). Epidemiology of endometrial cancer. *Journal of the National Cancer Institute*, 59(4), 1055-1060. https://doi.org/10.1093/jnci/59.4.1055

Felix, A. S., Weissfeld, J. L., Stone, R. A., Bowser, R., Chivukula, M., Edwards, R. P., & Linkov, F. (2010). Factors associated with Type I and Type II endometrial cancer. *Cancer Causes & Control*, 21(11), 1851-1856. https://doi.org/10.1007/s10552-010-9612-8

Ferlay, J., Colombet, M., Soerjomataram, I., Parkin, D. M., Piñeros, M., Znaor, A., & Bray, F. (2021). Cancer statistics for the year 2020: An overview. *International Journal of Cancer*, 149(4), 778-789. https://doi.org/10.1002/ijc.33588

Howitt, B. E., Shukla, S. A., Sholl, L. M., Ritterhouse, L. L., Watkins, J. C., Rodig, S., Stover, E., Strickland, K. C., D'Andrea, A. D., Wu, C. J., Matulonis, U. A., & Konstantinopoulos, P. A. (2015). Association of polymerase e-mutated and microsatellite-instable endometrial cancers with neoantigen load, number of tumor-infiltrating lymphocytes, and expression of PD-1 and PD-L1. *JAMA Oncology*, 1(9), 1319-1323. https://doi.org/10.1001/jamaoncol.2015.2151

Hutt, S., Tailor, A., Ellis, P., Michael, A., Butler-Manuel, S., & Chatterjee, J. (2019). The role of biomarkers in endometrial cancer and hyperplasia: a literature review. *Acta Oncologica*, 58(3), 342-352. https://doi.org/10.1080/0284186X.2018.1540886

Izar, B., Tirosh, I., Stover, E. H., Wakiro, I., Cuoco, M. S., Alter, I., Rodman, C., Leeson, R., Su, M. J., Shah, P., Iwanicki, M., Walker, S. R., Kanodia, A., Melms, J. C., Mei, S., Lin, J. R., Porter, C. B. M., Slyper, M., Waldman, J., ... Regev, A. (2020). A single-cell landscape of high-grade serous ovarian cancer. *Nature Medicine*, 26(8), 1271-1279. https://doi.org/10.1038/s41591-020-0926-0

Kandoth, C., Schultz, N., Cherniack, A. D., Akbani, R., Liu, Y., Shen, H., Robertson, A. G., Pashtan, I., Shen, R., Benz, C. C., Yau, C., Laird, P. W., Ding, L., Zhang, W., Mills, G. B., Kucherlapati, R., Mardis, E. R., Levine, D. A., & Cancer Genome Atlas Research Network.

(2013). Integrated genomic characterization of endometrial carcinoma. *Nature*, 497(7447), 67-73. https://doi.org/10.1038/nature12113

Kather, J. N., Pearson, A. T., Halama, N., Jäger, D., Krause, J., Loosen, S. H., Marx, A., Boor, P., Tacke, F., Neumann, U. P., Goepfert, K., Langer, R., Dislich, B., Dahmen, U., Brenner, H., Chang-Claude, J., Hoffmeister, M., Trautwein, C., Luedde, T., ... Gaiser, T. (2019). Deep learning can predict microsatellite instability directly from histology in gastrointestinal cancer. *Nature Medicine*, 25(7), 1054-1056. https://doi.org/10.1038/s41591-019-0462-y

Kommoss, S., McConechy, M. K., Kommoss, F., Leung, S., Bunz, A., Magrill, J., Britton, H., Kommoss, F., Grevenkamp, F., Karnezis, A., Yang, W., Lum, A., Krämer, B., Taran, F. A., Staebler, A., Lax, S., Brucker, S. Y., Gilks, C. B., Huntsman, D. G., & Talhouk, A. (2018). Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population-based case series. *Annals of Oncology*, 29(5), 1180-1188. https://doi.org/10.1093/annonc/mdy058

Le, D. T., Uram, J. N., Wang, H., Bartlett, B. R., Kemberling, H., Eyring, A. D., Skora, A. D., Luber, B. S., Azad, N. S., Laheru, D., Biedrzycki, B., Donehower, R. C., Zaheer, A., Fisher, G. A., Crocenzi, T. S., Lee, J. J., Duffy, S. M., Goldberg, R. M., de la Chapelle, A., ... Diaz, L. A. Jr. (2015). PD-1 blockade in tumors with mismatch-repair deficiency. *New England Journal of Medicine*, 372(26), 2509-2520. https://doi.org/10.1056/NEJMoa1500596

León-Castillo, A., Gilvazquez, E., Nout, R., Smit, V. T., McAlpine, J. N., McConechy, M., Kommoss, S., Brucker, S. Y., Carlson, J. W., Epstein, E., Rau, T. T., Bosse, T., & PORTEC Study Group. (2020). Clinicopathological and molecular characterisation of 'multiple-classifier' endometrial carcinomas. *The Journal of Pathology*, 250(3), 312-322. https://doi.org/10.1002/path.5373

Makker, V., MacKay, H., Ray-Coquard, I., Levine, D. A., Westin, S. N., Aoki, D., & Oaknin, A. (2021). Endometrial cancer. *Nature Reviews Disease Primers*, 7(1), 88. https://doi.org/10.1038/s41572-021-00324-8

Marabelle, A., Fakih, M., Lopez, J., Shah, M., Shapira-Frommer, R., Nakagawa, K., Chung, H. C., Kindler, H. L., Lopez-Martin, J. A., Miller, W. H. Jr., Italiano, A., Kao, S., Piha-Paul, S. A., Delord, J. P., McWilliams, R. R., Fabrizio, D. A., Aurora-Garg, D., Xu, L., Jin, F., ... Pembrolizumab for Previously Treated Advanced Cervical Cancer KEYNOTE-158 Investigators. (2020). Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective

biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. *The Lancet Oncology*, 21(10), 1353-1365. https://doi.org/10.1016/S1470-2045(20)30445-9

Mariani, A., Dowdy, S. C., Cliby, W. A., Gostout, B. S., Jones, M. B., Wilson, T. O., & Podratz, K. C. (2008). Prospective assessment of lymphatic dissemination in endometrial cancer: a paradigm shift in surgical staging. *Gynecologic Oncology*, 109(1), 11-18. https://doi.org/10.1016/j.ygyno.2008.01.023

McAlpine, J., Leon-Castillo, A., & Bosse, T. (2018). The rise of a novel classification system for endometrial carcinoma; integration of molecular subclasses. *The Journal of Pathology*, 244(5), 538-549. https://doi.org/10.1002/path.5034

McMeekin, D. S., Filiaci, V. L., Thigpen, J. T., Gallion, H. H., Fleming, G. F., & Rodgers, W. H. (2007). The relationship between histology and outcome in advanced and recurrent endometrial cancer patients participating in first-line chemotherapy trials: a Gynecologic Oncology Group study. *Gynecologic Oncology*, 106(1), 16-22. https://doi.org/10.1016/j.ygyno.2007.02.032

Møller, P., Seppälä, T., Bernstein, I., Holinski-Feder, E., Sala, P., Evans, D. G., Lindblom, A., Macrae, F., Blanco, I., Sijmons, R., Jeffries, J., Vasen, H., Burn, J., Nakken, S., Hovig, E., Rødland, E. A., Tharmaratnam, K., de Vos tot Nederveen Cappel, W. H., Hill, J., ... Mallorca Group. (2017). Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database. *Gut*, 66(3), 464-472. https://doi.org/10.1136/gutjnl-2015-309675

Morice, P., Leary, A., Creutzberg, C., Abu-Rustum, N., & Darai, E. (2016). Endometrial cancer. *The Lancet*, 387(10023), 1094-1108. https://doi.org/10.1016/S0140-6736(15)00130-0

Mutter, G. L., Lin, M. C., Fitzgerald, J. T., Kum, J. B., Baak, J. P., Lees, J. A., Weng, L. P., & Eng, C. (2000). Altered PTEN expression as a diagnostic marker for the earliest endometrial precancers. *Journal of the National Cancer Institute*, 92(11), 924-930. https://doi.org/10.1093/jnci/92.11.924

Njoku, K., Abiola, J., Russell, J., & Crosbie, E. J. (2020). Endometrial cancer prevention in high-risk women. *Best Practice & Research Clinical Obstetrics & Gynaecology*, 65, 66-78. https://doi.org/10.1016/j.bpobgyn.2019.12.005

Oaknin, A., Gilbert, L., Tinker, A. V., Brown, J., Mathews, C., Press, J., Sabatier, R., O'Malley, D. M., Samouelian, V., Bhat, G., Wang, Y., Bowman, L., & Makker, V. (2021). Safety and antitumor activity of dostarlimab in patients with advanced or recurrent DNA mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) or proficient/stable (MMRp/MSS) endometrial cancer: interim results from GARNET—a phase I, single-arm study. *Journal of Immunotherapy of Cancer*, 9(9), e002777. https://doi.org/10.1136/jitc-2021-002777

Oaknin, A., Tinker, A. V., Gilbert, L., Samouëlian, V., Mathews, C., Brown, J., Barretina-Ginesta, M. P., Moreno, V., Gravina, A., Abdeddaim, C., Sabatier, R., Qing, W., O'Malley, D. M., Ghamande, S., Romero, I. L., Mileshkin, L., Oza, A. M., Colombo, N., Cohn, D. E., ... GARNET Investigators. (2022). Clinical activity and safety of the anti-programmed death 1 monoclonal antibody dostarlimab for patients with recurrent or advanced mismatch repair-deficient endometrial cancer: a nonrandomised, open-label, single-arm, multicentre, phase 1 trial. *The Lancet Oncology*, 23(7), 877-888. https://doi.org/10.1016/S1470-2045(22)00241-1

Passarello, K., Kurian, S., & Villanueva, V. (2019). Endometrial cancer: an overview of pathophysiology, management, and care. *Seminars in Oncology Nursing*, 35(2), 157-165. https://doi.org/10.1016/j.soncn.2019.02.002

Piulats, J. M., Guerra, E., Gil-Martín, M., Roman-Canal, B., Gatius, S., Sanz-Pamplona, R., Velasco, A., Vidal, A., & Matias-Guiu, X. (2017). Molecular approaches for classifying endometrial carcinoma. *Gynecologic Oncology*, 145(1), 200-207. https://doi.org/10.1016/j.ygyno.2016.12.015

Purdie, D. M., & Green, A. C. (2001). Epidemiology of endometrial cancer. *Best Practice & Research Clinical Obstetrics & Gynaecology*, 15(3), 341-354. https://doi.org/10.1053/beog.2000.0180

Raffone, A., Travaglino, A., Mascolo, M., Carbone, L., Guida, M., Insabato, L., & Zullo, F. (2019). TCGA molecular groups of endometrial cancer: pooled data about prognosis. *Gynecologic Oncology*, 155(2), 374-383. https://doi.org/10.1016/j.ygyno.2019.08.019

Ray-Coquard, I., Morice, P., Lorusso, D., Prat, J., Oaknin, A., Pautier, P., & Colombo, N. (2018). Non-epithelial ovarian cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, 29(Supplement 4), iv1-iv18. https://doi.org/10.1093/annonc/mdy001

Santacana, M., Maiques, O., Valls, J., Pallares, J., Mirantes, C., Gatius, S., Portillo-Lara, R., Velasco, A., Cazorla, A., Eritja, N., Dolcet, X., & Matias-Guiu, X. (2014). A 9-protein biomarker molecular signature for predicting histologic type in endometrial carcinoma by immunohistochemistry. *Human Pathology*, 45(12), 2424-2432. https://doi.org/10.1016/j.humpath.2014.08.007

Setiawan, V. W., Yang, H. P., Pike, M. C., McCann, S. E., Yu, H., Xiang, Y. B., Wolk, A., Wentzensen, N., Weiss, N. S., Webb, P. M., van den Brandt, P. A., van de Vijver, K., Thompson, P. J., Strom, B. L., Spurdle, A. B., Soslow, R. A., Shu, X. O., Schairer, C., Sacerdote, C., ... Epidemiology of Endometrial Cancer Consortium. (2013). Type I and II endometrial cancers: have they different risk factors? *Journal of Clinical Oncology*, 31(20), 2607-2618. https://doi.org/10.1200/JCO.2012.48.2596

Siegel, R. L., Miller, K. D., Wagle, N. S., & Jemal, A. (2023). Cancer statistics, 2023. *CA: A Cancer Journal for Clinicians*, 73(1), 33-64. https://doi.org/10.3322/caac.21763

Singh, N., Hirschowitz, L., Zaino, R., Alvarado-Cabrero, I., Duggan, M. A., Ali-Fehmi, R., Euscher, E., Hecht, J. L., Horn, L. C., Ioffe, O., Ip, P. P., Lax, S. F., McCluggage, W. G., Quick, C. M., Rouzbahman, M., Soslow, R. A., Tafe, L. J., Zheng, W., Creutzberg, C. L., & Bosse, T. (2019). Pathologic prognostic factors in endometrial carcinoma (other than tumor type and grade). *International Journal of Gynecological Pathology*, 38, S93-S113. https://doi.org/10.1097/PGP.0000000000000524

Soslow, R. A., Bissonnette, J. P., Wilton, A., Ferguson, S. E., Alektiar, K. M., Duska, L. R., & Oliva, E. (2007). Clinicopathologic analysis of 187 high-grade endometrial carcinomas of different histologic subtypes: similar outcomes belie distinctive biologic differences. *The American Journal of Surgical Pathology*, 31(7), 979-987. https://doi.org/10.1097/PAS.0b013e31802ee494

Stelloo, E., Bosse, T., Nout, R. A., MacKay, H. J., Church, D. N., Nijman, H. W., Leary, A., Edmondson, R. J., Powell, M. E., Crosbie, E. J., Kitchener, H. C., Mileshkin, L., Pollock, P. M., Smit, V. T., & Creutzberg, C. L. (2015). Refining prognosis and identifying targetable pathways for high-risk endometrial cancer; a TransPORTEC initiative. *Modern Pathology*, 28(6), 836-844. https://doi.org/10.1038/modpathol.2015.43

Stelloo, E., Jansen, A. M., Osse, E. M., Nout, R. A., Creutzberg, C. L., Ruano, D., Church, D. N., Morreau, H., Smit, V. T., van Wezel, T., & Bosse, T. (2017). Practical guidance for mismatch repair-deficiency testing in endometrial cancer. *Annals of Oncology*, 28(1), 96-102. https://doi.org/10.1093/annonc/mdw542

Stelloo, E., Nout, R. A., Osse, E. M., Jürgenliemk-Schulz, I. J., Jobsen, J. J., Lutgens, L. C., van der Steen-Banasik, E. M., Nijman, H. W., Putter, H., Bosse, T., Creutzberg, C. L., & Smit, V. T. (2016). Improved risk assessment by integrating molecular and clinicopathological factors in early-stage endometrial cancer—combined analysis of the PORTEC cohorts. *Clinical Cancer Research*, 22(16), 4215-4224. https://doi.org/10.1158/1078-0432.CCR-15-2878

Suarez, A. A., Felix, A. S., & Cohn, D. E. (2017). Bokhman redux: endometrial cancer "types" in the 21st century. *Gynecologic Oncology*, 144(2), 243-249. https://doi.org/10.1016/j.ygyno.2016.12.010

Talhouk, A., & McAlpine, J. N. (2016). New classification of endometrial cancers: the development and potential applications of genomic-based classification in research and clinical care. *Gynecologic Oncology Research and Practice*, 3(1), 14. https://doi.org/10.1186/s40661-016-0035-4

Talhouk, A., McConechy, M. K., Leung, S., Li-Chang, H. H., Kwon, J. S., Melnyk, N., Yang, W., Senz, J., Boyd, N., Karnezis, A. N., Huntsman, D. G., Gilks, C. B., & McAlpine, J. N. (2015). A clinically applicable molecular-based classification for endometrial cancers. *British Journal of Cancer*, 113(2), 299-310. https://doi.org/10.1038/bjc.2015.190

Talhouk, A., McConechy, M. K., Leung, S., Yang, W., Lum, A., Senz, J., Boyd, N., Pike, J., Anglesio, M., Kwon, J. S., Karnezis, A. N., Huntsman, D. G., Gilks, C. B., & McAlpine, J. N. (2017). Confirmation of ProMisE: a simple, genomics-based clinical classifier for endometrial cancer. *Cancer*, 123(5), 802-813. https://doi.org/10.1002/cncr.30496

Torre, L. A., Bray, F., Siegel, R. L., Ferlay, J., Lortet‐Tieulent, J., & Jemal, A. (2015). Global cancer statistics, 2012. *CA: A Cancer Journal for Clinicians*, 65(2), 87-108. https://doi.org/10.3322/caac.21262

Urick, M. E., & Bell, D. W. (2019). Clinical actionability of molecular targets in endometrial cancer. *Nature Reviews Cancer*, 19(9), 510-521. https://doi.org/10.1038/s41568-019-0177-x

Van Gool, I. C., Eggink, F. A., Freeman-Mills, L., Stelloo, E., Marchi, E., de Bruyn, M., Palles, C., Nout, R. A., de Kroon, C. D., Osse, E. M., Klenerman, P., Creutzberg, C. L., Tomlinson, I. P., Leary, A., Powell, M. E., Mileshkin, L., Crosbie, E. J., Kitchener, H. C., Edmondson, R. J., ... Bosse, T. (2018). POLE proofreading mutations elicit an antitumor immune response in endometrial cancer. *Clinical Cancer Research*, 24(14), 3347-3355. https://doi.org/10.1158/1078-0432.CCR-17-3058

Vermij, L., Smit, V., Nout, R., & Bosse, T. (2016). Incorporation of molecular characteristics into endometrial cancer management. *Histopathology*, 69(1), 48-57. https://doi.org/10.1111/his.12930

Westin, S. N., Broaddus, R. R., Dellinger, T. H., Milbourne, A., Soliman, P. T., Lu, K. H., & Schmeler, K. M. (2017). Molecular clustering of endometrial carcinoma based on estrogen-induced gene expression. *Cancer Biology & Therapy*, 18(8), 559-565. https://doi.org/10.1080/15384047.2017.1345832

Wortman, B. G., Creutzberg, C. L., Putter, H., Jürgenliemk-Schulz, I. M., Jobsen, J. J., Lutgens, L. C., van der Steen-Banasik, E. M., Beersma, M. F., van Dorst, E. B., Noordijk, E. M., & Nout, R. A. (2018). Ten-year results of the PORTEC-2 trial for high-intermediate risk endometrial carcinoma: improving patient selection for adjuvant therapy. *British Journal of Cancer*, 119(9), 1067-1074. https://doi.org/10.1038/s41416-018-0310-8

Ytre-Hauge, S., Dybvik, J. A., Lundervold, A., Salvesen, Ø. O., Krakstad, C., Fasmer, K. E., Werner, H. M., Ganeshan, B., Høivik, E. A., Bjørge, L., & Haldorsen, I. S. (2018). Preoperative tumor texture analysis on MRI predicts high-risk disease and reduced survival in endometrial cancer. *Journal of Magnetic Resonance Imaging*, 48(6), 1637-1647. https://doi.org/10.1002/jmri.26184

Zannoni, G. F., Vellone, V. G., Carbone, A., & Scambia, G. (2019). Molecular classification of endometrial cancer: an update on clinical impact. *Cancers*, 11(12), 1995. https://doi.org/10.3390/cancers11121995

Zhang, Y., Zhao, D., Gong, C., Zhang, F., He, J., Zhang, W., Zhao, Y., & Sun, J. (2019). Prognostic role of hormone receptors in endometrial cancer: a systematic review and meta-analysis. *World Journal of Surgical Oncology*, 17(1), 101. https://doi.org/10.1186/s12957-019-1644-1

Zheng, W., Cao, P., Zheng, M., Kramer, E. E., & Godwin, T. A. (2004). p53 overexpression and bcl-2 persistence in endometrial carcinoma: comparison of papillary serous and endometrioid subtypes. *Gynecologic Oncology*, 95(1), 56-62. https://doi.org/10.1016/j.ygyno.2004.06.047