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Molecular Predictors for Fertility-Sparing Treatment in Endometrial Cancer and Atypical Hyperplasia

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Abstract

Introduction: Endometrial cancer (EC) is the most common gynecologic malignancy in developed nations. Incidence and mortality are rising each year. Standard treatment is hysterectomy, but 4% - 14% of cases occur in women under 45 who may desire fertility preservation. Fertility-sparing treatment (FST) with progestins is an option for selected patients with atypical endometrial hyperplasia (AEH) or early-stage, low-grade endometrioid EC. With this approach, however, treatment failure and recurrence risks remain high. The Cancer Genome Atlas (TCGA) and Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) frameworks divide EC into four subtypes: POLE-mutated (POLEmut), mismatch repair-deficient (MMRd), p53-abnormal (p53abn), and no specific molecular profile (NSMP). Each subtype has distinct prognostic and therapeutic impacts. Integration of molecular classification improves precision oncology in FST. Objective: This narrative review summarizes the current evidence on the role of molecular classification and additional biomarkers in FST outcomes for AEH and early-stage EC. It aims to guide patient selection and optimize conservative management strategies. Methods: A comprehensive literature search was conducted in PubMed, Cochrane Library, and Google Scholar. The search used MeSH terms and keywords for EC, FST, and molecular markers. Eligible studies included clinical trials, retrospective and prospective cohort studies, systematic reviews and meta-analyses, narrative reviews, clinical guidelines, and experimental or observational research. Eligibility was limited to studies published in English and we prioritized studies published from 2013 onward. Results: NSMP tumors are the most common FST candidates and have the best outcomes. Complete response (CR) rates are 72% - 92% with low recurrence rates (14% - 20%). MMRd tu-

mors show lower CR rates (33% - 71%) and higher recurrence rates (42% - 100%). The p53abn subtype has the poorest outcomes among all subgroups, with CR rates of 33% - 55% and recurrence rates of 33% - 100%. POLEmut outcomes are variable and despite their excellent post-surgical prognosis, the role of FST in this subtype remains unclear. Among additional biomarkers, progesterone receptor (PR) expression, particularly the PR-B isoform, is one of the strongest predictors of treatment response. PTEN, PIK3CA, and KRAS mutations may predict poor response. High Ki-67 expression links to higher recurrence rates and may be a useful marker during follow-up. CTNNB1, ARID1A, and L1CAM are emerging markers that may help refine NSMP risk. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are increasingly recognized as novel adjuncts to FST, supported by preclinical evidence of synergistic anti-tumor effects and early clinical data suggesting improved FST outcomes when combined with progestins. Conclusions: FST decision-making should integrate molecular classification to improve patient selection and treatment outcomes. NSMP tumors are the most suitable candidates for conservative management, while p53abn tumors should be excluded from FST approach. MMRd tumors require cautious selection and close surveillance. The role of FST for treatment of POLEmut tumors remains unclear. Additional biomarkers and emerging therapies such as GLP-1 RAs may refine FST strategies. Prospective trials are needed to validate these findings and establish and inform personalized treatment strategies.

Keywords

Endometrial Cancer, Fertility-Sparing Treatment, Molecular Classification, TCGA, ProMisE, POLE Mutation, Mismatch Repair Deficiency, p53, NSMP, Progestin Therapy, Biomarkers, GLP-1 Receptor Agonists

1. Introduction: Endometrial Cancer and Fertility Preservation Demand

Endometrial cancer (EC) is the most common gynecologic malignancy in developed nations. In limited resource countries, EC ranks second after cervical cancer [1]. Global EC incidence has risen about 1% each year since the mid-2000s. Projections show that it may be the fourth leading cause of cancer death among women by 2030, surpassing colorectal cancer [2] [3]. In 2025, endometrial cancer accounted for an estimated 69,120 new cases and 13,860 deaths in the United States, underscoring its significant public health burden [2]. In contrast to broader oncologic trends, EC is one of the few malignancies in which overall survival has worsened over the past 40 years. Notwithstanding advances in diagnosis and treatment, mortality rates rose by approximately 1.5% annually between 2013 and 2022, with non-endometrioid subtypes exhibiting a disproportionately higher increase of nearly 2.7% every year [4].

Although the median age at diagnosis is 60 years, women under 45 years ac-

count for 4% - 14% of EC cases [1] [3] [5]-[8]. This population presents a unique clinical challenge, as a significant proportion has not yet fulfilled their reproductive goals at the time of diagnosis.

Standard management of early-stage EC is total hysterectomy with bilateral salpingo-oophorectomy (TH/BSO), with or without lymphadenectomy. Five-year survival rates ranging from 74% to 91% reflect the generally favorable surgical outcomes associated with EC [2] [8]. The growing trend of delayed childbearing has increased the demand for fertility-sparing treatment (FST) in this population. Careful patient selection and appropriate therapy choice are essential to minimize the risk of disease progression and recurrence [8].

Advances in molecular profiling demonstrate how genetic alterations and molecular classification could be a useful tool for predicting response to FST. Clinical significance of these biomarkers, however, is not fully defined, and their clinical integration is still evolving [1] [5] [9]. We undertook a comprehensive narrative review that summarizes the current literature in EC and atypical endometrial hyperplasia (AEH) conservative management with a focus on FST.

2. Methodology

We searched PubMed, Cochrane Library and Google Scholar from January 2013 through January 2026. The strategy used Medical Subject Headings (MeSH) terms, keywords, and Boolean operators (AND, OR). Keywords included: "endometrial cancer", "fertility-sparing therapy", "fertility preservation", "conservative treatment", "molecular classification", "TCGA", "ProMisE", "POLE mutation", "mismatch repair deficiency", "MMRd", "microsatellite instability", "p53 abnormal", "NSMP", "hormonal therapy", "progestin therapy", "levonorgestrel intrauterine system", "Lynch syndrome", "Glucagon-Like Peptide 1", and specific molecular markers. We combined these terms with "endometrial cancer" or "fertility-sparing treatment" to find relevant and targeted publications.

Eligible articles addressed the role of molecular profiling in FST response, patient selection, or treatment development in early-stage EC. We included clinical trials, retrospective and prospective cohort studies, systematic reviews and meta-analyses, narrative reviews, clinical guidelines, and experimental or observational studies.

Only English-language publications were eligible, with studies published from 2013 onward prioritized to reflect the contemporary molecular landscape established by the landmark TCGA classification. Studies focusing on advanced-stage disease, non-endometrioid histologies without molecular data, or fertility preservation without hormonal factors were excluded. Studies were prioritized based on their applicability to the cohort of premenopausal women with early stage, non-invasive endometrial cancer.

The results follow a thematic narrative. This integration covers molecular subtypes, hormone sensitivity, biomarkers, and current guideline recommendations for FST. We focused on consensus, trends, and evidence gaps that warrant further

investigation.

3. Endometrial Cancer Classification

The diagnosis and management of EC have undergone significant changes over the past few decades, shifting from the dualistic clinicopathologic model proposed by Bokhman in 1983 towards molecular classification [10]. International guidelines from the World Health Organization (WHO), the European Society of Gynaecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO), the European Society of Pathology (ESP), the European Society for Medical Oncology (ESMO), the National Comprehensive Cancer Network (NCCN), and the International Federation of Gynecology and Obstetrics (FIGO) [2] [11]-[13] not only recognize but also include molecular classification data in their protocols.

The 1983 Bokhman model, which historically guided EC management, divided tumors into two categories, Type I and Type II (Table 1). Type I accounts for most cases, representing approximately 85% of ECs. These tumors are estrogen-dependent, associated with obesity and metabolic syndrome, and characterized by low-grade endometrioid histology. They typically demonstrate limited myometrial invasion, are diagnosed at an early stage, and carry a favorable prognosis. In contrast, Type II tumors are not estrogen-driven and comprise high-grade, aggressive histologies including serous, clear cell, undifferentiated carcinoma, and carcinosarcoma. These tumors often present at advanced stages, demonstrate poor response to progestin therapy, and carry a worse prognosis. Notably, grade 3 endometrioid carcinoma was placed in an intermediate prognostic category between Type I and Type II within this model [3] [11] [14]. This model was useful to clarify endometrial carcinogenesis. However, it failed to capture biological heterogeneity and outcomes across different subtypes. This limitation is clear for Grade 3 endometrioid carcinomas and mixed variants, which do not fit into either category [14].

Table 1. Traditional pathology classification. Adapted from [10].

	Type I	Type II
Etiology	Unopposed estrogen	Sporadic
Histology	Endometrioid (G1 and G2)	Non-endometrioid (serous, clear-cell, undifferentiated carcinosarcomas)
Grade	Usually low	Usually high
Stage	Often early	Often advanced
Hormone receptor expression	Positive	Negative

The Cancer Genome Atlas (TCGA) Research Network proposed a molecular classification for EC in 2013 based on integrated multi-platform genomic analyses. This study analyzed 373 EC tumors with a comprehensive genome-wide ap-

proach and identified four molecular subgroups: POLE ultramutated, microsatellite instability-hypermutated (MSI-H), copy-number low, and copy-number high tumors [15].

The TCGA classification established prognostic distinctions among its subgroups. Tumors harboring POLE exonuclease domain mutations demonstrate the most favorable progression-free survival, representing the best prognostic group, while copy-number high tumors, which frequently carry TP53 alterations, are associated with the worst outcomes. Additionally, the TCGA characterized mutation frequencies across key genes for each of the four subgroups [15]. Despite its scientific impact, widespread implementation in routine clinical practice has been limited by the high costs, technical complexity, and requirements for genomic sequencing. As a result, simplified molecular classification systems were developed to replicate TCGA subgroups using standard, readily available diagnostic techniques.

To address these limitations, Talhouk *et al.* proposed the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE), a pragmatic algorithm designed to approximate the TCGA molecular groups using immunohistochemistry (IHC) and targeted sequencing. ProMisE assigns classifies tumors into four molecular subgroups corresponding to TCGA classification (**Figure 1**): POLE-mutated (POLEmut), mismatch repair-deficient (MMRd), p53-abnormal (p53abn), and no specific molecular profile (NSMP) [16].

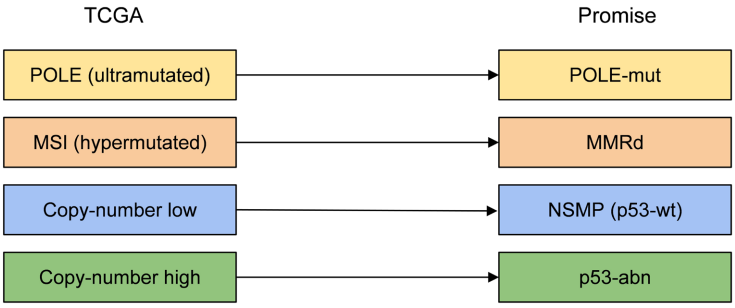

Figure 1. Correspondence between TCGA and Promise molecular groups.

The ProMisE algorithm (**Figure 2**) follows a sequential diagnostic approach. The first step involves immunohistochemistry (IHC) for four mismatch repair (MMR) proteins (MLH1, MSH2, MSH6, and PMS2), with loss of expression in any one protein classifying the tumor as MMR-deficient (MMRd). In tumors with preserved MMR protein expression, the second step requires targeted sequencing of the POLE exonuclease domain, focusing on hotspot regions in exons 9, 13, and 14, where pathogenic mutations define the POLE-mutated (POLEmut) subgroup. MMR-intact and POLE wild-type tumors then undergo p53 IHC as a surrogate marker for copy-number status. Aberrant p53 staining, defined as nuclear overexpression in over 80% of tumor cells or the complete absence of staining (null pattern). identifies the p53 abnormal (p53abn) subgroup, while normal p53 staining designates the no specific molecular profile (NSMP) or p53 wild-type (p53wt) group [15] [16].

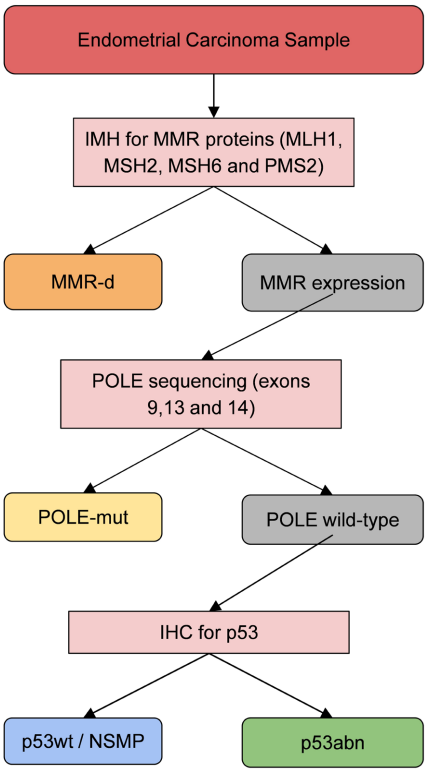

Figure 2. Promise molecular classification algorithm. Adapted from [16].

This hierarchical testing strategy is necessary because some tumors harbor alterations in multiple pathways simultaneously. By prioritizing the identification of MMR and POLE mutations before assessing p53 status, the algorithm ensures consistent and mutually exclusive classification. ProMisE demonstrates high concordance with TCGA classification while remaining more cost effective and feasible for routine pathology practice [15] [16].

The molecular subtypes described above carry distinct prognostic and therapeutic implications, and their integration into guidelines from NCCN, ESMO, ESGO/ESTRO/ESP, WHO, and FIGO has improved risk stratification and informed treatment decisions, including the selection of patients eligible for FST [2] [11]-[13] [17].

4. Indications for Fertility-Sparing Treatment

Clinical guidelines restrict FST to carefully selected patients, balancing oncologic safety with reproductive goals [18] [19]. Candidates for FST include women with AEH, also referred to as endometrial intraepithelial neoplasia (EIN) or early stage, low-grade endometrioid endometrial carcinoma (EEC) [2] [8].

Pre-treatment evaluation must exclude myometrial invasion or extrauterine disease through magnetic resonance imaging (MRI) or expert transvaginal ultrasound (TVUS), combined with histologic assessment via dilatation and curettage (D&C) or hysteroscopy. Patients should be counseled that FST is not the standard

of care for EC [2] [8] [19].

NCCN guidelines emphasize strict follow-up, including endometrial sampling every 3 - 6 months to assess treatment response. Patients achieving complete response (CR) may proceed with fertility attempts under close surveillance, while persistent disease, progression, or recurrence warrant definitive surgical management. These recommendations reinforce that FST is a temporary, closely monitored strategy reserved only for selected patients, with hysterectomy remaining the definitive treatment following childbearing or in cases of inadequate treatment response [2].

5. Risks and Management of FST

5.1. Treatment Modalities

FST relies primarily on progestin therapy, administered via oral or intrauterine routes. The most commonly prescribed oral agents are megestrol acetate (MA) and medroxyprogesterone acetate (MPA), while the NCCN guidelines designate the levonorgestrel-releasing intrauterine system (LNG IUS) as the preferred option. Combination therapy with LNG-IUS and oral progestins may also be considered in selected patients [2] [19].

Oral progestin dosing varies widely across FST protocols. MPA is typically 400 - 600 mg/day, with reported ranges from 80 - 1000 mg/day, while MA is used at 160 - 320 mg/day with ranges of 40 and 800 mg/day [19] [20].

LNG-IUS delivers approximately 20 mcg/day of levonorgestrel directly to the endometrium. A 2020 Cochrane review comparing LNG-IUS with oral progestins for endometrial hyperplasia found LNG-IUS to be associated with higher regression rates (RR 1.21, 95% CI 1.01 - 1.46), though the certainty of evidence was low [21]. The American College of Obstetricians and Gynecologists (ACOG) similarly notes that intrauterine progestins may achieve higher regression rates compared with oral therapy [22]. A 2025 Cochrane review further suggests that combining LNG-IUS with oral progestins improves complete response rates over oral therapy alone, though definitive evidence remains limited [23]. Compared with oral agents, LNG-IUS is associated with fewer systemic side effects, including weight gain, and depression, and it may improve patient adherence to treatment [21] [22].

Beyond progestin therapy, several adjunctive strategies have been investigated. Hysteroscopic resection followed by progestin therapy has demonstrated CR rates exceeding 90% with lower recurrence rates [24]. Metformin combined with progestins has been shown to improve response rates, with particular benefit in patients with insulin resistance or metabolic syndrome [23] [25]. Gonadotropin-releasing hormone agonists (GnRH-a) represent an additional option, particularly in obese patients, with some studies reporting longer progression free survival compared with oral progestins alone [26].

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as a promising adjunct to progestin-based FST. Originally developed for type 2 diabe-

tes, GLP-1 Ras have attracted growing interest in EC research given that GLP-1 receptors are expressed in both benign and malignant endometrial tissue. These agents activate cAMP-PKA and AMPK-mTOR pathways, exerting antiproliferative and proapoptotic effects [27]. Kanda *et al.* (2018) demonstrated that liraglutide inhibits tumor growth and induces autophagy via AMPK, with high GLP-1R expression correlating with positive ER/PR status and improved survival [28]. Hagemann *et al.* (2025) reported that semaglutide combined with levonorgestrel reduces tumor viability in organoid models, and semaglutide has also been shown to upregulate progesterone receptors, a mechanism that may help overcome progestin resistance [27] [29].

Clinical evidence for GLP-1RAs in EC is growing but remains mixed. Dai *et al.* (2025) reported an association between GLP-1RA use and reduced EC risk in obese adults [30]. In the FST setting, Hsieh *et al.* (2026) demonstrated that GLP-1RA combined with progestin significantly reduced hysterectomy rates compared with progestin alone at 18 months (10.2% vs. 23.4%; HR 0.41, 95% CI 0.29 - 0.58) [31] and Yen *et al.* (2026) similarly confirmed a reduced EC risk with this combination [32]. Conversely, a meta-analysis by Ko *et al.* (2025) found little effect on EC risk [33]. Prospective trials are warranted to define the role of GLP-1Ras in FST [27].

5.2. Treatment Outcomes

Reported CR rates vary by treatment modality and patient characteristics. Pooled analyses report CR rates of 76% - 85% for early stage EC [34]-[36], with even higher rates in AEH patients, where pooled CR rate of 85.6% has been reported [35]. Notably, CR probability continues to increase up to 24 months, suggesting that longer treatment duration may be appropriate in selected patients [37].

Median time to CR ranges from 6 to 12 months, though some patients require extended treatment [22] [37] [38]. Peng *et al.* (2024) demonstrated that time to CR varies significantly by molecular subtype, with POLEmut tumors achieving CR most rapidly (median 3.0 months) and MMRd tumors requiring the longest duration (median 7.9 months) [39].

5.3. Treatment Failure and Recurrence

Despite its potential benefits, FST carries inherent risks that must be addressed with patients. Although CR rates are high in selected candidates, response varies by histology, molecular subtype, and treatment approach [5] [38]. About 10% - 30% of patients fail to achieve CR with initial therapy [37] [38].

Recurrence after CR remains a major concern, with reported rates ranging from 20% to 40% [35] [38] [40]. Gallos *et al.* reported relapse rates between 26% and 41%, varying by initial diagnosis (AEH vs EC) [35]. Even among patients receiving progestin maintenance therapy, recurrence rates at 24 months can reach 31.3% [37].

Table 2 summarizes the risk factors for recurrence.

Table 2. Risk factors for recurrence.

Risk Factor	Hazard Ratio	Reference
Age > 35 years	HR 1.892; 95% CI 1.224 - 2.923	[41]
Nulliparity after achieving CR (Pregnancy after CR is protective)	HR 0.203; 95% CI 0.093 - 0.444	[41] [42]
Family history of cancer	HR 2.597; p = 0.039	[37]
Insulin resistance and metabolic syndrome		[25]
Mismatch repair deficiency (MMRd)		[2] [43]
Lack of maintenance therapy after CR		[26] [37] [42]
Initial treatment with megestrol acetate compared to other regimens	HR = 3.130; p = 0.021	[37]
Body mass index ≥25 kg/m²		[25] [40]

Disease progression during FST requires strict surveillance, with reported rates ranging from 1.9% to 16.6%. Higher progression rates are observed in patients with grade 2 tumors or superficial myometrial invasion [20] [40], and pre-treatment tumor size ≥ 2 cm has been independently associated with risk of disease progression (HR 5.456; 95% CI 1.34 - 22.14) [40].

5.4. Adverse Events

Although progestin-based FST is generally well tolerated, adverse events should be discussed when counseling patients. Weight gain is the most common grade 3-4 event associated with oral progestin therapy [21] [23], while LNG-IUS is associated with higher rates of irregular bleeding or spotting but lower rates of nausea and weight gain compared with oral progestins [21] [23]. Thromboembolic events are rare but are of particular concern in obese patients or those with additional thrombotic risk factors [22] [38]. Other common reported effects include mood changes, headache, and breast tenderness [21] [22].

5.5. Follow-Up Protocols

Given these risks, FST patients require intensive surveillance in accordance with current clinical guidelines. Endometrial evaluation should be performed every 3-6 months via hysteroscopy with directed biopsy, dilation and curettage (D&C), or office endometrial biopsy [2] [12] [22]. Magnetic resonance imaging (MRI) or transvaginal ultrasound (TVUS) is used to assess myometrial invasion and disease extent at baseline and during follow-up [38] [41]-[44]. If disease persists after 6 months, escalation to dual-progestin therapy or alternative regimens should be considered [2]. Failure to achieve CR within 9 - 12 months, or evidence of disease progression at any time, warrants definitive surgical management [2] [13].

Following CR, patients should be encouraged to pursue conception, with continued sampling every 3 - 6 months [2] [13] [22]. Referral to assisted reproductive technology (ART) centers is recommended to maximize pregnancy outcomes, as

live birth rates are higher with ART (39.4%) than with spontaneous conception (14.9%) [22]. For patients who do not wish to conceive, maintenance progestin-based therapy is associated with improved disease-free survival, with LNG-IUS representing the preferred option [2] [42].

After completing childbearing, TH/BSO and surgical staging is strongly recommended [2] [38] [45], as completion hysterectomy has been associated with improved oncologic outcomes, including one study reporting 0% recurrence with surgery vs. 22.4% without ($p = 0.055$) [45]. Ovarian preservation may be considered in carefully selected premenopausal patients with stage IA grade 1 endometrioid carcinoma, normal-appearing ovaries, no family history of ovarian cancer or Lynch syndrome, and absence of high-risk features such as p53 abnormality, MMRd, lymphovascular space invasion (LVSI), or positive cytology [2]. Patients who decline hysterectomy require lifelong surveillance with endometrial sampling every 6 - 12 months [2] [22].

6. Molecular Classification as a Predictive Tool for FST

The transition toward precision medicine in EC has been driven by molecular classification systems that improve patient selection for FST and predict hormonal therapy response. This framework, derived from The TCGA and later translated into clinical practice through ProMisE, is now considered a key tool for treatment optimization and risk stratification [13].

Among FST candidates, low-grade endometrioid tumors represent the primary study population. The most common molecular subtype in this population is NSMP, accounting for up to 64% of cases, followed by MMRd at 25%, POLEmut at approximately 6%, and p53abn at 5%. This distribution highlights that available FST data are largely driven by NSMP tumors, an important consideration for the interpretation of existing evidence [14].

Molecular subtypes exhibit distinct biological behavior and differential responses to hormonal therapy, influencing both patient selection and treatment outcomes in the fertility-sparing setting. **Figure 3** summarizes the distribution of patients undergoing FST and **Table 3** presents FST outcomes by molecular profile. It is important to separate predictive biomarkers for progestin response from biomarkers that are mainly prognostic for recurrence or survival. L1CAM, CTNNB1, and some KRAS evidence may be treatment-predictive, but much of the cited literature is prognostic rather than response-specific. Also of note, molecular classification for both response and relapse prediction focus on the experience of women with endometrial cancers and not preinvasive disease such as EIN.

6.1. POLE-Mutated EC

POLE-mutated tumors represent a small subset of early-stage EC, with reported prevalence ranging from 7% to 12% and a pooled prevalence of 5.8% [9] [39] [46]. Several studies include few or no POLEmut cases within FST cohorts, and these

tumors demonstrate paradoxical outcomes in the FST setting, contrasting sharply with their excellent prognosis following definitive surgical management [47] [48].

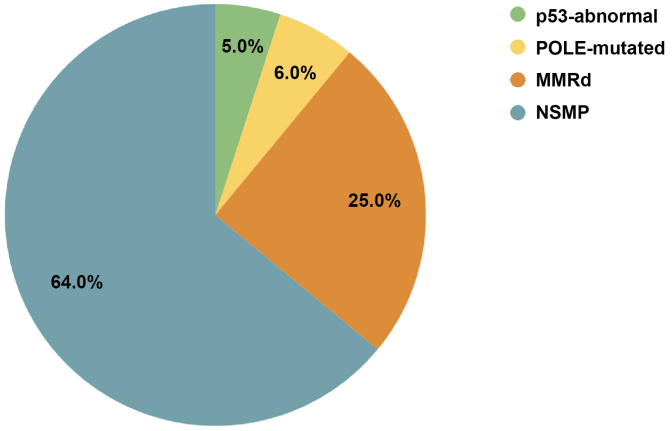

Figure 3. Distribution of TCGA molecular groups according to FST candidates (low-grade endometrioid tumors). Adapted from [14].

Table 3. Molecular subtypes and FST outcomes.

Subtype	Prevalence in FST (%)	CR Rate (%)	Recurrence Rate (%)	Time to CR (months)	Progression Rate (%)	FST Suitability	Key Molecular Features	References
NSMP (p53wt)	64 - 86.7	72 - 92 Highest	14 - 20 Lowest	3.7 - 10	Low	IDEAL - Most suitable	PTEN (69-80%), PIK3CA (33%), KRAS, CTNNB1 (up to 50%); ER/PR positive; low-grade endometrioid	[1] [5] [9] [39] [49] [50] [56] [57] [59] [60] [62] [63]
POLEmut	7 - 12	66.6 - 100 Variable	14.3 - 33	3.0	Up to 50% in some studies	Unclear - More data needed	Pathogenic EDM mutations; ultramutated; excellent post-surgical prognosis but paradoxical FST response	[5] [6] [9] [13] [39] [46]-[48] [50] [57]
MMRd/ MSI-H	9 - 25	33 - 71	42 - 100	7.9 Longest	37.5 - 44.4	Cautious - Only highly selected cases	MLH1, MSH2, MSH6, PMS2 loss; Lynch syndrome association; low ER/PR; high PD-L1; ARID1A loss	[1] [5] [9] [13] [39] [43] [50] [51] [53] [55] [57] [58] [63] [64]
p53abn	2 - 8	33 - 55	33 - 100	3.5	44.4	Not recommended	TP53 mutations; copy number high; aggressive biology; often high-grade/ serous features	[1] [5] [6] [9] [13] [18] [39] [50] [56]-[58]

The largest meta-analysis to date (Ferrari *et al*., 2025; n = 363) reported a CR rate of 66.6% and a recurrence rate of 14.3% among POLEmut tumors treated with FST [9]. Outcomes across Individual studies are highly variable; small cohorts report CR rates of 100% (n = 5), while others describe progression rates of up to 50% during treatment [46] [49]. Peng *et al.* (2024) similarly reported a 100% CR rate in POLEmut tumors, though this finding was based on only five patients; notably, this subgroup also demonstrated the shortest median time to CR at 3 months [12].

In the Ferrari meta-analysis, POLEmut tumors did not demonstrate superior treatment outcomes compared with other molecular subgroups. This paradox, excellent surgical prognosis alongside inconsistent hormonal response, suggests that these tumors may not be as hormone-sensitive as previously hypothesized. ESGO/ESHRE/ESGE guidelines acknowledge that the role of FST in POLEmut tumors remains uncertain, and that additional evidence is required before firm recommendations can be established [13].

6.2. Mismatch Repair-Deficient (MMRd) EC

MMRd tumors account for 9% - 25% of ECs in FST cohorts and are characterized by deficiencies in the DNA mismatch repair system. Emerging evidence suggests that MMRd status may be a potent predictor for progestin resistance with these tumors demonstrating lower CR rates at 33-71%, a longer median time to CR of 7.9 months, and high recurrence rates from 42% to 100% [1] [5] [9] [14] [39] [50] [51].

A 2024 meta-analysis by Zhang *et al*., evaluating MSI-H/MMRd tumors (66 patients from 10 studies), confirmed these findings reporting a CR rate of 61.8% and recurrence rate of 41.2%. Among 12 patients with Lynch syndrome, 75% achieved CR; however, 77.8% subsequently experienced disease recurrence [51]. Chung *et al.* (2020) were among the first to demonstrate the influence of MMR status on FST outcomes, reporting significantly lower CR rates at 6 months in MMRd tumors compared with p53 wild-type tumors (11.1% vs. 53.3%; $p = 0.010$); four of nine MMRd patients required immediate hysterectomy due to treatment failure, and three had upstaged disease at surgery [50]. The Ferrari meta-analysis (2025; $n = 363$ patients) further confirmed lower CR rates and higher recurrence rates in MMRd tumors compared with NSMP tumors ($p < 0.001$ and $p = 0.01$, respectively) [9].

The mechanisms underlying poor MMRd response to FST remain incompletely understood. MMRd tumors frequently exhibit low estrogen and progesterone receptor expression, which limits hormone therapy [50] [52] [53]. Some studies suggest that mismatch repair deficiency may interact with ARID1A loss, a tumor suppressor gene alteration that may contribute to progestin resistance [7] [52]. It was also hypothesized that the elevated mutational burden of these tumors may activate alternative oncogenic pathways that are less dependent on hormone receptor signaling [6] [53] [54].

Lynch syndrome patients warrant focused consideration, as germline mutations in MMR genes (MLH1, MSH2, MSH6, PMS2) confer distinct clinical behavior. Catena *et al.* (2022) highlighted prognostic differences between sporadic MMRd and Lynch syndrome-associated tumors, noting that while all Lynch syndrome patients in their cohort responded to FST, none achieved pregnancy and all experienced recurrence [43]. These findings support the potential benefit of universal MMR screening in EC patients and underscore the importance of genetic counseling and enhanced surveillance in this population [2].

In light of these findings, ESGO/ESTRO/ESP guidelines recommend caution when offering FST to MMRd patients, limiting its use to carefully selected cases with close monitoring given the elevated risk of disease progression [13].

MMRd tumors also exhibit the highest rates of PD-L1 positivity among EC molecular subtypes [55]. Although immune checkpoint inhibitors are not currently part of standard fertility-sparing management, they represent a promising therapeutic strategy for progestin-resistant MMRd cases [50]. The impact of these agents on fertility preservation and subsequent pregnancy outcomes remains an important area of research [54].

6.3. p53 Abnormal EC

The p53abn subtype is characterized by a high copy-number genomic profile and aggressive clinical behavior [56], with a prevalence of 2% - 8% in FST cohorts [5] [9] [14] [39] [57]. Abnormal p53 expression is associated with the worst oncologic outcomes among EC molecular subtypes, including high recurrence rates and increased progestin resistance [1] [58], with reported CR rates of 33%-55% and recurrence rates from 30% - 100% [1] [5] [9] [57].

Peng *et al.* (2024) reported a median time to CR of 3.5 months in patients with p53abn tumors, shorter than the 7.9 months observed in MMRd tumors, though small sample sizes limit the interpretation of this finding [39].

Clinical data in this subtype remains limited given its rarity in fertility-sparing cohorts. Due to the aggressive tumor biology and elevated risk of disease progression, FST is generally not recommended for p53abn tumors, a position reflected in ESGO/ESTRO/ESP, NCCN, and ESMO guidelines, which uniformly classify p53abn as the highest-risk molecular group [2] [6] [11] [13].

6.4. p53 Wild-Type (p53wt) or No Specific Molecular Profile (NSMP) EC

The p53 wild-type (p53wt), also referred to as the no specific molecular profile (NSMP) group, represents the majority of low-grade endometrioid carcinomas, accounting for 64-86.7% of FST cases. This subtype demonstrates the highest CR rates and lowest recurrence rates among all molecular subtypes with the Ferrari meta-analysis (2025) reporting a CR rate of 78.4% and a recurrence rate of 18.4% [9], consistent with other studies reporting CR rates of 72% to 92% and recurrence rates of 14% to 20% [1] [5] [39] [50] [57] [59].

Although response variation within this subgroup likely reflects its underlying biological heterogeneity [6], the consistently high CR and low recurrence rates support current FST protocols and establish p53wt/NSMP tumors as the most suitable candidates for fertility preservation [1] [9]. However, the conclusions on NSMP as the best FST group and p53abn should be viewed cautiously, as the current studies are small, and mainly retrospective cohorts.

Emerging data support extending FST consideration to selected patients with superficial myometrial invasion or grade 2 histology under strict surveillance. The

GORILLA-2001 study Lee *et al.* (2023) demonstrated feasibility in stage I grade 2 EC without myometrial invasion, and in grade 1 - 2 tumors with superficial myometrial invasion [40] and Centini *et al.* (2025) further discussed potential expansion of FST eligibility criteria to these categories [3].

NSMP tumors typically harbor mutations in PTEN, PIK3CA, KRAS, and CTNNB1 [49] [60] [61] and present as low-grade, endometrioid, hormone receptor-positive tumors well-suited to progestin-based FST [14] [62]. However, their biological heterogeneity has prompted ongoing research into refining biomarkers, including CTNNB1 mutations or L1CAM expression, to improve risk stratification and treatment outcomes [6] [44] [60].

7. Advanced Biomarkers and Treatment Predictors

Beyond established molecular classification, several additional biomolecular and genetic markers are under investigation to refine patient selection for FST [61]. Evidence for rare molecular subtypes remains limited, and existing studies report conflicting results (**Table 4**); however, emerging biomarkers hold promise for improving patient stratification and personalizing treatment strategies to optimize FST outcomes.

Table 4. Molecular and immunohistochemical biomarkers predicting FST outcomes.

Biomarker	Mechanism	Impact on FST	Evidence
PTEN mutation	PI3K/AKT pathway [79]	Associated with poorer response to progestin	Conflicting
PIK3CA mutation	PI3K signaling activation	Lower CR rates and longer time to CR	Emerging
KRAS mutation	MAPK pathway activation [61]	Associated with disease progression	Emerging
CTNNB1	Wnt signaling pathway [80]	Reduced disease-free survival	Emerging
ARID1A mutation	Chromatin remodeling	Reduced PR expression and progesterone sensitivity	Emerging
Progesterone receptor (PR)	Hormonal signaling	High PR associated with better response to progestin	Strong
Estrogen receptor (ER)	Hormonal signaling	Baseline ER not strongly predictive	Limited
Ki-67	Cellular proliferation marker	High levels associated with recurrence	Moderate
L1CAM expression	Cell adhesion molecule	Associated with aggressive behavior	Prognostic

Gene Mutation Markers

PTEN

PTEN is a tumor suppressor gene whose inactivation is a key driver of endometrioid EC, with somatic mutations occurring in 70 to 80% of these tumors [63]-[65]. Through its role in the PI3K/AKT signaling pathway, PTEN loss has been associated with progestin resistance [52].

The impact of PTEN mutations on FST outcomes remains unclear, with existing studies reporting mixed results. A 2018 meta-analysis by Travaglino *et al.* found that PTEN loss did not significantly affect therapy failure (RR = 1.24, 95% CI 0.88 - 1.76; $p = 0.21$) [66], while Xu *et al.* (2023) reported an association between PTEN

mutation and lower CR rates (HR 0.61, 95% CI 0.38 - 0.98; $p = 0.046$) [49]. Hirano *et al.* (2025) further reported longer times to CR in patients harboring these mutations [60].

PIK3CA

PIK3CA is among the most frequently mutated genes in EC, with TCGA data reporting a prevalence of 52% [67]. PIK3CA and PTEN mutations commonly co-occur, reflecting their shared involvement in the PI3K/AKT signaling pathway [68]. In the FST setting, PIK3CA mutations have been associated with prolonged time to CR and potentially lower CR rates [49] [60], though further studies are needed to confirm these findings.

KRAS

KRAS mutations occur in 16% - 20% of endometrioid EC and have been implicated in tumor initiation, progression, and invasion [61] [69] [70]. While KRAS mutations do not appear to significantly influence CR rates, recent studies have reported a meaningful association with increased risk of disease progression during FST [49] [61].

CTNNB1

CTNNB1 mutations occur in up to 50% of grade 1 - 2 ECs and are particularly prevalent in the NSMP molecular subgroup [6]. These mutations may cooperate with PTEN and KRAS alterations and have been associated with increased tumor proliferation and disease progression [61].

Ruz-Caracuel *et al.* (2021) demonstrated that CTNNB1 exon 3 mutations were independently associated with reduced disease-free survival in low-grade, early-stage tumors ($p = 0.010$), regardless of FIGO stage, tumor grade, MMR status, or LVSI [71]. Although the role of CTNNB1 mutations in FST has not yet been fully established, they represent a promising tool for refining risk stratification within the biologically heterogeneous NSMP subgroup [6].

ARID1A

ARID1A is a tumor suppressor gene mutated in approximately 40% of endometrioid EC cases, and its loss of function has been associated with MLH1 epigenetic silencing and microsatellite instability (MSI) [72] [73].

Recent studies have demonstrated a potential relationship between ARID1A alterations and reduced progesterone receptor (PR) expression. Asaka *et al.* (2023) reported significantly lower PR expression in ARID1A-deficient tumors compared with ARID1A-intact tumors ($p = 0.0002$) and Xing *et al.* (2023) further demonstrated that ARID1A knockout reduced both PR and MLH1 expression while increasing MSI in experimental models [74] [75]. Collectively, these findings suggest that ARID1A mutations may impair hormonal therapy sensitivity through down-regulation of progesterone receptor expression.

8. Immunohistochemical Markers

Estrogen receptor (ER) and progesterone receptor (PR)

ER and PR are the most studied immunohistochemical markers in FST. High

baseline PR expression is associated with favorable response to progestin therapy, while reduced PR expression during follow-up may signal disease recurrence [76].

Changes in PR isoform expression may also influence treatment outcomes. An increase in progesterone receptor B (PR-B) expression combined with a reduction in progesterone receptor A (PR-A) during follow-up has been associated with post-treatment relapse and PR-B is considered one of the most promising predictors of FST outcomes [7].

In contrast, baseline ER expression does not appear to correlate with treatment response, though reduced ER expression following CR may indicate an increased risk of recurrence [7].

Ki67

Ki-67 is a well-established marker of cell proliferation. While high baseline Ki-67 expression does not predict FST remission, elevated levels are frequently observed in patients who experience recurrence after CR [7]. Westin *et al.* (2021) demonstrated that a Ki-67 was associated with poorer FST outcomes [77], and MMRd tumors, which commonly exhibit high Ki-67 expression, may partly explain the elevated recurrence rates observed in this subtype [73].

L1CAM

L1 cell adhesion molecule (L1CAM) overexpression is common in the p53abn tumors but, when present in the NSMP subgroup, appears to confer a prognosis comparable to that of p53abn subtype [14]. A 2026 meta-analysis linked L1CAM expression to poor survival outcomes, particularly in MMRd and NSMP subtypes [78]. In L1CAM-positive NSMP tumors, PR expression may also be reduced, suggesting that L1CAM overexpression could attenuate hormonal therapy response, an observation with important implications for risk stratification within this subgroup [6]. Although direct evidence for L1CAM in the FST setting remains limited, these findings highlight the biological heterogeneity of the NSMP subgroup, which, despite being considered the most suitable FST candidate, can harbor aggressive variants [6].

9. Conclusions and Future Directions

The integration of molecular classification into the management of AEH and early-stage EC represents a major step toward precision medicine in fertility-preserving strategies, with the ProMisE/TCGA molecular framework providing a practical basis for refining patient selection and guiding FST decisions.

Among the molecular subtypes, NSMP ER positive tumors represent the best FST candidates, demonstrating the highest response rates and the lowest recurrence risk [9]. In contrast, the p53abn subtype is considered unsuitable for conservative management due to progestin resistance and poor oncologic outcomes [56] [58]. MMRd tumors require close surveillance given their slow treatment response and high recurrence rates [50] [51], while the role of POLEmut tumors in FST remains uncertain, with current guidelines emphasizing the need for further evidence before recommendations can be made [13].

Hormone receptor status is also an important predictor of treatment response. PR expression appears to be a stronger predictor than ER expression, and among receptor isoforms, PR-B represents one of the most promising predictive markers for FST response [7].

Beyond molecular classification, additional biomarkers may further predict treatment outcomes. PTEN, PIK3CA, and KRAS mutations have been associated with reduced progestin response and increased risk of disease progression [49] [60] [61], and elevated Ki-67 expression has been linked to higher recurrence rates, supporting its utility as a follow-up marker [7]. Additional biomarkers, including CTNNB1, ARID1A and L1CAM, may further refine risk stratification, though their specific roles in FST have yet to be established.

Future research should validate these biomarkers in large prospective cohorts. Ongoing studies are evaluating hormonal regimens including LNG-IUS, oral progestins, and metformin, and advances in next-generation sequencing and multigene panels may identify molecular signatures to guide personalized treatment [60]. Emerging therapies such as immune checkpoint inhibitors may offer new options for progestin-resistant MMRd tumors, though their impact on fertility and pregnancy outcomes remains to be determined [55] [64].

Despite meaningful advances in molecular classification, current evidence remains largely limited to retrospective studies with small sample sizes and heterogenous treatment protocols [6]. Well-designed prospective trials are therefore essential to clarify the role of molecular classification in FST and to establish personalized management strategies for women with early-stage EC who wish to preserve fertility [79]-[81].

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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