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Review Article

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Navigating the future of fertility preservation: advanced predictive strategies for treatment outcomes of endometrial atypical hyperplasia and carcinoma

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ABSTRACT

Due to the decreasing age of onset and the postponement of childbearing, there is a growing number of patients with endometrial carcinoma (EC) and endometrial atypical hyperplasia (EAH) seeking fertility-sparing treatments. Progestogen-based therapy serves as the principal conservative approach for EC. However, the variability in treatment outcomes hampers the potential for delivering more tailored therapies in clinical practice. To better guide the treatment of patients with fertility preservation needs, we conducted a comprehensive review of existing literature to explore factors related to molecular classification, biomarkers and artificial intelligence (AI) technology that may predict fertility-sparing treatment outcomes, we also looked ahead to future research directions in this field. The pathology before and after treatment is the primary basis for assessing the effectiveness of fertility-sparing treatment for EC and EAH. However, it is challenging to predict the therapeutic outcomes based on the pathological morphology of the initial diagnosis. Traditional immunohistochemical markers, such as estrogen and progesterone receptors, are also very limited in predicting therapeutic response. In recent years, the prognosis of fertility-sparing treatment has also been considered to be correlated with the molecular classification and gene mutation markers of EC. However, there are currently few direct clinical studies available, and our focus will be on reviewing these studies and assessing their applicability. In addition, there are some studies utilizing AI to predict the molecular classification, genes and therapeutic response of EC. The integration of these features will aid in the development of advanced predictive strategies for fertility-sparing treatment of EC and EAH.

Keywords: Endometrial Cancer; Atypical Endometrial Hyperplasia; Molecular Pathology; Fertility Preservations; Artificial Intelligence

INTRODUCTION

The incidence of endometrial carcinoma (EC) has been rising in recent years, particularly among premenopausal women, with up to 14% of cases being diagnosed in women who have not yet reached menopause [1]. Seventy percent of women under 40 years old with EC

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are nulliparous at the time of diagnosis [2]. Today's women are postponing childbearing, resulting in an unprecedented increase in the number of patients requiring conservative treatment [3]. As the precursor lesion of EC, endometrial atypical hyperplasia (EAH) has at least a 32.6% chance of progressing to EC [4], therefore, the standardized conservative treatment for young EAH patients is also of great significance. However, fertility-sparing treatment for patients with EC and EAH is characterized by a low complete response (CR) rate, a high disease recurrence rate, and even disease progression [5]. Accurately predicting which patients can benefit from fertility-sparing treatment is a crucial step for treatment success. In recent years, with the widespread application of genetic testing, studies have emerged demonstrating the impact of molecular classification and gene mutation markers on fertility-sparing treatment. Yet their predictive significance has not been fully summarized or widely recognized. Therefore, we will review and explore the molecular classification, genetic and immunohistochemical biomarkers as well as artificial intelligence (AI) technology related to fertility-sparing treatment, to better predict treatment outcomes at early diagnostic stage, aiming to provide an optimal individualized treatment strategy.

FERTILITY-SPARING TREATMENT OPTIONS AND PROGRESS

Hysterectomy is typically the primary mode of treatment for EC, whereas patients with early-stage disease who wish to preserve their fertility may consider receiving ongoing progestin-based treatment, as well as those with EAH. Fertility-sparing treatment encompass hysteroscopic resection surgery and hormone therapies such as megestrol acetate, medroxyprogesterone, or an intrauterine device containing levonorgestrel. Additional medications used in progesterone therapy include gonadotropin-releasing hormone agonists (GnRH-a), letrozole [6], aspirin [7], metformin [8-10] and statins [11,12]. Most studies suggested that the median time for EC/EAH to regress is between 4 to 6 months [13]. However, a longer course of treatment may be required if risk factors such as obesity and insulin resistance are present. Therefore, it is recommended that patients undergo treatment for 6 to 12 months, with endometrial biopsy conducted every 3 to 6 months during this period to monitor progress [14]. According to established standards [14,15], **Fig. 1** outlines the fertility-preserving management procedure for EC. The current guidelines primarily recommend fertility-sparing treatment for stage IA G1 endometrioid endometrial carcinoma (EEC). However, recent studies have shown that the CR rate of fertility-sparing treatment in G2 EEC is comparable to that of G1 EEC [16]. There have also been reports of successful pregnancies and births in patients with stage II EC after achieving CR [17]. Currently, there is an ongoing clinical trial exploring the possibility of extending fertility-sparing treatment indications to G2 EC and determining the optimal therapeutic regimen.

In 2 meta-analyses, patients with early-stage EC who received fertility-sparing treatment achieved a CR rate of 79.7%–84.6%, the total pregnancy rate and live birth rate were 26.7%–37.9% and 20.5%–39.3%, respectively [18,19]. Compared to EC, EAH is linked to a better prognosis [20]. It has been discovered that morphology, body mass index (BMI), and therapy duration are the key clinicopathological variables linked to CR [21,22]. In a review, 53.2% of patients with EAH/EC treated with progesterone achieved a long-term CR following a medium follow-up period of 39 months. However, 23.2% of those with EAH and 35.4% of EC relapsed after their initial response to treatment [23]. Factors such as EC G1, duration to CR of 6 months or longer, lack of maintenance therapy, and not being pregnant are associated with a substantially greater probability of recurrence [21].

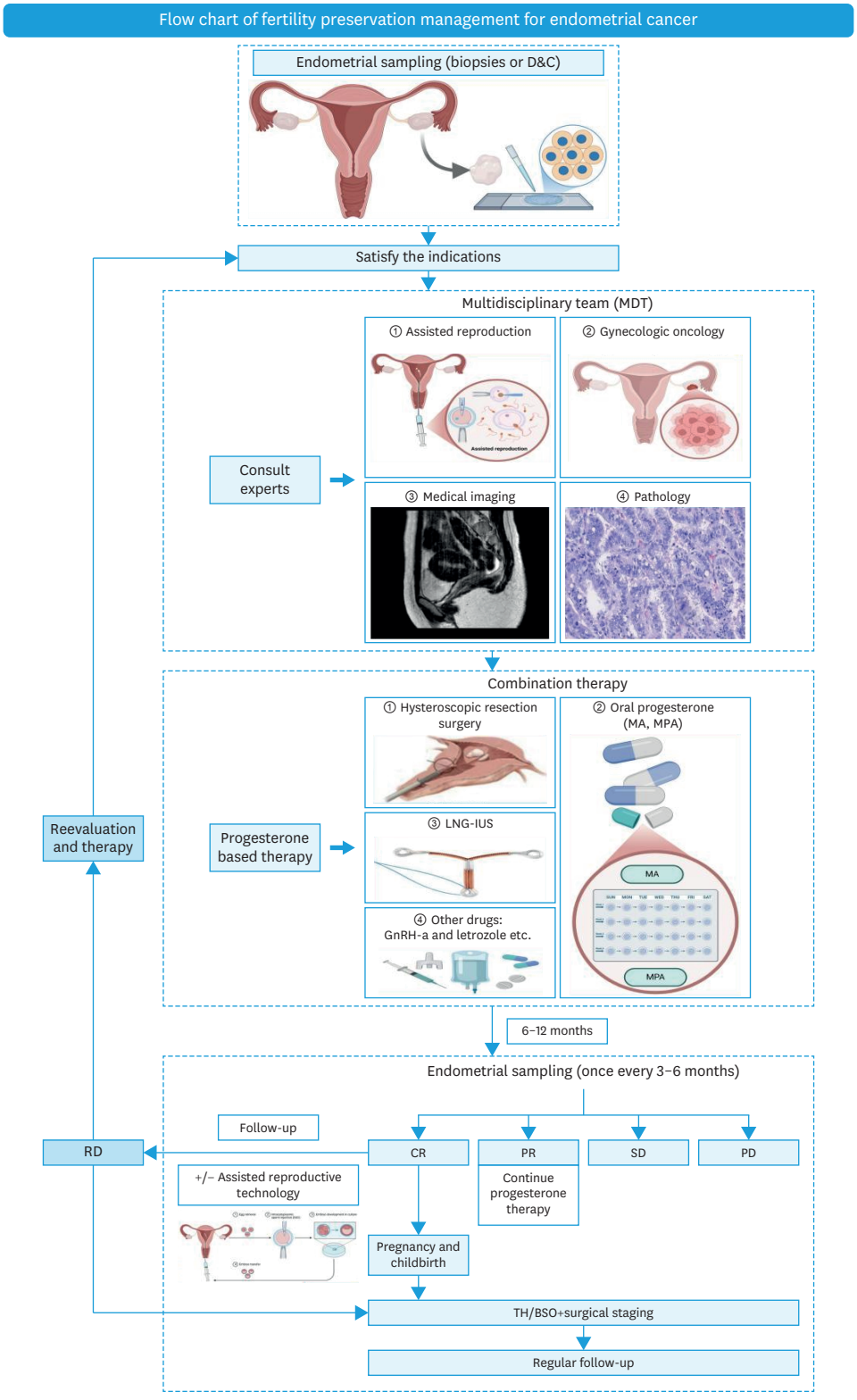

Fig. 1. Flow chart of fertility preservation management for endometrial cancer.
CR, complete response; D&C, dilation and curettage; GnRH-a, gonadotropin-releasing hormone agonists; LNG-IUS, levonorgestrel releasing intrauterine system; MA, megestrol acetate; MPA, methylprogesterone acetate; PD, progressive disease; PR, partial response; SD, stable disease; TH/BSO, total hysterectomy and bilateral salpingo-oophorectomy.

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Given these findings, it is recommended that women with reproductive needs try to conceive as soon as possible after achieving CR. Several factors can help with pregnancy, including the use of proper assisted reproductive technology [21,24], maintaining a normal BMI, achieving CR in a shorter duration, undergoing long-term treatment for up to 3 months, minimizing the number of hysteroscopy operations, and having a thicker endometrium [24].

MOLECULAR CLASSIFICATION TO PREDICT FERTILITY-SPARING TREATMENT OUTCOMES

Traditionally, EC is divided into 2 categories based on its dependence on estrogen. However, there is considerable molecular heterogeneity within this classification [25]. The Cancer Genome Atlas (TCGA) employed sequencing technology to categorize EC into 4 types based on molecular characteristics in 2013. Building on this, Talhouk et al. [26,27] created the Proactive Molecular Risk Classifier for EC (ProMisE) as an innovative molecular classifier to evaluate the prognostic risk of EC. In recent years, descriptions of molecular classification have been incorporated into EC guidelines and consensuses [28], and the 2023 Federation International of Gynecology and Obstetrics (FIGO) staging system has also been refined to accommodate molecular classification. Stage I–II EC patients with *POLE* ultramutated (*POLEmut*), confined to the uterine corpus or with cervical extension, regardless of the degree of lymphovascular space invasion (LVSI) or histological type, is now classified as Stage $IAm_{POLEmut}$, whereas a p53 abnormal (p53abn) EC confined to the uterine corpus with any myometrial invasion, with or without cervical invasion and regardless of the degree of LVSI, is classified as Stage $IICm_{p53abn}$ [29]. Although FIGO 2023 guidelines recommend molecular classification for all ECs, molecular testing of biopsy specimens for EC and EAH that are intended for fertility-sparing treatment has not yet been incorporated into the guidelines to date.

Generally speaking, the recurrence is rare in *POLEmut* patients and the prognosis is excellent. Patients with p53abn have the worst prognosis, while those with mismatch repair-deficient (MMRd) and non-specific molecular profile (NSMP) have moderate prognoses. The *POLEmut* group tends to be the youngest and have a lower BMI, typically presenting in stage I and high-grade ECs [30]. NSMP patients are mostly type I and G1–G2 ECs [31], which are, estrogen-dependent, and these patients often have metabolic syndromes such as obesity and diabetes, resulting in a higher BMI. MMRd and p53abn ECs are more likely to occur in high-risk ECs such as IB G3 EEC and all stages of non-endometrioid EC, and are associated with advanced stages (III–IV) [32,33] and the presence of LVSI [34].

In EC patients receiving conservative treatment, researches have demonstrated that hysteroscopic surgery can provide a sample for comprehensive molecular typing and genetic risk assessment [35,36], and these samples have shown good consistency with the final hysterectomy specimens [37]. Among women under 50 years old, NSMP tumors account for 64% of all ECs, with MMRd coming in second at 19%, and *POLEmut* tumors at 13%, and p53abn tumors having the lowest incidence of 4% [32]. Therefore, fertility-sparing treatment is primarily targeted at the NSMP group. Nowadays, several studies have explored the outcomes of EC/EAH patients with different molecular classifications after fertility-sparing treatment, and we have summarized the data from relevant articles in **Table 1** [25,26,28,35,36,38-46].

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Table 1. Outcomes of fertility-sparing treatment for 4 molecular classifications of endometrial atypical hyperplasia and endometrial carcinoma

Studies	No. of cases	Median age (yr)	Molecular classification method	No. of molecular types	Fertility-sparing treatment	Disease and fertility outcomes					Median follow-up time
						Characteristics	*POLEmut*/ *POLE* EDM/ *POLE*	MMRd/ MMR-D/ MSI-H	NSMP/p53wt/ CNL/*TP53*wt	p53abn/ CNH/ *TP53*abn	
[38]	EEC (39), EAH (20)	33.4 (19–44)	TCGA classification [25]	*POLE* (3), MSI-H (4), CNL (49), CNH (3)	Progesterone	Overall CR rate	3/3 (100.0)	1/4 (25.0)	35/49 (71.4)	1/3 (33.3)	16.8 (4–104) mo
[39]	EEC (57)	33 (19–45)	ProMisE [26]	*POLE* EDM (2), MMR-D (9), p53wt (45), p53abn (1)	Oral MA, oral MPA, LNG-IUS + MPA	CR rate at 6 mo	1/2 (50.0)	1/9 (11.1)	24/45 (53.3)	1/1 (100.0)	38.4 (2.9–163.5) mo
						Overall CR rate	1/2 (50.0)	4/9 (44.4)	37/45 (82.2)	1/1 (100.0)	
						Recurrence rate after CR	1/1 (100.0)	1/4 (25.0)	16/37 (43.2)	1/1 (100.0)	
						Hysterectomy	2/2 (100.0)	4/9 (44.4)	22/45 (48.9)	0/1 (0.0)	
[36]	EEC (22), EAH (36)	56.4 (24.3–91.1)	ProMisE [26]	*POLE* EDM (4), MMR-D (6), p53wt (44), p53abn (4)	LNG-IUS ± MA, MPA or leuprolide	Progression or received definitive treatment	1/4 (25.0)	2/6 (33.3)	6/44 (13.6)	2/4 (50.0)	28.8 (3.3–141.5) mo
[35]	EEC (15)	37 (25–40)	ProMisE [26]	*POLE* EDM (1), MMR-D (7), p53wt (7), p53abn (0)	Hysteroscopic resection surgery + LNG-IUS	CR rate at 6 mo	1/1 (100.0)	5/7 (71.4)	7/7 (100.0)	-	106 (24–134) mo
						Recurrence rate after CR	0/1 (0.0)	1/5 (20.0)	2/7 (28.6)	-	
						Hysterectomy	0/1 (0.0)	2/7 (28.6)	2/7 (28.6)	-	
[40]	EEC (12)	29.8 (23–37)	ProMisE [26]	*POLE* EDM (0), MMR-D (3), p53wt (8), p53abn (1)	MA, MPA, goserelin acetate, or LNG-IUD	Overall CR rate	-	2/3 (66.7)	6/8 (75.0)	1/1 (100.0)	46 (11–138) mo
						Recurrence rate after CR	-	0/2 (0.0)	1/6 (16.7)	0/1 (0.0)	
						Hysterectomy	-	1/3 (33.3)	4/8 (50.0)	0/1 (0.0)	
[41]	EEC (13), EAH (7)	35 (25–48)	Classification based on clinical sequencing and immunohisto-chemistry [42]	*POLE* (1), MSI-H (3), CN-L (16), CN-H (0)	LNG-IUS, oral MA, LNG-IUS + oral progesterone	Overall CR/PR rate	0/1 (0.0)	0/3 (0.0)	10/16 (63.0)	-	48 (12–123) mo
						Recurrence rate after CR	-	-	4/10 (40.0)	-	
						Hysterectomy	1/1 (100.0)	3/3 (100.0)	12/16 (75.0)	-	
						Fertility outcomes	14/20 (70.0): ovarian stimulation and oocyte retrieval 12/14 (85.7): successful oocyte retrieval 2/3 (66.7): live births after embryo transfers (1 vaginal delivery and 1 cesarean delivery)				
[43]	EEC (34), EAH (59)	Not mention	ProMisE [26]	*POLE* EDM (6), MMR-D (15), p53wt (67), p53abn (5)	LNG-IUS	Overall CR rate	6/6 (100.0)	11/15 (73.3)	57/67 (85.1)	2/5 (40.0)	Not mention
						Recurrence rate after CR	0/6 (0.0)	4/11 (36.4)	7/57 (12.3)	2/2 (100.0)	
						IVF-ET success	2/4 (50.0)	1/4 (25.0)	16/32 (50.0)	0/0 (0.0)	
						Natural conception success	1/2 (50.0)	0/3 (0.0)	7/18 (38.9)	0/0 (0.0)	
[44]	EEC (82), EAH (53)	32 (19–45)	WHO pathological classification 2020 [28]	*POLEmut* (1), MMRd (14), NSMP (117), p53abn (3)*	Oral MA, oral MPA, LNG-IUS, LNG-IUS + oral MA, GnRH-a + oral letrozole	CR rate at 16 wk	0/1 (0.0)	3/14 (21.4)	30/108 (27.8)	0/1 (0.0)	Not mention
						CR rate at 32 wk	0/1 (0.0)	8/14 (57.1)	64/106 (60.4)	0/1 (0.0)	
						CR rate at 48 wk	0/1 (0.0)	11/13 (84.6)	88/102 (86.3)	0/1 (0.0)	
[45]	EEC (90)†	31 (22–42)	NGS classification panel [46]	*POLEmut* (6), MSI-H (5), *TP53*wt (78), *TP53*abn (1)	Oral MA, oral MPA, LNG-IUS, LNG-IUS + oral MA, GnRH-a + oral letrozole	CR rate at 16 wk	0/6 (0.0)	0/5 (0.0)	25/78 (32.1)	0/1 (0.0)	59.8 (19.1–104.0) wk
						CR rate at 32 wk	4/6 (66.7)	3/5 (60.0)	49/78 (62.8)	0/1 (0.0)	
						Overall CR rate	5/6 (83.3)	5/5 (100.0)	75/78 (96.2)	0/1 (0.0)	
						Recurrence rate after CR	0/5 (0.0)	3/5 (60.0)	9/75 (12.0)	-	

CNH, copy number-high; CNL, copy number-low; CR, complete response; EAH, endometrial atypical hyperplasia; EC, endometrial carcinoma; EEC, endometrioid endometrial cancer; GnRH-a, gonadotropin-releasing hormone analogues; IVF-ET: in vitro fertilization-embryo transfer; LNG-IUS, levonorgestrel releasing intrauterine system; MA, megestrol acetate; MMRd (MMR-D), mismatch repair deficient; MPA, medroxyprogesterone acetate; MSI-H, microsatellite instability-high; NSMP, non-specific molecular profile; p53wt, p53 wild type; p53abn, p53 abnormal; PR, partial response; ProMisE, Proactive Molecular Risk Classifier for Endometrial Carcinoma; *POLE* EDM, polymerase-ε exonuclease domain mutation; *POLEmut*, *POLE* ultramutated; *TP53*abn, null/missense p53 mutation; *TP53*wt, wild-type p53; TCGA, The Cancer Genome Atlas; WHO, World Health Organization.

*Two of these 3 patients were lost to follow-up, and one patient progress disease at 19.43 weeks.

†These patients include those who were initially diagnosed with EC and those who progressed to EC during the course of treatment.

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1. Outcome of *POLEmut* patients

Generally speaking, patients with *POLEmut* have a favorable prognosis and a low recurrence rate, which may be related to the immunogenicity caused by the high mutation load, allowing for conservative treatment approaches [47]. In most studies, the *POLEmut* group exhibited the favorable outcomes of fertility-sparing treatment and all of them could achieve CR regardless of histological type and therapeutic regimen [35,38,43]. *POLE* mutations are uncommon because most individuals receiving fertility-sparing treatment are G1 EEC [48]; in fact, several studies reported only 1–2 *POLEmut* instances or none at all [39-41,44]. In these individual cases, some *POLEmut* patients experienced failure of fertility-sparing treatment. In Chung et al.'s study [39], among 2 patients with *POLEmut*, one experienced relapsed after 66 months of CR, and the other had disease progression during drug treatment. Both patients ultimately underwent hysterectomy. In general, the *POLEmut* group responds well to conservative treatment, and the majority of them achieve CR after fertility-sparing treatment. Some research, however, indicated a poor prognosis and showed that this group might not be sensitive to progestogen-based therapy; the application of GnRH-a and letrozole as the initial therapy yielded greater benefits than progesterone [45]. More clinical evidence is required to determine the best therapeutic regimen for *POLEmut* patients.

2. Outcome of MMRd patients

Because MMRd type patients exhibit low expression of estrogen receptor (ER) and progesterone receptor (PR), the progesterone efficacy in these patients may be poor [49]. Studies have found that MMRd patients show a poor overall response, and their CR/PR rate is significantly lower than that of patients with NSMP [39,41]. In addition, MMR deficiency appeared to specifically predict EC/EAH recurrence [50]. A systematic review by Zhang et al. [51] also showed that EC/EAH patients with the MMRd subtype have a low remission rate and high recurrence rate after fertility-sparing treatment. It was found that MMRd patients had the highest positive rate of PD-L1 expression [43]. Although immune checkpoint inhibitor, such as PD-1 inhibitors, are not currently used in the women's fertility-sparing management, they represent a promising therapeutic strategy [52]. In addition, there have been cases of pregnancy after immunotherapy [53].

Some patients with MMR deficiency have germline mutations in the *MMR* gene, which is referred to as Lynch syndrome (LS), 25%–60% women with LS will develop EC during their lifetimes [54]. Studies have shown that women with LS can also achieve CR after fertility-sparing treatment [55], and some have even successfully conceived and delivered [56]. However, such patients often relapse after CR and eventually undergo hysterectomy [57]. Although most LS patients can achieve CR after initial fertility-sparing treatment, they are highly likely to experience relapse, and the outcomes of treatment after relapse are not favorable and may even progress rapidly [58]. Therefore, the LS population requires vigilant monitoring for recurrence and progression during fertility-sparing treatment, and surgical intervention can be considered once recurrence occurs.

3. Outcome of NSMP patients

The positive rates of ER and PR are 92% and 83.9% in this subtype, respectively [59]. Therefore, hormone therapy is most likely to be beneficial for NSMP ECs. However, the CR rate in NSMP patients after progesterone treatment varies from 63% to 96.2% across different studies [38,39,41,43,46]. Overall, NSMP responds well to fertility-sparing treatment, but the fluctuation in CR rates may be attributed to heterogeneity within the NSMP group. It is imperative to conduct detailed and stratified management for NSMP patients who wish to preserve fertility.

4. Outcome of p53abn patients

According to the TCGA study, copy-number high group, in which *TP53* mutations are frequent observed is generally more biologically aggressive and associated with a poor prognosis, often progressing or relapsing in a shorter period of time [60]. This group exhibits the lowest positive rate of ER and PR, at 67.4% and 44.7%, respectively [59]. Consequently, these patients have the lowest CR rate after fertility-sparing treatment [43], and the proportion of recurrence as well as the eventual need for surgical resection is high [36]. Although there is limited clinical data about fertility-sparing treatment for p53abn EC/EAH, the prognosis and molecular characteristics of this subtype do not favor conservative treatment.

GENE MUTATION MARKERS TO PREDICT FERTILITY-SPARING TREATMENT OUTCOMES

To better explore the prognosis of the disease, researchers have been striving to further refine and stratify the existing molecular classification of EC [61]. Genetic mutations are often observed among molecular classifications of EC. *POLEmut* group is associated with mutations in *POLE*, *PTEN*, *FBXW7*, *PIK3R1*, *PIK3CA*, *TP53*, *KRAS*, *DMD*, *CSMDI* and *FAT4* [34,62]. The MMRd group is linked to mutations in the *MMR* gene (*MLH1*, *MSH6*, *MSH2* or *PMS2), PTEN*, *KRAS*, *PIK3R1*, *PIK3CA*, *RPL22* and *ARID1A*. Regarding the NSMP group, it is relevant to alterations in *CTNNB1*, *PIK3R1*, *PIK3CA*, *ARID1A* and *PTEN* genes. Lastly, the p53abn group is characterized by mutations in *TP53*, *PIK3CA*, *FBXW7* and *PPP2R1A* [34,62,63]. For these common gene mutations associated with EC, we reviewed the existing literature related on fertility-sparing treatment and summarized the information of mutated genes in **Table 2** [25,31,45,62,64-72].

1. *PTEN*

PTEN is a tumor suppressor gene, and its inactivation serves as a major driver of EC, with somatic mutations occurring in 69%–80% of EEC [66]. *PTEN* is involved in the phosphoinositide 3-kinase (PI3K) pathway, which is associated with progesterone insensitivity. The study revealed that *PTEN* mutation may predict a poor prognosis of progesterone-based fertility-sparing treatment. The mutant group exhibited a lower CR rate and a longer treatment duration to achieve CR [45], along with a higher cumulative recurrence rate one year after CR [44].

2. *KRAS*

KRAS mutation is associated with the occurrence, progression and invasion of EEC, and influences the mitogen-activated protein kinase, PI3K, and the Ral-GEFs pathway [68]. It can also cause hypermethylation changes [65]. In a study on fertility-sparing treatment for EC/EAH,

Table 2. Information regarding genetic mutations linked to molecular classification in fertility-sparing treatment

Mutated genes	Molecular classification [25,62]	Associated mutation	Signaling pathway
PTEN	*POLEmut*, MMRd, NSMP	*PIK3CA*, *MSH6* [64]	MAPK [65], PI3K/AKT/mTOR [66]
KRAS	*POLEmut*, MMRd, NSMP [67]	*MLH1 hypermethylation* [65]	MAPK, PI3K/AKT/mTOR, Ral-GEFs [68]
PIK3CA	*POLEmut*, MMRd, NSMP, p53abn	*PTEN*, *POLE* [64]	PI3K/AKT/mTOR
POLE	*POLEmut*	*PTEN* [67]	WNT, AMF/PGI, AMFR/gp78 [69]
TP53	p53abn, *POLEmut*, MMRd [45]	*PIK3CA* [62]	P53
MSI	MMRd	*PIK3CA*, *CTNNB1*, *MMR* [70]	PI3K/AKT/mTOR, NOTCH, WNT [70]
CTNNB1	NSMP	*PTEN*, *KRAS* [71]	WNT [71]
ARID1A	MMRd, *POLEmut* [31], NSMP	*PTEN*, *PIK3CA*, *MLH1 hypermethylation* [72]	PI3K/AKT/mTOR, DRR [64]

MMRd, mismatch repair deficient; NSMP, non-specific molecular profile; p53abn, p53 abnormal; *POLEmut*, *POLE* ultramutated.

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KRAS mutation did not significantly impact CR rates [44]. Xu et al. [45] demonstrated that *KRAS* mutations were significantly correlated with disease progression in ECs and patients who progressed to EC during fertility-sparing treatment, however, there was no difference in CR rates at 16 weeks and 32 weeks.

3. *PIK3CA*

PIK3CA is one of the most frequently mutated genes in EC, often co-occurring with mutations in *PTEN* and *POLE* [64]. Studies have found that although there was no significant difference in cumulative CR rate and cumulative live birth rate between the *PIK3CA* mutant group and non-mutant group after fertility-sparing treatment [44], the time taken for the mutant group to achieve CR was longer, and multi-factor regression analysis suggested that it may be an independent predictor of a lower cumulative CR rate [45].

4. *CTNNB1*

In G1-G2 EC, *CTNNB1* mutation occur in up to 50%, which is usually occur in NSMP tumors [73]. It is associated with the WNT pathway and can cooperate with *PTEN* and *KRAS* mutations [71]. Activation of WNT pathway is associated with tumor proliferation and progression. Current studies have generally demonstrated that *CTNNB1* mutation leaded to a higher risk of recurrence in early-stage low-grade EC [71]. At present, the significance of *CTNNB1* in the fertility-sparing treatment of EC has not been established, but it has important potential value for refining and stratifying of NSMP group.

5. *ARID1A*

ARID1A is a tumor suppressor gene involved in chromatin remodeling and is associated with PI3K and DRR signaling pathways [64]. There was a strong correlation between *ARID1A* deletion and sporadic microsatellite instability, but not with Lynch-associated tumors. It acts as a causative gene for microsatellite instability by contributing to epigenetic silencing of *MLH1* genes in EC [72]. The study found that genomic alterations in *ARID1A* were synchronized with its RNA and protein expression levels in EC, and showed reduced transcription levels of PR [74]. Therefore, EC/EAH with *ARID1A* mutations may not respond well to hormone therapy.

IMMUNOHISTOCHEMICAL MARKERS TO PREDICT FERTILITY-SPARING TREATMENT OUTCOMES

1. ER and PR

PR and ER are the most comprehensively studied prognostic factors in the fertility-sparing treatment of EC/EAH, high PR expression before treatment is associated with better response, while low PR levels during follow-up period suggest a better response [75]. Among them, increased expression of progesterone receptor B (PRB) and reduced expression of progesterone receptor A (PRA) during the follow-up are related to relapse after treatment [76]. PRB is currently the most promising marker for predicting the outcome of fertility-sparing treatment. As for ER, its initial level does not seem to correlate with treatment outcome [77,78], but low levels of ER indicate the likelihood of relapse after CR [79]. In addition, Raffone et al. [77] found that ER and PR were predictive biomarkers only when intrauterine progesterone was used and could not be used to predict the outcome of oral progesterone therapy.

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2. Ki-67

Ki-67 is regarded as a marker of cell proliferation, and its increase generally indicates tumor progression, metastasis, and poor prognosis. Initial high levels of Ki-67 did not appear to be significantly associated with remission after fertility-sparing treatment of EC/EAH [80], but are more common in groups that relapse after CR [79]. MMRd group is found with high expression of Ki-67, which may explain why this group is faced with the recurrence of fertility-sparing treatment [49]. Furthermore, study have found that higher Ki-67 expression after treatment also predicts a poor response to fertility-sparing treatment [81] and a higher likelihood of recurrence [80].

3. PTEN

The involvement of PTEN, an activator of the PI3K/AKT/mTOR pathway is found to be a potential indicator of the failure in fertility-sparing treatment for EC/EAH. However, the absence of PTEN expression alone does not have significant prognostic value [82]. When PTEN is abnormally expressed along with other molecules in this pathway, such as p-AKT, it is more likely to be unresponsive to fertility-sparing treatment [83]. PR, an important target of fertility-sparing treatment, is also related to the PI3K/AKT/mTOR pathway [84]. The interaction between different molecules in this pathway is an important research direction for predicting prognosis after fertility-sparing treatment.

4. L1CAM

Overexpression of L1CAM was most prevalent in the p53abn subgroup [85]. It was found that the prognosis of L1CAM overexpression group in NSMP was similar to that of p53abn subgroup [86]. Studies have shown that L1CAM expression depends on TGF-β and WNT signaling pathways, and their activity was normally inhibited by progesterone [85,87]. Therefore, PR expression may be lower in the L1CAM overexpression group, although there is no direct study evidence of L1CAM in EC/EAH fertility-sparing treatment, we speculate that the NSMP-L1CAM positive subgroup may not respond well to hormone therapy. This provides a target for hierarchical management of NSMP groups.

AIs TO PREDICT FERTILITY-SPARING TREATMENT OUTCOMES

At present, the applications of AI in ECs mainly focus on the prediction of genetic and molecular information based on hematoxylin and eosin (H&E)-stained whole slide images (WSIs), with preliminary research also being conducted on the prediction of response after fertility-sparing treatment. It is difficult for pathologists to distinguish the molecular classification and the microsatellite status of EC based on morphology alone, however, AI technology could, and it also has provided us with some connections between molecular classification and morphological characteristics [88-90]. Using WSIs, a specific multi-resolution deep convolutional neural network can forecast 18 frequent gene mutations as well as the histological and molecular classification of EC [91]. AI technology can detect morphological features that humans do not notice, and the prediction of fertility-sparing treatment for EC/EAH is also related to pathomorphology. Morular metaplasia is a benign metaplasia of endometrium, and favorable fertility-sparing treatment outcomes have been discovered when MM occurs before treatment and disappears after it [92]. Based on the morphological characteristics of WSIs in endometrial tissue samples, the unsupervised deep learning model has been used to predict patients' response to hormone therapy with a AUC of 0.79 [93].

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CHALLENGE AND FUTURE DIRECTIONS

Based on the results of existing studies on fertility-sparing treatment of EC and EAH, we summarized the results of some feasible markers in **Fig. 2**.

Through literature review, we discovered that molecular classification does play an essential role in the fertility-sparing treatment for EC/EAH. Currently, FIGO 2023 recommends comprehensive molecular classification to be encouraged in all EC cases, as a potential factor in risk stratification and treatment options [29]. According to the new staging criteria, the

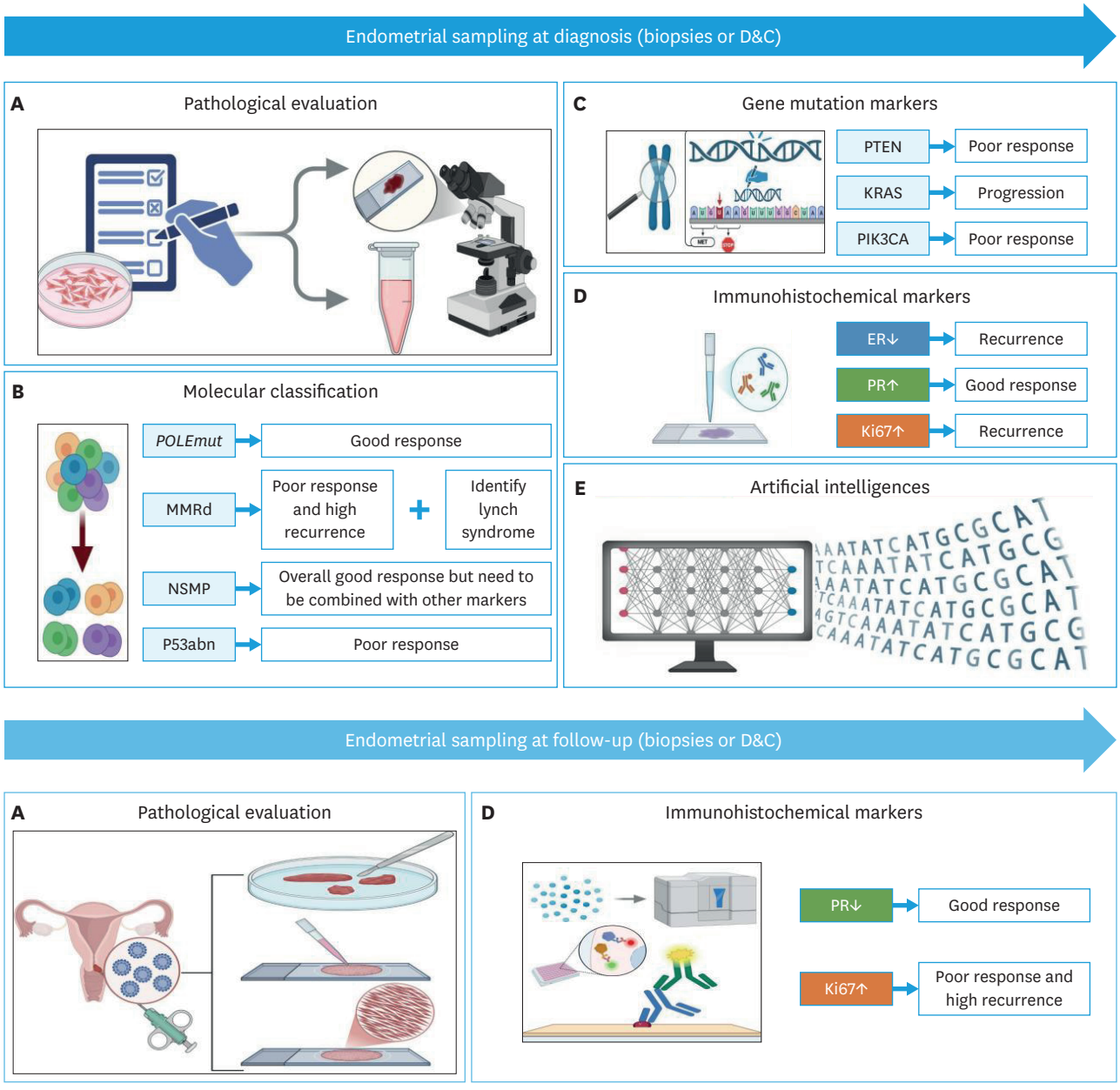

Fig. 2. Prediction of fertility-sparing treatment for endometrial cancer and endometrial atypical hyperplasia.
D&C, dilation and curettage; ER, estrogen receptor; MMRd, mismatch repair deficiency; NSMP, non-specific molecular profile; p53abn, p53 abnormal; *POLEmut*, *POLE* ultramutated; PR, progesterone receptor.

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stage I–II *POLEmut* EC is changed to $IAm_{POLEmut}$, which provides more conservative treatment possibilities for this group [29]. It is generally believed that MMRd patients may have a poor response to hormone therapy due to its low PR level and have a high recurrence rate after CR [41]. The role of immune checkpoint inhibitors in the fertility-sparing treatments of this group is worth exploring. There is significant heterogeneity of NSMP tumors, and specific gene or immunohistochemical markers need to be introduced in the future to better rationalize stratified management and precision therapy. However, fertility-sparing treatment is generally not recommended for the p53abn group.

Compared with ER, PR plays a more important role in the fertility-sparing treatment of EC/EAH [78] and it has the potential to appropriately expand the application of treatment for G2 EEC with high PR expression [94]. Therefore, the PI3K/AKT/mTOR pathway, which is related to PR, is a key target for identifying biomarkers of progesterone-based fertility-sparing treatment. As we know, *PTEN*, *KRAS* and *PIK3CA* mutations in this pathway seemed to predict a poor response to progesterone therapy [44]. In addition, increased Ki-67 expression is associated with relapse after treatment [44,79], providing a risk basis for detecting disease recurrence. At present, there is no direct evidence for the role of *CTNNB1* and *ARID1A* mutations, as well as L1CAM expression in fertility-sparing treatment for EC/EAH. However, they are very promising biomarkers, which are expected to further accurately predict fertility-sparing treatment outcomes based on molecular classification. Furthermore, these genetic and immunohistochemical markers are associated with the pathogenesis of EC, and their abnormalities can indicate the possibility of potential tumors in biopsy samples to pathologists, which is helpful for clinical diagnosis.

H&E-stained pathological images provide the most intuitive representation of the characteristics of disease, however, due to the complexity of shape and the subjective nature of interpretation, it is challenging to find out the relationship between pathologic characteristics and the extent of response to fertility-sparing treatment for EC/EAH. The classification of grade in endometrial biopsy specimens can occasionally be difficult to interpret due to the small sample size. The application of AI is anticipated to make a more objective diagnosis and screen a larger range of patients who can receive fertility-sparing treatment [95]. AI technology can also predict molecular information based on morphology, and suggest the morphological changes that may indicate underlying molecular alterations [90], significantly reducing the cost and time of molecular detection. In the future, AI technology may also provide us more insights into therapy responsiveness and pathological morphology, which combining molecular information can achieve more objective and accurate prediction effects.

Historically, histology and immunohistochemistry have been used to forecast fertility-sparing effectiveness, but the outcomes have not been satisfactory. The relationship between morphology and therapeutic outcome is subjective and not highly significant. Currently, the use of hormone receptors alone to forecast response is likewise restricted, insufficient, and imprecise [15,77]. It is necessary to introduce new technologies like genetic testing and molecular classification. The proliferation of next-generation sequencing has led to a steady rationalization and control of the cost of genetic testing, with an average price of $1,297 in one Canadian count for molecular classification, which varies across countries and test platforms [96]. Additionally, identifying *POLE* pathogenic mutations combined with MMR and P53 proteins to interpret molecular classification is a more cost-effective approach and has universal clinical applicability [97]. Nowadays, most clinicians think that molecular

detection is essential [98]. In a cost-effectiveness analysis, they found that molecular testing for high-risk early-stage EC is cost-effective, especially for *POLEmut* [99]. Molecular detections can expand the indications of fertility-sparing treatment, increase the success rate, reduce the recurrence rate, and have significant long-term economic benefits [99,100]. Besides, due to the long treatment period and hardship in follow-up, patients' final fertility outcomes after fertility-sparing treatment have seldom been fully tracked. In future studies, we need more follow-up data to analyze whether there are differences in fertility outcomes among patients with different molecular classifications and gene mutations.

CONCLUSION

Although pathological examination still occupies a central position in the assessment of fertility-sparing treatment for EC and EAH, the introduction and application of other assessment methods are gradually changing the evaluation model in this field. In recent years, there has been an increasing focus on the study and application of molecular classification, gene detection, protein expression and AI with molecular classification being particularly notable. However, heterogeneity within molecular groups requires more specific biomarkers and pathomorphology to distinguish. Conservative management of EC is becoming increasingly practiced in clinic, and it is time to further explore prognostic predictors of fertility-sparing treatment. More research data are needed to support prognostic predictor's introduction into clinical practice. With the continuous advancement of medical technology and the development of multidisciplinary integration, the assessment of fertility-sparing treatment will become more comprehensive, accurate, and personalized.

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