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Molecular classification defines outcomes and opportunities in young women with endometrial carcinoma

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HIGHLIGHTS

- Management of young women with endometrial carcinoma (EC) presents unique challenges, impacting fertility and menopause.
- Better tools are needed to help direct management, identifying patients for whom conservative management is safe.
- Molecular classification enables consistent categorization of ECs and biologically relevant information to guide care.
- Molecular subtype is prognostic in young women with EC and achievable on biopsies enabling risk stratification from first diagnosis.

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ABSTRACT

Objective. Approximately 15% of endometrial carcinomas (ECs) arise in young women who may wish to avoid surgical menopause and/or preserve fertility. Our aim was to evaluate the prognostic significance of Proactive Molecular risk classifier for Endometrial Carcinoma (ProMisE) in young (<50 yo) women with EC.

Methods. ProMisE was applied to a retrospective cohort of women with ECs <50 yo at diagnosis, and associations between the four ProMisE molecular subtypes (MMR deficient (MMRd), *POLE* mutated (POLE), p53 wild type (p53wt), and p53 abnormal (p53abn)) and clinicopathological parameters, including outcomes, were assessed.

Results. Of 257 ECs, there were 48 (19%) MMRd, 34 (13%) POLE, 164 (64%) p53wt and 11 (4%) p53abn. ProMisE subtypes were associated with differences in all measured clinicopathological parameters except for presence of synchronous ovarian tumours and fertility. Age at diagnosis was youngest and BMI highest in women with p53wt ECs. MMRd and p53abn tumours were more likely to be advanced stage (III/IV), high-risk (ESMO), and receive chemotherapy. ProMisE subtypes were strongly associated with outcomes (overall, disease-specific, and progression-free survival ($p < 0.0001$ for all)). Advanced stage, grade, LVSI, myometrial invasion and ESMO risk groups showed associations with some but not all survival parameters. ProMisE maintained a strong association with OS and DSS on multivariable analysis.

Conclusions. ProMisE molecular classification is prognostic in young women with EC, enabling early stratification and risk assignment to direct care. Further studies can assess response to therapy, fertility, and cancer-related outcomes within the framework of molecular subtype.

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1. Introduction

Endometrial carcinoma (EC) is the most prevalent gynecologic malignancy and fourth most prevalent cancer among women in developed nations [1]. Both incidence and mortality attributed to EC are increasing

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[2–4]. In North America, approximately 15% of ECs arise in women <50 years of age with more than two-fold higher incidence recorded in other countries [3,5,6]. Traditional staging for uterine cancer includes hysterectomy and bilateral salpingo-oophorectomy (BSO), ±lymph node sampling and additional biopsies with consequences of loss of fertility and surgical menopause. These options may be undesired or unacceptable to young women who may not have completed childbearing and/or wish to avoid surgical menopause and its related comorbidities [7,8]. Consequently, deviation from standard practice, including hormonal therapy or hysterectomy with ovarian preservation have ensued [9]. The safety of these changes in management are as yet unclear and our ability to counsel women with regard to their prognosis, likelihood to achieve successful pregnancy, likelihood of responding to hormonal therapy, or risk of synchronous or metastatic ovarian tumour are severely limited.

We have previously characterized a large cohort of ECs in young women based on clinical features [10]. Through chart review, we observed approximately two thirds of young women with EC had either high/excess estrogen from endogenous e.g., obesity, PCOS, or exogenous (e.g., tamoxifen) sources (termed 'High Estrogen') or were suspected Lynch syndrome carriers (termed 'Lynch-like'), based on family history (>70% of this subset, as defined by Amsterdam II criteria) or rarely, molecular testing: abnormal mismatch repair (MMR) immunohistochemistry (IHC) or germline testing. However, the remaining one third of young women in this cohort lacked either of these traditional risk factors (categorized as 'Neither').

Herein, our objective is to characterize a large cohort of young women (<50 years of age) with EC within the framework of a modern TCGA-based molecular classification system that has been validated and is known to be of prognostic value in non-age stratified large cohorts of ECs [11–13]. The Proactive Molecular Risk Classifier for Endometrial Carcinoma (ProMisE) uses pragmatic molecular tests to identify ECs with mismatch repair deficiency (MMRd), mutations in the exonuclease domain of DNA polymerase epsilon (*POLE*) associated with highly favorable outcomes, and wild type or aberrant p53 expression (p53wt, equivalent to 'no specific molecular profile' [14,15], and p53abn, respectively), the latter associated with aggressive disease and the worst observed clinical outcomes [11–13,15]. ProMisE can be achieved on diagnostic endometrial biopsy or curetting specimens with high concordance to hysterectomy specimens [16,17], offering earlier pre-surgical staging information that may aid in risk assessment and guide management. In this series, we determine the distribution of ProMisE molecular subtypes of EC in women <50, and correlate molecular subtype with clinical and pathological parameters, including clinical risk group and patient outcomes. We are interested in assessing the prognostic value of this molecular algorithm specifically in young women with EC, and hypothesize that molecular subtypes may be predicted by clinical risk groups/phenotypes defined above. Our goal is to determine if molecular subtype, with or without additional clinicopathological parameters, will inform prognosis and may influence management of young women with EC.

2. Materials and methods

2.1. Case selection

We identified ECs in women aged 49 or younger from retrospective cohorts [10–13] where tissue was available and clinicopathological parameters and outcomes known (details in supplementary methods).

2.2. Immunohistochemical analysis

Formalin-fixed paraffin-embedded (FFPE) blocks were sectioned (0.3-0.6 microns) and stained with antibodies for PMS2, MSH6, and p53, as previously described [11–13]. Scoring was performed by a single sub-specialist pathologist (CBG) per current standards, [12,13] and detailed in our supplementary methods.

2.3. Molecular analysis for POLE mutations

DNA extraction and quantification are outlined in the supplementary methods and previously published [12,13]. PCR reactions were performed using targeted primers (Supplementary Table S1) for the exonuclease domain (exons 9–14) of *POLE* and treated with ExoSAP-IT™ (ThermoFisher). Sanger sequencing (Source BioScience) was performed using universal M13 tags and sequenced in both the forward and reverse directions. Resulting DNA chromatograms were analyzed using Mutation Surveyor (SoftGenetics) to identify *POLE* mutations.

2.4. ProMisE subtype stratification

Results from MMR IHC, *POLE* sequencing, and p53 IHC stratified patients as per the ProMisE algorithm. First, cases were separated into functional/intact vs deficient/loss mismatch repair protein expression (MMRd). The MMR intact group was next subdivided into *POLE* wild-type or mutant (POLE) and ECs without identifiable *POLE* mutations were segregated into p53 wild type (p53wt) or p53 abnormal (p53abn) subtypes [11,12].

2.5. Clinical risk group assignment

A subset of patients had been previously characterized by clinical 'risk groups'/perceived phenotypes. Categories included 'High Estrogen,' with recognized conditions of excess estrogen such as obesity (BMI > 30 kg/m^2), polycystic ovarian syndrome (PCOS), or tamoxifen therapy; 'Lynch-like,' with either a family history (Amsterdam II criteria) suggesting Lynch syndrome or more rarely germline or somatic mismatch repair testing had been performed (era preceding routine testing for all ECs); and a 'Neither' subgroup in which these classical risk factors were not identified [10]. Follow-up data (fertility and cancer-associated outcomes) were updated on this cohort through chart review and contacting their primary care physicians. Lack of clinical data specific to this system of 'risk group' assignment (e.g. diagnosis of polycystic ovarian disease, tamoxifen use, or family history of cancer) precluded clinical risk group assignment of all cases in the larger cohort of young women.

2.6. Statistical methods

Clinicopathologic, fertility-related, treatment, and outcome parameters were compared across all ECs in young women and within clinical risk groups. Definitions of all parameters are found in the supplementary methods. All parameters were tested for normality. The association of molecular ProMisE subtypes with demographic, clinical, or pathological features was compared with one-way ANOVA in the case of continuous data and $\chi 2$ test for nominal data. Statistical significance level was at $p < 0.05$, and p-values were not corrected for multiple comparisons.

Univariable survival analysis was performed for both the ProMisE molecular subtypes (MMRd, POLE, p53wt, and p53abn) and clinical risk groups ('High Estrogen', 'Lynch-like', 'Neither') for overall survival (OS), disease-specific survival (DSS), and progression-free survival (PFS). Multivariable (MV) analysis was performed correcting for parameters that would be available from time of first diagnostic endometrial biopsy or curettage diagnosis to emulate future clinical application; age, BMI, histotype, grade, and ProMisE subtype were assessed. We also performed MV analysis encompassing additional parameters available post-staging, including stage and LVS,I and adjusted for treatment. Median follow-up rates were calculated with a reverse Kaplan-Meier survival curve.

Analyses were performed according to the REMARK reporting criteria [18] and were conducted using the statistical software R v3.3.2 (R Core Team, 2016).

3. Results

3.1. Full cohort

A total of 257 women with EC < 50 years of age had sufficient clinical, pathological and outcome data, and successful molecular testing to enable inclusion in the study. The principal reason for exclusion was inability to access tissue for molecular testing, as these cases came from across a large geographic area. Median follow-up time was 5.2 years. A total of 30 women experienced recurrence of their disease, with 13 endometrial cancer-associated (disease-specific) deaths, and17 death recorded.

Over half of our young women cohort was nulliparous (51.9%) and, although data on ethnicity was missing in the majority of the cohort, representation was highest for 'Asian' (56%, encompassing East and South East Asian, not including women of Indian or Pakistani descent), and Caucasian (32%) races. Twenty-eight percent (28%) of the full cohort was under the age of 40 years, with ~10% under age 35.

ProMisE breakdown of the 257 young women ECs is given in Fig. 1A and includes 48 (18.7%) MMRd, 34 (13.2%) POLE, 164 (63.8%) p53wt, and 11 (4.3%) p53abn. Summary statistics on the molecular features within the full cohort are given in Supplementary Table S2 with specifics on *POLE* mutations outlined in Supplementary Table S3. As per ProMisE algorithm, even though all molecular tests were performed on these cases, subtype assignment was based on sequential assignment of MMR-deficient cases, then ECs with *POLE* EDMs, then lastly the mismatch repair proficient, *POLE* wildtype remaining cases are discerned by p53 IHC status. Ten cases (3.9%) were identified as having more than one molecular feature; two were MMRd with *POLE* mutations, and 8 were MMRd with p53 abnormalities (7 null and 1 overexpression on IHC) (Supplementary Table S4).

Univariable analysis revealed statistically significant associations of molecular subtype with almost all measured clinical and pathological parameters (Table 1). Age at diagnosis was youngest in the p53wt group (mean 41.8, 14% ≤ 35, 21% between 35 and 39 and 64% age 40–49), representing 92% of all diagnoses below the age of 35. All but one p53abn ECs were in the 41–49 age bracket with a median age of 46.3. 49% of the full cohort of young women with EC were obese (BMI 30 or >), 82% of which were in women with p53wt ECs although representation of obese individuals across all molecular subtypes was observed. p53wt ECs were low grade (78% grade 1), low stage (85% confined to the uterus), endometrioid (97%), and when fully staged/reported node negative (95%) and LVSI negative (94%). MMRd and p53abn were more likely to be advanced stage (III/IV), high risk by 2013 ESMO risk stratification and receive chemotherapy, Table 1. Consistent with prior publications, women with *POLE* mutated ECs were thin (BMI < 30 kg/m^2 in 83%) and often had aggressive molecular features, with 72% receiving some form of adjuvant therapy (radiation, chemotherapy, or both).

Twenty-five of 257, or 10%, of our full young women cohort had synchronous endometrial and ovarian carcinomas (SEOCs) with no apparent associations seen with ProMisE subtypes ($p = 0.15$). Nodal status and pregnancy outcomes were the only other measured parameters that did not appear to be associated with ProMisE subtype, with data missing in a large proportion of cases (Table 1).

Data was available on progesterone therapy for conservative management (delayed hysterectomy) in only 16% of our cohort, of which 49% were taking medroxyprogesterone, 36% megestrol acetate, 10% using progesterone intrauterine systems (IUS), and 5% combined oral with an IUS. Progesterone therapies were observed to have been given across all molecular subgroups except p53abn ECs.

3.2. Concordance statistics: ProMisE assessment of diagnostic and hysterectomy specimens

The full cohort of 257 samples included 83 ECs where molecular classification was performed on endometrial biopsy or dilatation and curettage diagnostic specimens, 137 samples from hysterectomies, and 37 cases where both biopsy/curettage and hysterectomy were available in the same individual and both samples tested. Concordance metrics of ProMisE subtype assignment were highly favorable in the 37 cases where both specimens were able to be tested; overall accuracy 0.92(95% confidence interval: 0.78–0.98), and Cohen's kappa statistic of 0.87 (95% CI: 0.68–0.98) ($p < 0.0001$). In total, just three discordant results were recorded; one EC classified as MMRd by biopsy, p53wt on hysterectomy and two ECs assigned p53wt on diagnostic samples and POLE on final hysterectomy. Where discordant, ProMisE assignment from diagnostic biopsy sample was used for final analysis.

3.3. Clinical risk groups

In a subset of cases ($n = 189$), previously characterized by clinical chart review [10], we had designated patients into one of three clinical risk groups: 'High Estrogen' ($n = 105$, >55%), 'Lynch-like' ($n = 18$,

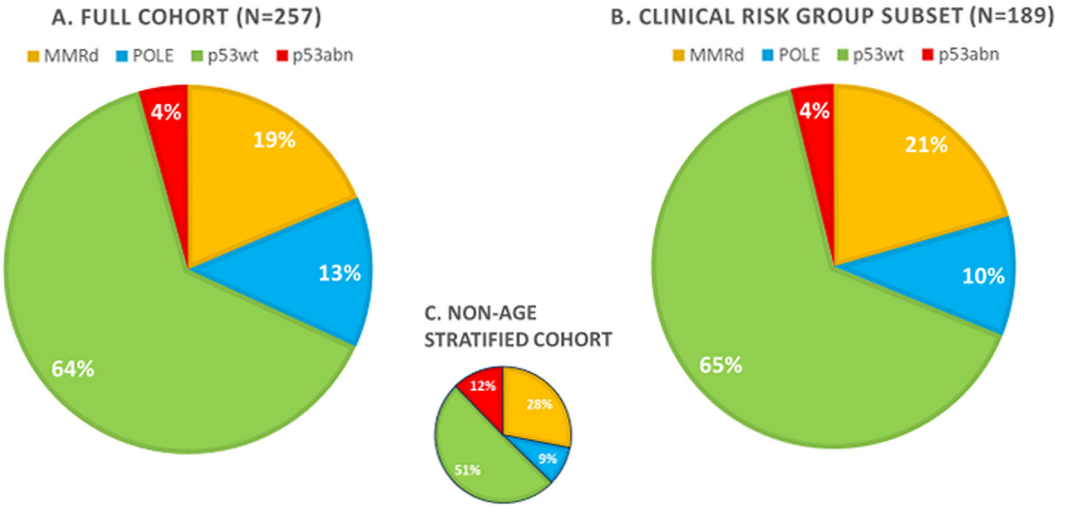

Fig. 1. ProMisE subtype distribution across A. the full cohort of young women ($N = 257$) and B. within the subset of young women where clinical risk group was defined. Inset C. demonstrates ProMisE distribution within a population based, non-age stratified cohort from the University of Tubingen [13] ($n = 452$).

Table 1
Univariable associations of clinicopathological parameters by ProMisE molecular subytpe.

Parameter	Measure	MMRd	POLE	p53wt	p53abn	Total[a]	*p* Value
Total	*N*	48	34	164	11	257	
Age at surgery	Mean (SD)	44.7 (±4.5)	44.8 (±3.8)	41.8 (±6.1)	46.3 (±3.9)	42.9 (±5.6)	**0.000**
	Median	46.2	45.8	42.8	47.7	44.4	
Age at surgery (grouped)	<35	2(4.2%)	0(0%)	23(14%)	0(0%)	25(9.7%)	**0.017**
	35–39	5(10.4%)	6(17.6%)	35(21.3%)	1(9.1%)	47(18.3%)	
	40–49	41(85.4%)	28(82.4%)	106(64.6%)	10(90.9%)	185(72%)	
BMI	Mean (SD)	29 (±7.9)	25 (±4.5)	34 (±11.1)	32.5 (±9.4)	31.6 (±10.2)	**0.000**
	Median	26.1	25.5	32.4	27.9	28.6	
FIGO 2009 stage	I	26(55.3%)	29(85.3%)	132(85.2%)	5(50%)	192(78%)	**0.000**
	II–IV	21(44.7%)	5(14.7%)	23(14.8%)	5(50%)	54(22%)	
Tumour grade	Grade 1/2	31(66%)	26(76.5%)	149(93.1%)	5(50%)	211(84.1%)	**0.000**
	Grade 3	16(34%)	8(23.5%)	11(6.9%)	5(50%)	40(15.9%)	
Histological subtype	Endometrioid	39(86.7%)	28(87.5%)	150(97.4%)	8(72.7%)	225(93%)	**0.001**
	Non-endometrioid	6(13.3%)	4(12.5%)	4(2.6%)	3(27.3%)	17(7%)	
LVSI	Negative	9(60%)	13(81.2%)	50(94.3%)	3(60%)	75(84.3%)	**0.005**
	Positive	6(40%)	3(18.8%)	3(5.7%)	2(40%)	14(15.7%)	
Myometrial invasion	None	2(13.3%)	7(43.8%)	33(62.3%)	2(40%)	44(49.4%)	**0.020**
	<50%	7(46.7%)	5(31.2%)	16(30.2%)	2(40%)	30(33.7%)	
	>50%	6(40%)	4(25%)	4(7.5%)	1(20%)	15(16.9%)	
Nodal status	Negative	8(53.3%)	11(68.8%)	38(71.7%)	4(80%)	61(68.5%)	0.239
	Positive	3(20%)	0(0%)	2(3.8%)	0(0%)	5(5.6%)	
	Not tested	4(26.7%)	5(31.2%)	13(24.5%)	1(20%)	23(25.8%)	
Radiation[b]	No	18(51.4%)	15(60%)	99(83.9%)	5(71.4%)	137(74.1%)	**0.000**
	Yes	17(48.6%)	10(40%)	19(16.1%)	2(28.6%)	48(25.9%)	
ChemoRx	No	20(57.1%)	17(68%)	107(90.7%)	3(42.9%)	147(79.5%)	**0.000**
	Yes	15(42.9%)	8(32%)	11(9.3%)	4(57.1%)	38(20.5%)	
Post-surgical treatment[c]	No	11(33.3%)	5(25%)	69(74.2%)	0(0%)	85(56.7%)	**0.000**
	Yes	22(66.7%)	15(75%)	24(25.8%)	4(100%)	65(43.3%)	
Progesterone therapy	No/not recorded	34(87.2%)	16(80%)	91(74%)	7(100%)	148(78.3%)	0.162
	Yes	5(12.8%)	4(20%)	32(26%)	0(0%)	41(21.7%)	
ESMO risk group	Low	4(26.7%)	10(62.5%)	44(83%)	3(60%)	61(68.5%)	**0.001**
	Intermediate	2(13.3%)	3(18.8%)	2(3.8%)	0(0%)	7(7.9%)	
	High	9(60%)	3(18.8%)	7(13.2%)	2(40%)	21(23.6%)	
Synchronous	No	44(91.7%)	27(79.4%)	151(92.1%)	10(90.9%)	232(90.3%)	0.152
	Yes	4(8.3%)	7(20.6%)	13(7.9%)	1(9.1%)	25(9.7%)	
Clinical phenotype	High Estrogen	13(33.3%)	4(20%)	84(68.3%)	4(57.1%)	105(55.6%)	**0.000**
	Lynch-Like	14(35.9%)	1(5%)	2(1.6%)	1(14.3%)	18(9.5%)	
	Neither	12(30.8%)	15(75%)	37(30.1%)	2(28.6%)	66(34.9%)	
Ethnicity	Asian	7(63.6%)	3(50%)	24(55.8%)	0	34(56.7%)	–
	Caucasian	2(18.2%)	2(33.3%)	15(34.9%)	0	19(31.7%)	
	Other	2(18.2%)	1(16.7%)	4(9.3%)	0	7(11.7%)	
Number of pregnancies	0	18(48.6%)	7(38.9%)	55(56.1%)	2(40%)	82(51.9%)	0.501
	>0	19(51.4%)	11(61.1%)	43(43.9%)	3(60%)	76(48.1%)	
Pregnancies > 20 weeks	0	10(34.5%)	2(16.7%)	8(19.5%)	0(0%)	20(23.3%)	0.275
	>0	19(65.5%)	10(83.3%)	33(80.5%)	4(100%)	66(76.7%)	

Note: Nodal status and ethnicity were missing data in over half the cohort, (167 and 197 respectively) limiting statistical comparisons. Statistical significance ($p < 0.05$) indicated in bold.
[a] Where totals do not *add up to* 257 data for that parameter is missing.
[b] Radiation includes vaginal brachytherapy and external beam pelvic radiotherapy (recorded separately but grouped together for this table).
[c] Post-surgical treatment encompasses chemotherapy or radiation or both.

9.5%), and 'Neither' ($n = 66$, 34.5%). The majority of 'High Estrogen' ECs were assigned secondary to obesity (80%) with 17% having PCOS (± obesity) and 3% on tamoxifen therapy.

Associations of clinical risk groups with clinical, pathological and molecular parameters are shown in Table 2. Notably, ProMisE subtype was associated with clinical risk group ($p < 0.0001$). Clinicopathological differences associated with clinical risk group included a higher proportion of advanced stage, high grade, non-endometrioid tumours receiving adjuvant chemotherapy in 'Lynch-like' ECs. Distribution of SEOCs differed across clinical risk groups ($p = 0.016$) with over half (54%) of all SEOCs identified in the 'Neither' cohort (22% of all women with ECs categorized as 'Neither' had SEOCs). Racial differences across clinical risk group/phenotypes were also observed ($p = 0.001$), with higher representation of Asian women in the 'Neither' subgroup (25 of a total 34 Asian women (71.4%) lacked traditional risk factors of excess estrogen or suspected Lynch syndrome). No statistically significant differences were observed in progesterone therapy (oral, IUD, or combination) or measured fertility parameters across clinical risk groups.

ProMisE subtype distribution within the subset of young women cases where clinical risk group could be defined ($N = 189$) (Fig. 1B) essentially mirrored the distribution of the full cohort. This distribution is also comparable to what has been reported in larger non-age stratified population-based cohorts (Fig. 1C) [13] with the main difference being a slightly larger proportion of p53wt and fewer p53abn ECs in young women.

Distribution of ProMisE molecular subtypes within clinical risk groups differed markedly (Fig. 2A–C). The dominant subtype in the 'High Estrogen' cohort was p53wt (80%) with 12.4% MMRd and just 3.8% each of POLE and p53abn tumours (Fig. 2A.). 'Lynch-like' ECs encompassed mismatch repair abnormalities in the majority (77.8% MMRd), with rare POLE ($n = 1$), p53abn ($n = 1$) or p53wt ECS ($n = 2$) (Fig. 2B). The 'Neither' subgroup, although p53wt predominant (56%), included more than twice the usual distribution of POLE mutated ECs (22.7%) (Fig. 2C).

3.4. Survival analyses

Kaplan-Meier survival analyses within this non-age stratified cohort of young women ($n = 257$) showed ProMisE subtypes were associated with overall (OS), and disease-specific survival

Table 2
Univariable associations of clinicopathological parameters by clinical risk group/phenotype.

Parameter	Measure	High estrogen	Lynch-like	Neither	Total	*p* Value
Total	*N*	105	18	66	189	
Age at surgery	Mean (SD)	42 (±6)	42 (±6)	43 (±5)	42.9 (±5.5)	0.398
	Median	43.2	44	44.1	44.4	
Age at surgery (grouped)	<35	13(12.4%)	3(16.7%)	4(6.1%)	20(10.6%)	0.441
	35–39	26(24.8%)	3(16.7%)	13(19.7%)	42(22.2%)	
	40–49	66(62.9%)	12(66.7%)	49(74.2%)	127(67.2%)	
BMI	Mean (SD)	40.4 (±8.9)	26.0 (±6.1)	23.9 (±3.4)	32 (±10)	**0.000**
	Median	39.7	25.2	24.1	28.6	
FIGO 2009 Stage	I	87(87.9%)	5(29.4%)	40(64.5%)	132(74.2%)	**0.000**
	II–IV	12(12.1%)	12(70.6%)	22(35.5%)	46(25.8%)	
Tumour grade	Grade 1/2	92(90.2%)	11(64.7%)	49(76.6%)	152(83.1%)	**0.008**
	Grade 3	10(9.8%)	6(35.3%)	15(23.4%)	31(16.9%)	
Histological subtype	Endometrioid	97(98%)	13(76.5%)	54(91.5%)	164(93.7%)	**0.002**
	Non-endometrioid	2(2%)	4(23.5%)	5(8.5%)	11(6.3%)	
Radiation[a]	No	45(72.6%)	6(46.2%)	31(63.3%)	82(66.1%)	0.161
	Yes	17(27.4%)	7(53.8%)	18(36.7%)	42(33.9%)	
ChemoRx	No	52(83.9%)	4(30.8%)	35(71.4%)	91(73.4%)	**0.000**
	Yes	10(16.1%)	9(69.2%)	14(28.6%)	33(26.6%)	
Post-surgical treatment[b]	No	42(67.7%)	2(14.3%)	24(48%)	68(54%)	**0.001**
	Yes	20(32.3%)	12(85.7%)	26(52%)	58(46%)	
Progesterone therapy	No/not recorded	77(73.3%)	17(94.4%)	54(81.8%)	148(78.3%)	0.092
	Yes	28(26.7%)	1(5.6%)	12(18.2%)	41(21.7%)	
ESMO risk group	Low	9(69.2%)	0	1(12.5%)	10(47.6%)	–
	Intermediate	0(0%)	0	3(37.5%)	3(14.3%)	
	High	4(30.8%)	0	4(50%)	8(38.1%)	
Synchronous?	No	99(94.3%)	14(77.8%)	54(81.8%)	167(88.4%)	**0.016**
	Yes	6(5.7%)	4(22.2%)	12(18.2%)	22(11.6%)	
ProMisE subtype	MMRd	13(12.4%)	14(77.8%)	12(18.2%)	39(20.6%)	**0.000**
	POLE	4(3.8%)	1(5.6%)	15(22.7%)	20(10.6%)	
	p53wt	84(80%)	2(11.1%)	37(56.1%)	123(65.1%)	
	p53abn	4(3.8%)	1(5.6%)	2(3%)	7(3.7%)	
Ethnicity	Asian	6(26.1%)	3(50%)	25(80.6%)	34(56.7%)	**0.001**
	Caucasian	14(60.9%)	2(33.3%)	3(9.7%)	19(31.7%)	
	Other	3(13%)	1(16.7%)	3(9.7%)	7(11.7%)	
Number of pregnancies	0	43(53.8%)	8(47.1%)	31(50.8%)	82(51.9%)	0.862
	>0	37(46.2%)	9(52.9%)	30(49.2%)	76(48.1%)	
Pregnancies > 20 weeks	0	7(17.9%)	3(25%)	10(29.4%)	20(23.5%)	0.511
	>0	32(82.1%)	9(75%)	24(70.6%)	65(76.5%)	

Parameters with high number of missing values included ethnicity (missing in 60 women), and pregnancy history missing in 83 women. Table 1 which includes this cohort of 189 as well as cohort of new/sadditional cases has details on LVSI, myoinvasion and LN status. Note: Statistical significance ($p < 0.05$) indicated in bold.
[a] Radiation includes vaginal brachytherapy and external beam pelvic radiotherapy (recorded separately but grouped together for this table).
[b] Post-surgical treatment encompasses chemotherapy or radiation or both.

(DSS)(log rank $p < 0.001$ for both) (Fig. 3A–B) with a non-significant trend for association with progression-free survival (log rank $p = 0.12$, not shown). Survival analysis within the smaller subsets of 'High estrogen' and 'Neither' ECs suggested ProMisE was associated with OS and DSS (log rank $p = 0.019$, $p < 0.001$, $p = 0.004$, $p = 0.004$ respectively) (Fig. 3C–E). Clinical risk groups were not associated with measured outcome parameters ($p = ns$ for all, data not shown).

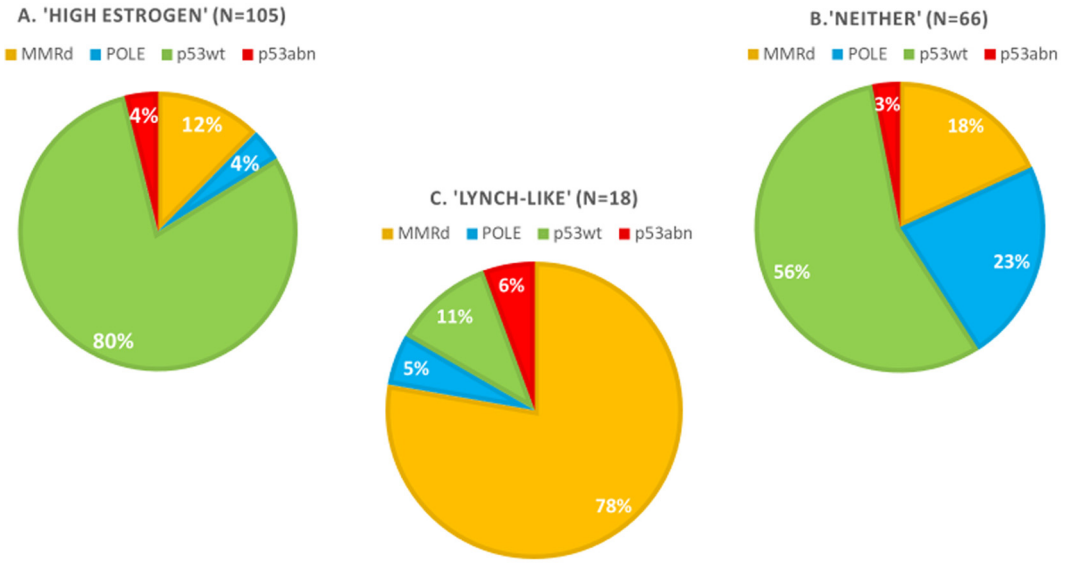

Fig. 2. ProMisE subtype distribution across clinical risk groups: A. 'High Estrogen', B. 'Lynch-Like' and C. 'Neither'.

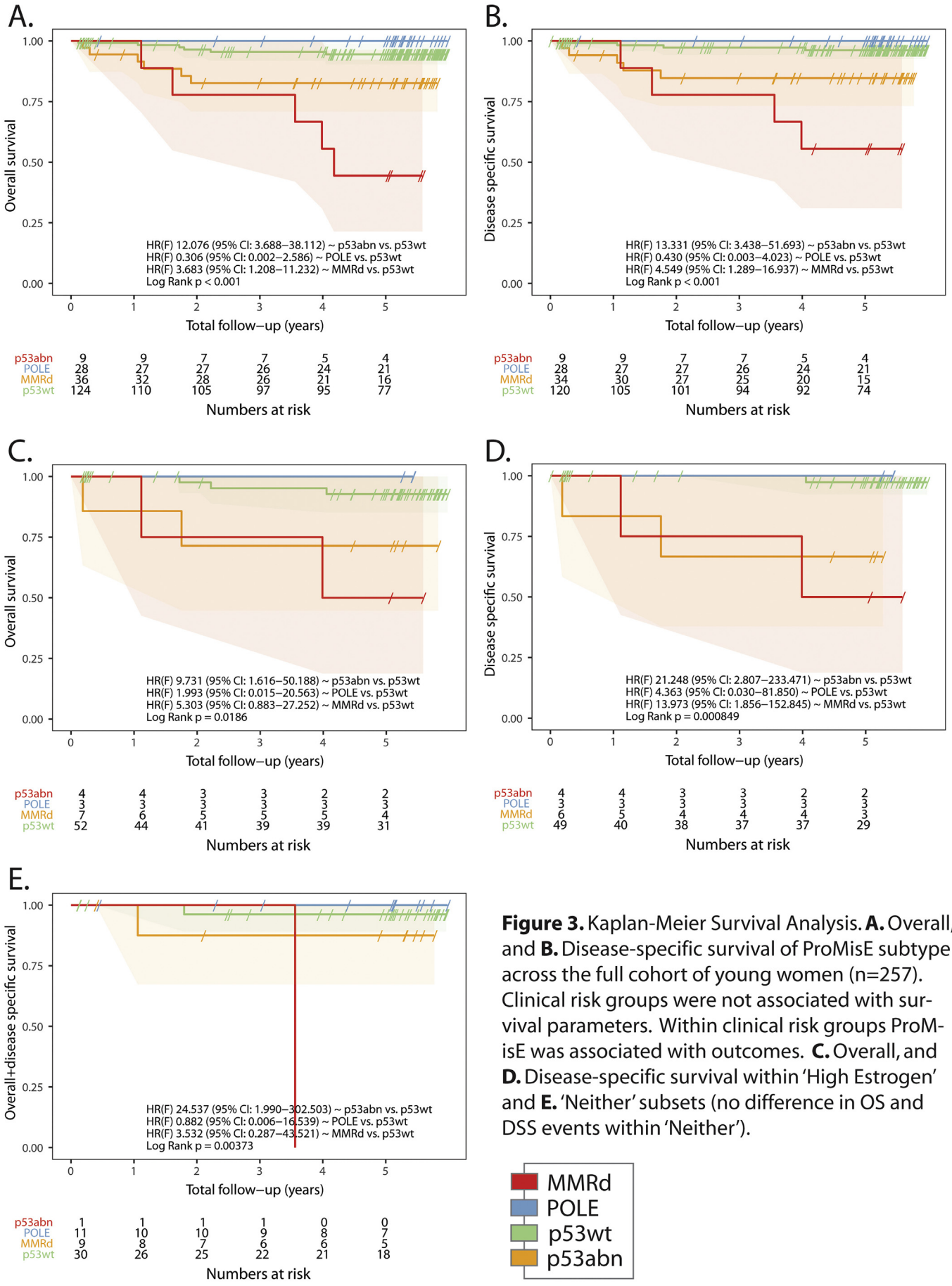

Figure 3. Kaplan-Meier Survival Analysis. **A.** Overall, and **B.** Disease-specific survival of ProMisE subtype across the full cohort of young women (n=257). Clinical risk groups were not associated with survival parameters. Within clinical risk groups ProMisE was associated with outcomes. **C.** Overall, and **D.** Disease-specific survival within 'High Estrogen' and **E.** 'Neither' subsets (no difference in OS and DSS events within 'Neither').

Fig. 3. Kaplan-Meier Survival Analysis.

Univariable survival analysis confirmed the strong association of OS and DSS observed with ProMisE molecular subtype assignment (LRT p-value = 0.0001, 0.0005 respectively) but stage, grade, LVSI, myometrial invasion, ESMO risk group and parity were also associated with OS and DSS. Further details can be found in Supplementary Table S5.

Multivariable survival analysis with correction of parameters that are available/known from the time of first diagnostic biopsy; age, BMI, tumour grade and histotype, and correcting for the administration of treatment (potential confounder) demonstrated ProMisE molecular classification maintained an association with overall and disease-specific survival. Hazard ratios (HRs) and confidence intervals are shown in Table 3. Using p53wt subtype as the reference, the HRs for MMRd and p53abn subtypes were 5.2 And 12.8 for OS ($p = 0.017$) and 8.9 and 24.2 for DSS ($p = 0.010$) with POLE assignment associated with improved outcomes; HR 0.45 OS, and 0.75 for DSS, rounded up to one decimal point for tables. High grade/grade 3 tumours were also associated with increased HR; 6.7 and 8.6 for OS and DSS and a marginally increased hazard ratio was demonstrated with increasing BMI (OS, DSS only) (Table 3). MV analysis with the addition of parameters available post-staging (LVSI, stage) also demonstrated ProMisE association with overall and disease-specific survival (LRT p-value 0.036, 0.02 respectively).

3.5. Missing data analyses

We assessed if missing data from the multiple parameters collected in this series impacted our results and found no differences in distribution of missing values across ProMisE subgroups except for number of pregnancies achieved beyond 20 weeks (Supplementary Table S6).

4. Discussion

Management of endometrial cancer in young women can be challenging. Those who are premenopausal and interested in i) future fertility or ii) maintaining their ovaries may consider management that deviates from traditional standard of care. What is safe, in terms of delay of hysterectomy or ovarian preservation, or how likely an individual is to respond to hormonal management or successfully achieve pregnancy is not known, and evidence-based guidelines are lacking [19–22]. Although well intended, deviations from standard practice could negatively impact cancer-related outcomes [23,24]. Both patients and clinicians need better ways to inform management, possibly through assessment of clinicopathological or molecular features of tumours, to allow for more individualized care.

New models of molecular classification in ECs provide reproducible categorization, prognostic information, enable stratification of clinical trials, and earlier referrals for hereditary cancer testing [11–13,15]. ProMisE molecular classifier can be applied to endometrial biopsy/curetting specimens, demonstrating high concordance with final hysterectomy; in this series $\kappa = 0.87$, consistent with the literature $\kappa = 0.86$ [16] and 0.88 [13]. Thus, biologically relevant information can be available from the time of first diagnosis, particularly relevant for young women with EC where decision making after definitive hysterectomy may be 'too late'. Three of 37 cases where both biopsy/curettage and hysterectomy were assessed yielded discordant results. In two of these, *POLE* mutations were only detected in the hysterectomy and not in the biopsy; this most probably reflects the lack of sensitivity of the Sanger sequencing method used for detection of *POLE* mutations in this study. With next-generation sequencing there will be improved sensitivity, and this should lead to fewer false negative results due to low tumour cellularity and improved concordance.

ProMisE has been studied in non-age stratified cohorts of ECs and the distribution of molecular subtypes and relevance within the subpopulation of young women with EC not yet determined. Results from our interrogation of this large cohort of ECs in women <50 years of age demonstrated that the distribution of molecular subtypes/ProMisE is similar to what has been observed in non-age stratified population-based series [13] with the exception of a slightly higher proportion of p53wt tumours (64% compared to 50% in non-age stratified general population). These results are consistent with the overweight/obese/morbidly obese status of over 50% of our cohort. MMRd and p53abn tumours were diagnosed at slightly lower frequencies in this cohort of young women (19% and 4%, respectively) compared with the population-based series (28% and 12%, respectively). The prevalence of POLE ECs in the full cohort of young women (13%) is consistent with the literature (range of 6–13%) [13,25–27].

ProMisE was strongly prognostic in young women with EC, with the most favorable outcomes again observed in women with *POLE* mutated ECs and the worst survival in those with p53abn subtype. The predominantly obese p53wt cohort appeared to have indolent disease, with survival curves almost matching POLE. Importantly, even in this cohort of mostly low stage, low-grade endometrioid cancers, diversity of clinicopathological parameters and outcomes exist and ProMisE can help discern these differences.

Phenotypic characterization of young women with ECs in our prior series had stemmed from the recognized high proportion of conditions of excess estrogen, both exogenous, e.g. unopposed estrogen or tamoxifen therapies, and endogenous, e.g. obesity or polycystic ovarian syndrome (PCOS) [28]. We had also recognized a cohort of young women suspected to have Lynch syndrome. We were most interested, however, in a third cohort of young women who did not appear to have either of these traditional risk factors [10]. What was driving the development of EC in these individuals? We were interested in characterizing this subset in terms of molecular features and outcomes, to determine if in some of these 'Neither' cases conservative approach or deviation from standard of care would be inappropriate.

Clinical risk group classification did reveal significant differences in ProMisE subtype, and several demographic and clinicopathological parameters (race/ethnicity, grade, histotype, stage, chemotherapy or radiation treatment, and synchronous endometrial and ovarian carcinomas (SEOCs)). However, these phenotypes were not associated with any of the measured outcome parameters (OS, DSS or PFS), thus the clinical value of these assignments is questionable. In contrast, the prognostic strength of ProMisE is apparent across the full cohort, even within clinical risk groups ('High estrogen', 'Lynch-like').

The most notable differences in the 'Neither' clinical risk group warrant consideration as they all could influence management decisions. Firstly, 'Neither' ECs harboured the highest representation of POLE subtype; 22% or twice the normal frequency observed in non-age restricted cohorts and 4–7 times the frequency seen in the 'High Estrogen' and 'Lynch-like' clinical risk groups. Secondly, the 'Neither' cohort had a high proportion of women of Asian race (73% of 'Neither' ECs were Asian). Thirdly, the highest proportion of SEOCs were within the 'Neither' clinical risk group; 54% of all SEOCs were within 'Neither' clinical risk group, and 22% of 'Neither' clinical risk group had SEOCs (SEOCs in 10% of full young women cohort).

Comparing our racial distribution findings with the literature is challenging as the majority of epidemiologic studies have been done in non-Hispanic Caucasian women. Representation of women of Asian descent was high in our series; over half of the total population studied. There are small series in China, Japan, and the United States [29–32] as well as one large prospective Multiethnic Cohort (MEC) [33] trial in the US that included a significant proportion of Japanese American women. In the MEC trial it was observed that the Japanese American women, who were leaner than women of other MEC ethnic groups, had an increase in EC risk with a much smaller weight gain; 5% vs. 35% needed to cause the same effect in the other ethnic cohorts. Distribution of adipose tissue is also recognized to differ between races, with Asian women having a higher body fat percentage than non-Hispanic whites with similar BMIs. The MEC trial demonstrated higher circulating levels of estrogen in Japanese Americans compared with non-Hispanic whites independent of BMI. Higher circulating estrogen levels have been

Table 3
Multivariable analysis of relation of ProMisE and measured clinicopathological parameters to survival (OS/DSS/PFS). We evaluated parameters available from time of first diagnosis (e.g. prior to surgical staging); age, body mass index, grade, histological subtype and adjusting for treatment. Reference groups for comparison of categorical variables are noted in brackets. For continuous variables (age, BMI) hazard ratios reflect the risk associated with incremental increases.

	# of events/total *n*		Hazard Ratio (95% CI)	LRT *p*-value
OS	8/86			
ProMisE subtype (reference: p53wt)		MMRd	5.2 (0.9–46.7)[F]	**0.017**
		POLE	0.5 (0.0–9.3)[F]	
		p53abn	12.8 (0.6 ≥ 100)[F]	
Age at surgery			1.1 (0.9–1.3)[F]	0.535
BMI			1.1 (1.0–1.3)[F]	**0.004**
Tumour grade (reference: grade 1/2)		Grade 3	6.7 (0.8–131.1)[F]	**0.044**
Histology (ref: endometrioid)		Non-endometrioid	1.0 (0.1–8.4)[F]	0.756
DSS	7/84			
ProMisE subtype (reference: p53wt)		MMRd	8.9 (1.0 ≥ 100)[F]	**0.010**
		POLE	0.8 (0.0–33.2)[F]	
		p53abn	24.2 (0.74 ≥ 100)[F]	
Age at surgery			1.04 (0.8–1.4)[F]	0.640
BMI			1.2 (1.0–1.3)[F]	**0.005**
Tumour grade (reference: grade 1/2)		Grade 3	8.6 (0.9 ≥ 100)[F]	**0.030**
Histology (ref: endometrioid)		Non-endometrioid	1.0 (0.07–8.9)[F]	0.725
PFS	14/86			
ProMisE subtype (reference: p53wt)		MMRd	1.4 (0.2–7.4)[F]	0.139
		POLE	1.0 (0.09–6.6)[F]	
		p53abn	33.9 (1.1–62)[F]	
Age at surgery			0.87 (0.8–0.9)[F]	**0.004**
BMI			1.01 (1.0–1.1)[F]	0.594
Tumour grade (reference: grade 1/2)		Grade 3	1.2 (02–5.6)[F]	0.909
Histology (ref: endometrioid)		Non-endometrioid	0.6 (0.0–5.3)[F]	0.221

F = Firth's penalized maximum likelihood bias reduction to estimate hazard ratio for parameters with low number of measured events. Note all HRs and CIs have been rounded to one decimal place for table presentation (rounded up for 0.5 values). Statistical significance ($p < 0.05$) indicated in bold.

recorded in Japanese American women as compared to non-Hispanic Caucasians. These data support the concept that the threshold of 'too much' or 'estrogen/progesterone imbalance' may be different between individuals [33].

The literature on the prevalence of synchronous endometrial and ovarian carcinomas (SEOCs) is somewhat discordant, perhaps secondary to age of cohort studied, and pathology criteria used to define SEOC [24,34]. In young women, Walsh et al., reported up to 25% of apparent organ-confined ECs may have coexisting ovarian carcinomas [24]. In our study, SEOCs were seen in 25 (10%) of the full cohort of 257. Only four of 25 (16%) SEOCs in the full cohort were MMRd, consistent with the literature demonstrating that most SEOCs are MMR intact [35,36]. Given the challenges in detecting SEOCs, even with imaging, intraoperative assessment, and tumour markers, the high frequency of SEOCs in the 'Neither' subset may suggest conservative management options of delayed hysterectomy or hysterectomy with preservation of the ovaries is inappropriate.

We were unable to demonstrate clear differences in progesterone management across this cohort, with most women missing data, and specific decision criteria were not available even for those where treatment was documented, e.g. when/why definitive hysterectomy vs. continued conservative management. Our results mirror other retrospective series where diverse treatments (dose, duration, delivery), patient populations (<40 years of age, <50), and outcome measures (cancer-specific, fertility) prohibit drawing clear conclusions [22,37]. Even through meta-analysis or systematic reviews of conservative/fertility sparing management of atypical hyperplasia or endometrial cancer in young women, no clear predictive biomarkers associated with remission, recurrence, pregnancy or progression have been identified that held up on multivariate analysis [21,34,38,39].

Strengths of this series includes a very high number of cases for a proportionally rare subgroup (~14% of ECs in our catchment [6]) that is often transient and challenging to obtain accurate clinical data and follow-up on. We used a validated tool (ProMisE) with established molecular methods and confirmed associations of ProMisE subtype with clinicopathological parameters and outcomes as witnessed in non-age stratified EC cohorts. There were multiple influencing factors that could not be reliably obtained in this cohort (e.g., diabetes, OCP use) and, even for parameters obtained, data was not complete in all individuals. However, missing data analyses do not show evidence of biases introduced. We acknowledge the artificial and imperfect definitions of our clinical risk groups, with our earlier publication being from an era when mismatch immunohistochemistry was not routinely performed [10].

In summary, we have completed a comprehensive first step in characterization of young women with EC; demonstrating clinicopathological, molecular and survival differences and the prognostic value of a pragmatic classification tool. ProMisE subgroup, not clinical risk group, was associated with outcomes, and that association was maintained on multivariable analysis with correction for other clinicopathological parameters. ProMisE can provide a framework within which predictive biomarkers and treatment (conventional, hormonal, immune) efficacy can be assessed in future trials. We foresee and support the development of clinical algorithms for young women with EC where molecular classification (e.g. ProMisE) of diagnostic biopsy/curettage will begin to direct care. In the short-term, ProMisE can immediately impact management in young women by identifying women with MMRd ECs who could receive expedited HCP referrals and testing prior to any surgical decision-making. If Lynch syndrome was identified and depending on age and specific mutation [40] she may be directed *against* conservative management (e.g. delayed hysterectomy/BSO). Similarly, women with p53abn tumours would be recommended to undergo standard surgical staging ± adjuvant therapy, and conservative management would be inappropriate. This cohort confirmed prior observations that *POLE* -mutated ECs have aggressive histopathological features yet have excellent outcomes and 'need' for treatment in these individuals is still unclear. We hypothesize that the greatest benefit in progesterone management will be seen in women with non-ultramutated (POLE) and non-hypermutated (MMRd) tumours, e.g., p53wt ECs that encompass the majority of young women cases. ProMisE stratification will enable study within these select cohorts. At present there are minimal evidence-based or biologically-informed guidelines for young women with EC, therefore these steps towards molecular refinement of EC in

young women are encouraging. We look forward to an era of greater precision, determining care based on tumour characteristics, host factors, and patient choice.

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Conflict of interest statement

The Authors have no conflicts of interest to declare.

Author contribution

JMc and CBG conceived, planned, and summarized the project. Cases (with clinical data and outcomes) were contributed by JMc, CBG, AB, MK, SB, and SK. Dataset assembly/organization by HB and SL with molecular methodologies performed by HB, LH, KS, WY, and AL. MMc provided intellectual contribution and edits. SL and AT performed the statistical analyses. All authors contributed to manuscript writing and editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.03.098.

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