Supplementary Information

Paired genomic profiling reveals a continuum of genomic relatedness in synchronous endometrial and ovarian carcinomas

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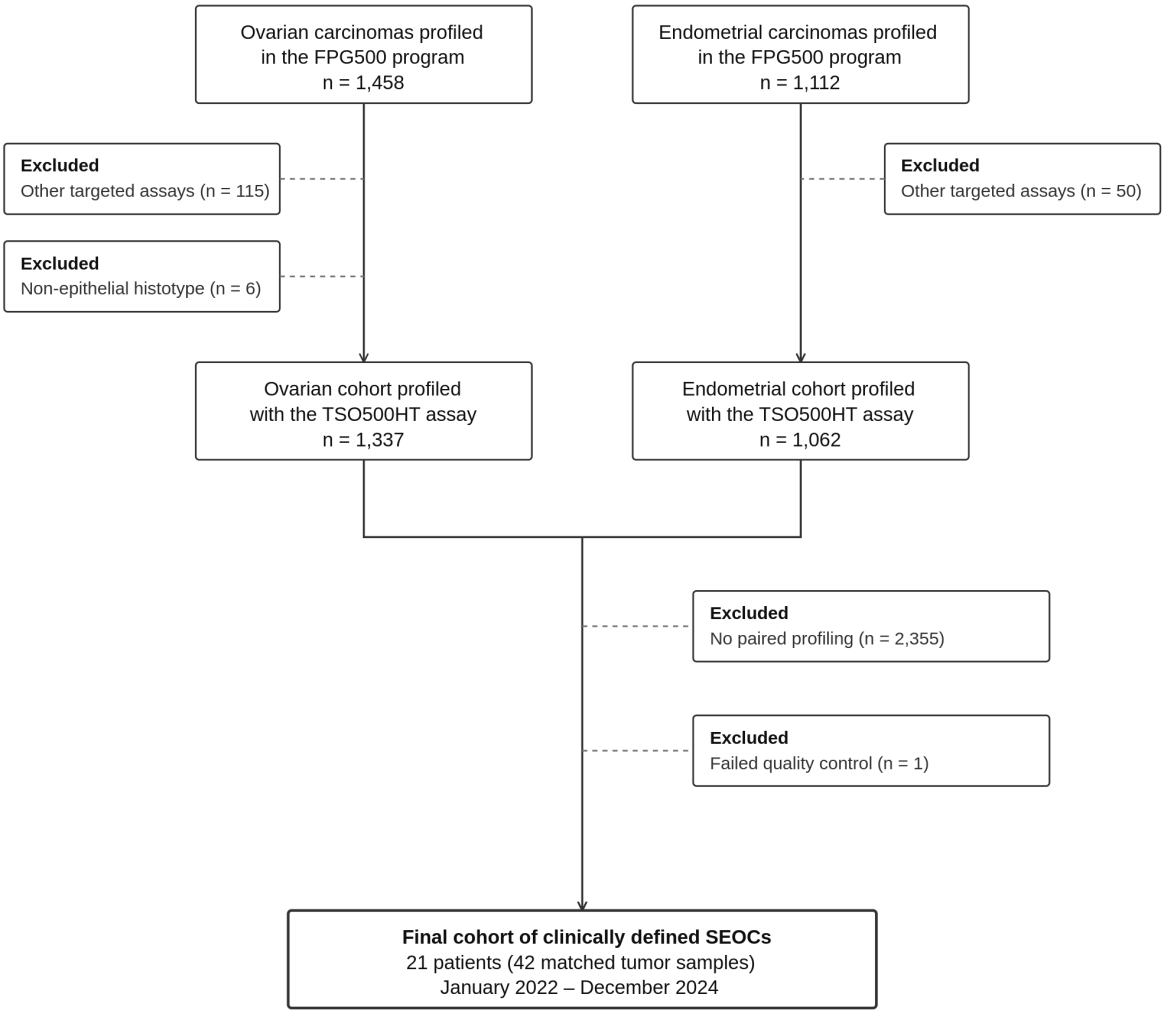
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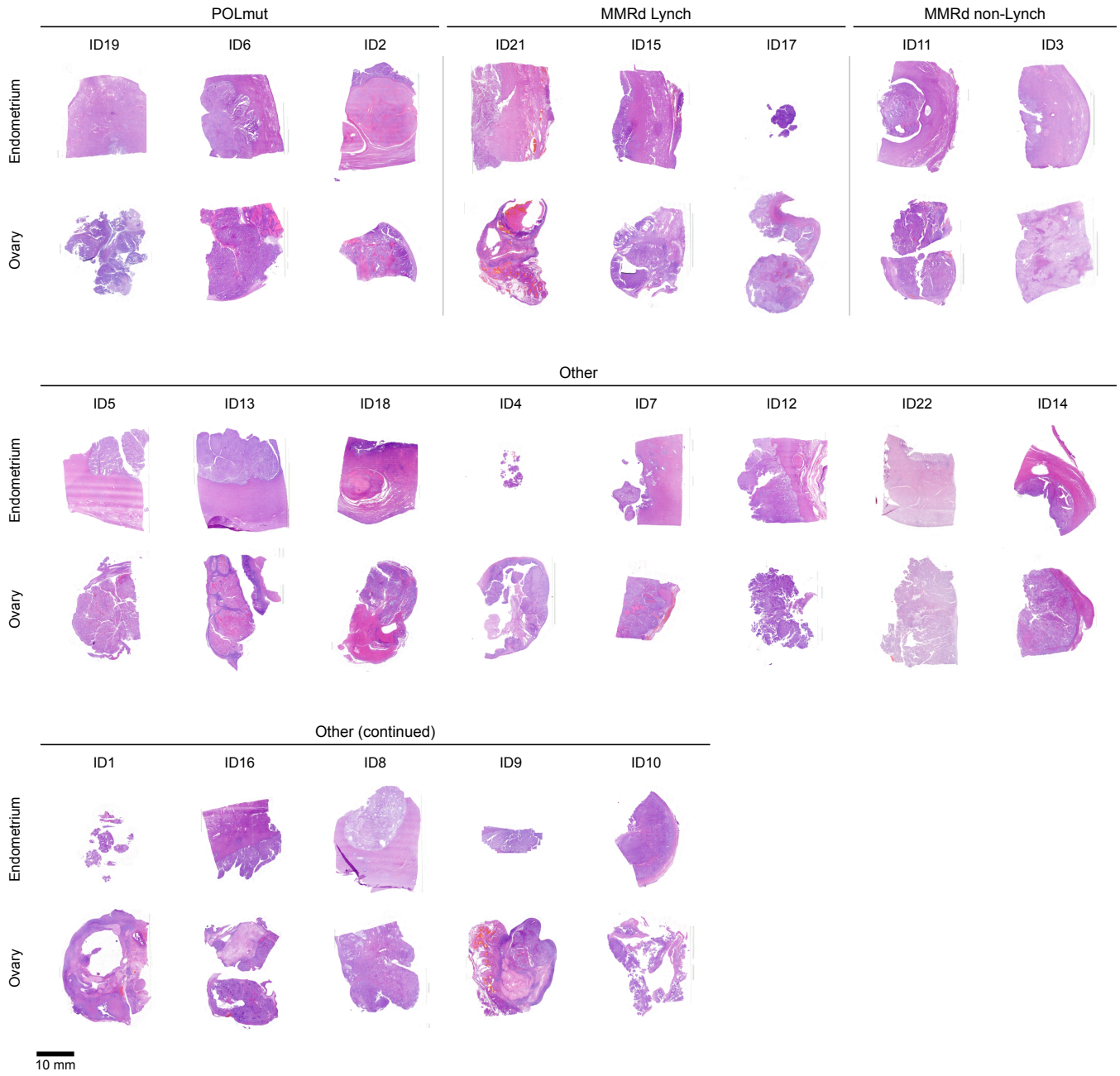
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Supplementary Figure 1 | Study flow diagram.

Ovarian and endometrial carcinomas profiled within the institutional FPG500 comprehensive genomic profiling program between January 2022 and December 2024 were restricted to tumors analyzed with the TruSight Oncology 500 High-Throughput (TSO500HT) assay and, for ovarian tumors, to epithelial histotypes. Patients with both an endometrial and an ovarian tumor profiled were retained; one patient (ID20) was excluded because one tumor component failed quality control, yielding 21 patients with clinically defined SEOC (42 matched tumor samples). Counts refer to tumor samples, except for the quality-control exclusion, which refers to one patient.

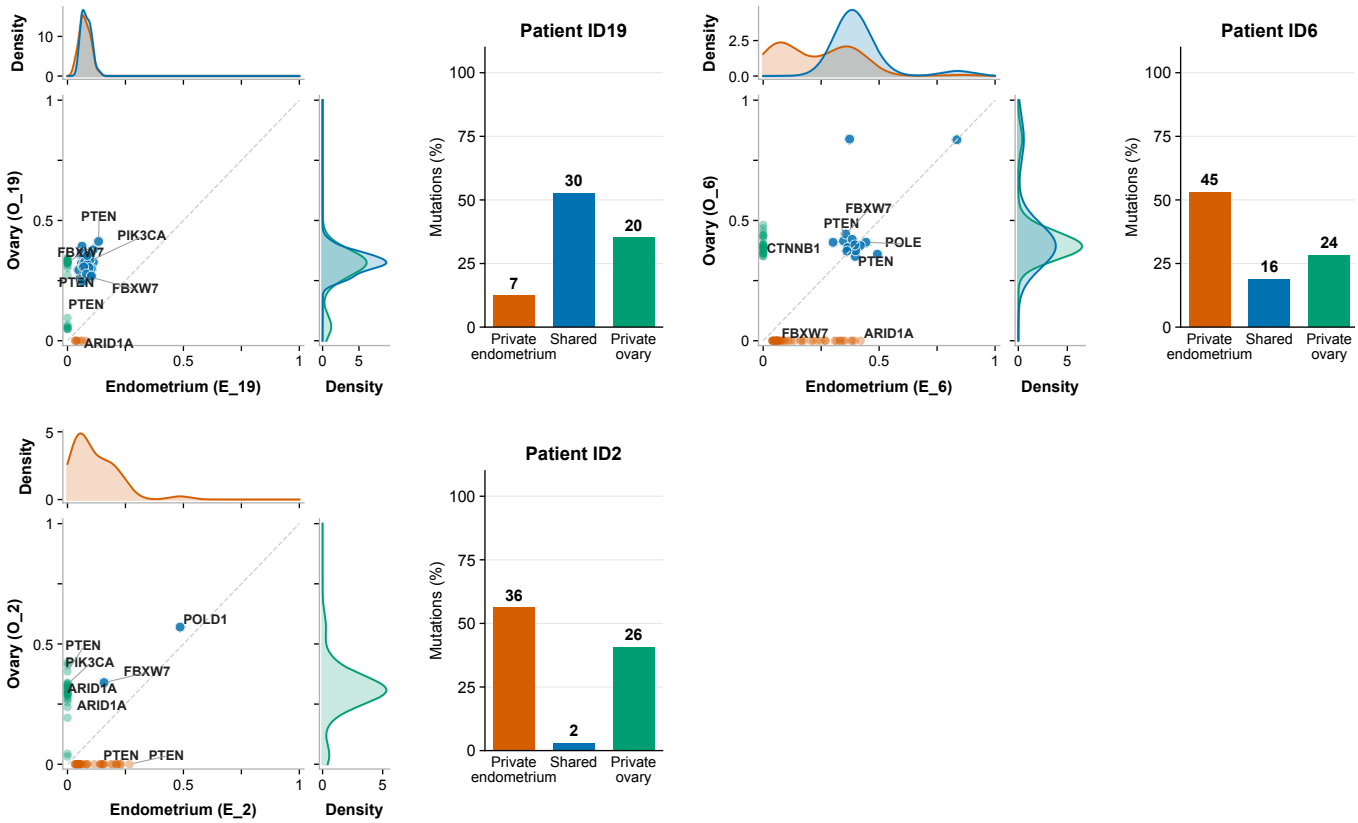


Supplementary Figure 2 | Hematoxylin and eosin-stained sections of the profiled specimens.

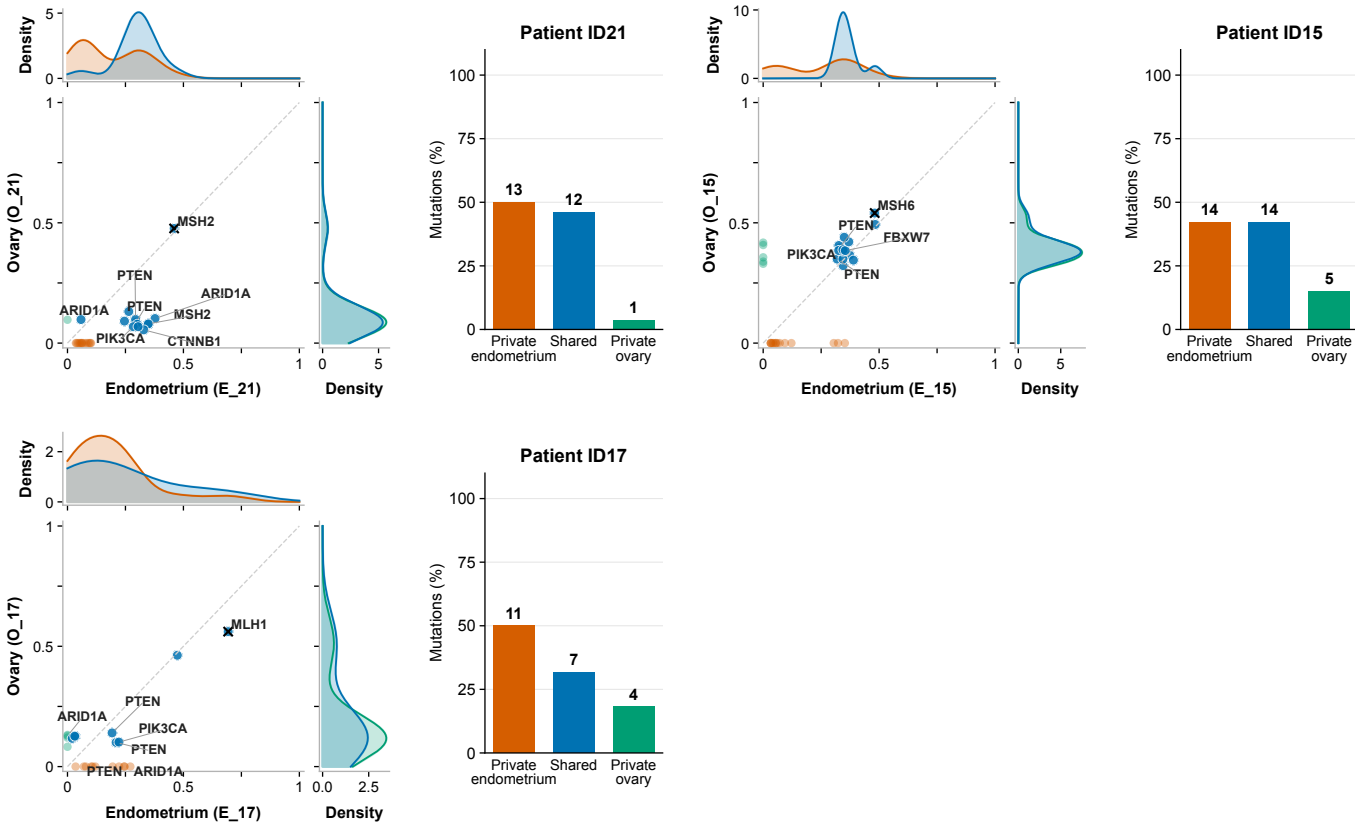
Whole-section scans of the endometrial (top) and ovarian (bottom) specimens profiled in each of the 21 patients, grouped by molecular subgroup and ordered as in Figure 2a. All sections are shown at the same scale; scale bar, 10 mm.

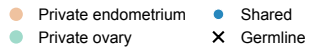
Supplementary Figure 3 (1 of 3)

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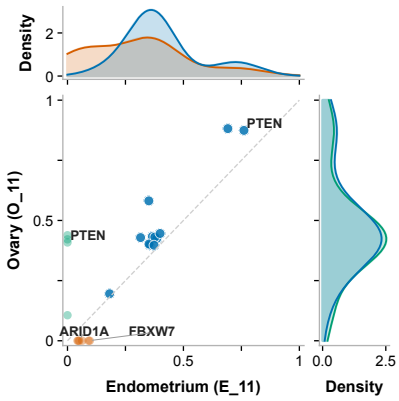
MMRd Lynch

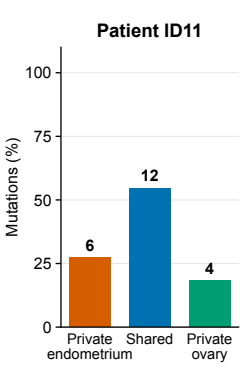


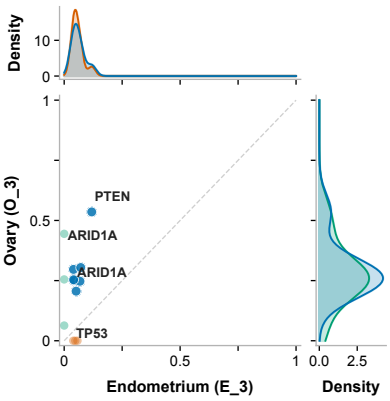


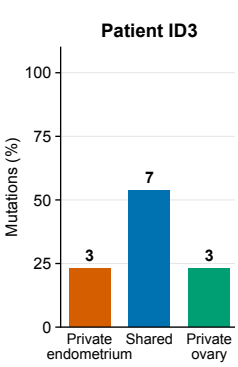
Supplementary Figure 3 (continued, 2 of 3)

MMRd non-Lynch

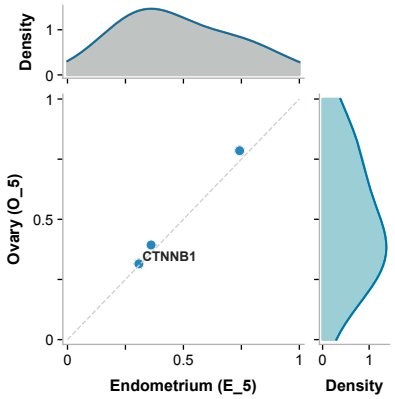


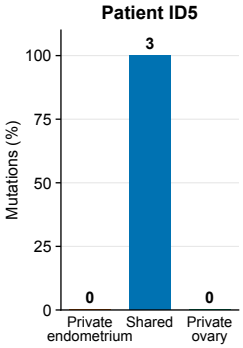


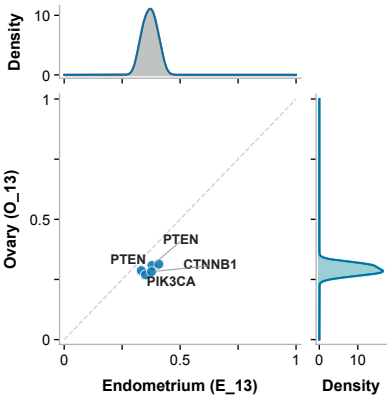


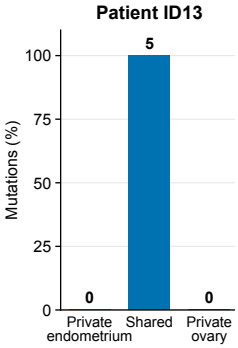


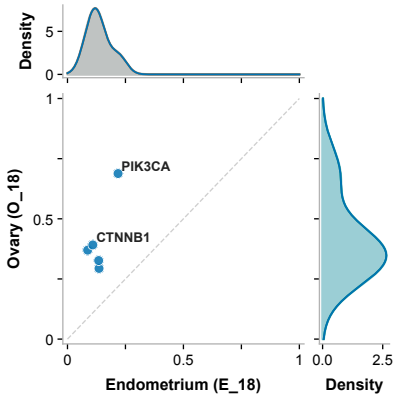
Other

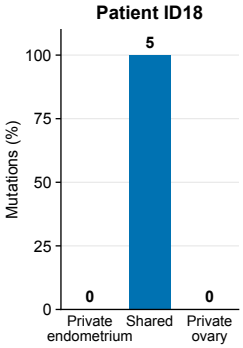


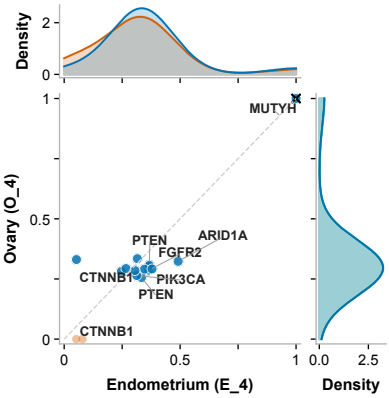


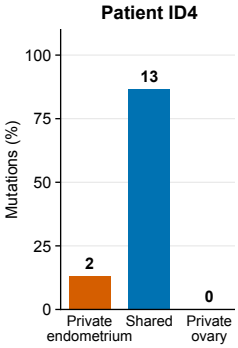


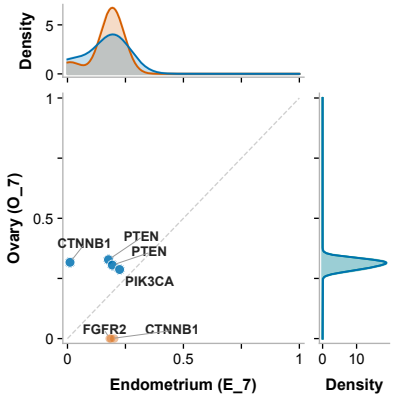


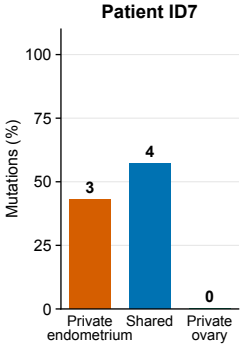


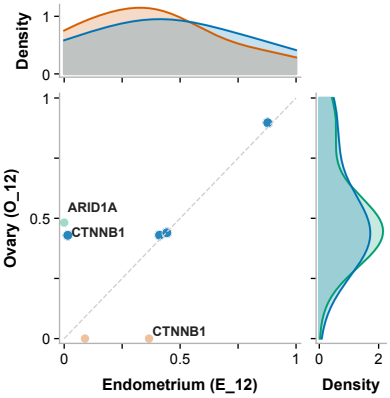


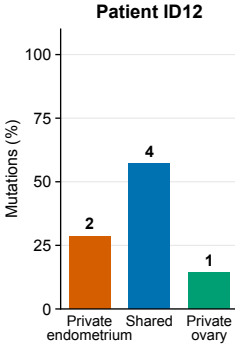








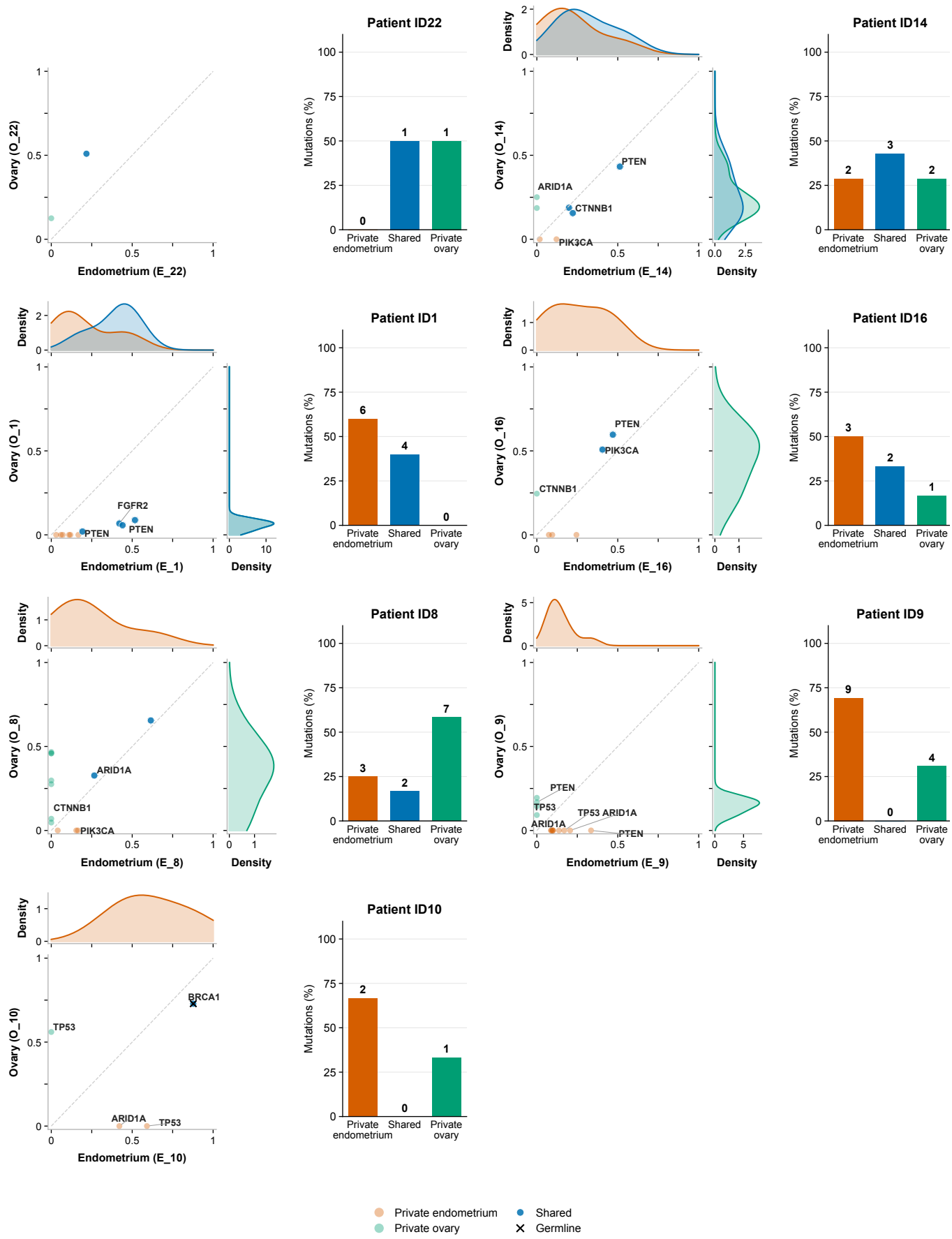




Private endometrium
Shared
Private ovary
Germline

Supplementary Figure 3 (continued, 3 of 3)

Other (continued)



Supplementary Figure 3 | Paired variant architecture of all 21 synchronous endometrial–ovarian tumor pairs.

For each pair, grouped by molecular subgroup and ordered as in Figure 2a: left, variant allele fractions (VAF) of retained variants in the endometrial (x axis) and ovarian (y axis) tumor, with marginal density plots (omitted when fewer than three variants are available); variants private to the endometrium, private to the ovary or shared are colored as indicated, confirmed germline variants are marked with a cross, and selected genes are labeled. Right, shared and private mutations as a percentage of the pair total, with counts above the bars. Pairs shown in detail in Figures 3–5 are included for completeness.

Supplementary Table 1 | Clinical and histopathological characteristics of the synchronous endometrial–ovarian cohort (n = 21), by molecular subgroup.

Patient	Ovary						Endometrium							Endometriosis	TMB (mut/Mb)	
	Histotype	Grade	Stage	Laterality	p53	MMR	Histotype	Grade	Stage	Myom. invasion	LVSI	p53	MMR		Ovary	Endometrium
POLmut																
ID2	Endometrioid	G3	IC2	Unilateral	wt	proficient	Endometrioid	G2	IA	<50%	absent	wt	proficient	present	89.6	100.1
ID6	Endometrioid	G3	IIB	Unilateral	wt	proficient	Carcinosarcoma	G3	IB (IIC)	>50%	substantial	wt	proficient	present	239.1	383.3
ID19	Endometrioid	G2	IC2	Bilateral	wt	indeterminate*	Endometrioid	G1	IA1	<50%	absent	wt	proficient	absent	409.4	214.7
MMRd Lynch																
ID15	Endometrioid	G2	IIA	Unilateral	wt	deficient	Endometrioid	G2	IA	<50%	absent	wt	deficient	present	55.7	67.2
ID17	Mixed	G3	IC2	Bilateral	wt	deficient	Endometrioid	G2	IA1	<50%	absent	wt	deficient	present	23.6	32.3
ID21	Endometrioid	G2	IA	Unilateral	wt	deficient	Endometrioid	G2	IA	<50%	absent	wt	deficient	absent	43.3	58.9
MMRd non-Lynch																
ID3	Mixed	G3	IC2	Bilateral	wt	deficient	Endometrioid	G2	IA	<50%	absent	wt	deficient	present	20.2	7.2
ID11	Endometrioid	G3	IIA	Unilateral	wt	deficient	Endometrioid	G2	IA	<50%	absent	wt	deficient	absent	48.7	49.7
Other																
ID1	Endometrioid	G2	IC2	Unilateral	wt	proficient	Endometrioid	G1	II	<50%	absent	wt	deficient	present	1.6	14.2
ID4	Endometrioid	G2	IB	Bilateral	wt	proficient	Endometrioid	G2	IIIC1	>50%	substantial	wt	proficient	present	11.8	15.1
ID5	Endometrioid	G2	IA	Unilateral	wt	proficient	Endometrioid	G2	IA	<50%	absent	wt	proficient	present	6.3	5.5
ID7	Endometrioid	G3	IC2	Unilateral	wt	proficient	Endometrioid	G2	IA	<50%	absent	wt	proficient	absent	3.9	7.1
ID8	Endometrioid	G3	IIA	Unilateral	wt	proficient	Endometrioid	G2	IA	<50%	absent	wt	proficient	present	11.8	5.5
ID9	HGSC	G3	IIB	Unilateral	mut	proficient	Endometrioid	G2	IA	<50%	absent	wt	proficient	absent	4.7	11.0
ID10	HGSC	G3	IC2	Bilateral	mut	unk	HGSC	G3	II	>50%	absent	mut	proficient	absent	4.8	7.9
ID12	Endometrioid	G2	IIB	Unilateral	wt	proficient	Endometrioid	G2	II	>50%	substantial	wt	proficient	present	6.3	4.7
ID13	Endometrioid	G2	IC1	Unilateral	wt	proficient	Endometrioid	G3	IA (IIC)	<50%	absent	wt	proficient	absent	5.5	4.7
ID14	Endometrioid	G3	IC1	Unilateral	wt	indeterminate*	Endometrioid	G2	IA2	<50%	absent	wt	indeterminate*	absent	8.7	5.5
ID16	Endometrioid	G2	IA	Unilateral	wt	proficient	Endometrioid	G2	IA	<50%	absent	wt	deficient	present	2.4	7.8
ID18	Endometrioid	G2	IC1	Unilateral	wt	proficient	Endometrioid	G1	IA	<50%	absent	wt	proficient	absent	4.0	4.8
ID22	Endometrioid	G2	IC2	Unilateral	wt	proficient	Endometrioid	G2	IA (IA2)	<50%	absent	wt	proficient	absent	1.6	0.8

LVSI, lymphovascular space invasion; Myom., myometrial; MMR, mismatch repair status (by immunohistochemistry); p53, p53 immunohistochemistry (wt, wild-type; mut, mutant pattern); HGSC, high-grade serous carcinoma; Mixed, mixed clear cell–endometrioid carcinoma. *Indeterminate IHC; unk, not available. Laterality refers to ovarian involvement. Endometriosis, histologically documented endometriosis. TMB, tumor mutational burden (mutations per megabase).

Supplementary Table 2 | Clinically or biologically relevant germline variants identified in the cohort.

Patient	Neoplasm	Gene	Nomenclature p.	Nomenclature c.	VAF in tumor (%)	Genetic Note	Clinical Note
ID4	Endometrium	MUTYH	p.?	c.463-1G>A	100	Homozygous germline	Consistent with MUTYH-associated polyposis (biallelic)
ID4	Ovary	MUTYH	p.?	c.463-1G>A	100	Homozygous germline	Consistent with MUTYH-associated polyposis (biallelic)
ID7	Endometrium	CHEK2	p.I157T	c.470T>C	44	Heterozygous germline	Moderate-penetrance germline variant; no evidence of tumor involvement
ID7	Ovary	CHEK2	p.I157T	c.470T>C	51.2	Heterozygous germline	Moderate-penetrance germline variant; no evidence of tumor involvement
ID9	Endometrium	MUTYH	p.G396D	c.1187G>A	39.9	Heterozygous germline	Monoallelic MUTYH carrier; no evidence of tumor involvement
ID9	Ovary	MUTYH	p.G396D	c.1187G>A	59.4	Heterozygous germline	Monoallelic MUTYH carrier; no evidence of tumor involvement
ID10	Endometrium	BRCA1	p.E1373*	c.4117G>T	88	Heterozygous germline + LOH (biallelic inactivation)	Consistent with HRD due to biallelic BRCA1 inactivation
ID10	Ovary	BRCA1	p.E1373*	c.4117G>T	73.4	Heterozygous germline + LOH (biallelic inactivation)	Consistent with HRD due to biallelic BRCA1 inactivation
ID15	Endometrium	MSH6	p.R482*	c.1444C>T	47.7	Heterozygous germline	Consistent with Lynch syndrome
ID15	Ovary	MSH6	p.R482*	c.1444C>T	54.5	Heterozygous germline	Consistent with Lynch syndrome
ID17	Endometrium	MLH1	p.E663D	c.1989G>T	69.7	Heterozygous germline	Consistent with Lynch syndrome
ID17	Ovary	MLH1	p.E663D	c.1989G>T	55.7	Heterozygous germline	Consistent with Lynch syndrome
ID21	Endometrium	MSH2	p.Q239*	c.715C>T	46.7	Heterozygous germline	Consistent with Lynch syndrome
ID21	Ovary	MSH2	p.Q239*	c.715C>T	47.7	Heterozygous germline	Consistent with Lynch syndrome

VAF, variant allele frequency in tumor tissue; LOH, loss of heterozygosity; HRD, homologous recombination deficiency.

Supplementary Table 3 | Paired mutational and copy-number architecture of the 21 synchronous endometrial–ovarian tumor pairs, by molecular subgroup.

Patient	Somatic mutations							Copy number (gene level)								
	Endometrium-private, n	Shared, n	Ovary-private, n	Total, n	Shared fraction	Directional imbalance	Architecture label	Endometrium, altered fraction	Ovary, altered fraction	Altered genes (union), n	State-concordant, n	Endometrium-private, n	Ovary-private, n	Discordant state, n	CN Jaccard index	CN private imbalance
POLmut																
ID19	7	30	20	57	0.53	−0.48	intermediate	0.016	0.016	14	2	6	6	0	0.14	0.00
ID6	45	16	24	85	0.19	0.30	intermediate	0.016	0.019	16	2	6	8	0	0.12	−0.12
ID2	36	2	26	64	0.03	0.16	independent-like / highly divergent	0.016	0.072	41	4	4	33	0	0.10	−0.71
MMRd Lynch																
ID21	13	12	1	26	0.46	0.86	intermediate	0.006	0.016	8	3	0	5	0	0.38	−0.62
ID15	14	14	5	33	0.42	0.47	intermediate	0.054	0.047	50	2	26	22	0	0.04	0.08
ID17	11	7	4	22	0.32	0.47	intermediate	0.004	0.008	4	2	0	2	0	0.50	−0.50
MMRd non-Lynch																
ID11	6	12	4	22	0.55	0.20	intermediate	0.099	0.142	82	42	9	31	0	0.51	−0.27
ID3	3	7	3	13	0.54	0.00	intermediate	0.027	0.045	30	7	7	16	0	0.23	−0.30
Other																
ID5	0	3	0	3	1.00	NE	low-count complete overlap	0.082	0.070	51	27	15	9	0	0.53	0.12
ID13	0	5	0	5	1.00	NE	low-count complete overlap	0.008	0.012	8	2	2	4	0	0.25	−0.25
ID18	0	5	0	5	1.00	NE	low-count complete overlap	0.041	0.158	86	15	5	65	1	0.17	−0.70
ID4	2	13	0	15	0.87	1.00	clonal-like	0.019	0.014	16	1	9	6	0	0.06	0.19
ID7	3	4	0	7	0.57	1.00	intermediate	0.027	0.025	27	0	14	13	0	0.00	0.04
ID12	2	4	1	7	0.57	0.33	intermediate	0.109	0.091	64	37	17	8	2	0.58	0.14
ID22	0	1	1	2	0.50	−1.00	intermediate	0.014	0.074	38	7	0	31	0	0.18	−0.82
ID14	2	3	2	7	0.43	0.00	intermediate	0.021	0.051	29	8	3	18	0	0.28	−0.52
ID1	6	4	0	10	0.40	1.00	intermediate	0.058	0.006	32	1	29	2	0	0.03	0.84
ID16	3	2	1	6	0.33	0.50	intermediate	0.016	0.082	45	5	3	37	0	0.11	−0.76
ID8	3	2	7	12	0.17	−0.40	intermediate	0.010	0.033	19	3	2	14	0	0.16	−0.63
ID9	9	0	4	13	0.00	0.38	independent-like / highly divergent	0.014	0.014	13	1	6	6	0	0.08	0.00
ID10	2	0	1	3	0.00	0.33	independent-like / highly divergent	0.370	0.259	256	46	123	66	21	0.18	0.22

Mutations: retained somatic variants (confirmed germline variants excluded), matched between tumors by chromosome, position, reference and alternate allele. Shared fraction = S/(E+S+O); directional imbalance = (E−O)/(E+O), NE (not evaluable) when no private variants are present. Architecture labels are descriptive: low-count complete overlap, all variants shared and <10 variants; independent-like/highly divergent, shared fraction ≤0.10; clonal-like, shared fraction ≥0.70 with ≥10 variants; intermediate, all other pairs. Copy number: gene-level calls for the 514 panel genes (median-centered log2 fold change ≥0.4, gain; ≤−0.4, loss); altered fraction = fraction of panel genes altered in each tumor. Genes altered in at least one tumor (union) are state-concordant (same non-neutral state in both), endometrium- or ovary-private, or discordant (altered in both with different states). CN Jaccard index = state-concordant/union; CN private imbalance = (endometrium-private − ovary-private)/union. Rows are ordered as in Figure 2a. CN, copy number; E, endometrium-private; O, ovary-private; S, shared.

Supplementary Table 4 | Sensitivity of the copy-number Jaccard index to the gain/loss threshold.

Patient	Gain/loss threshold (centered log2 fold change)						
	±0.2	±0.3	±0.4 (main analysis)	±0.5	±0.6	±0.8	Caller's native calls
POLmut							
ID19	0.20	0.17	0.14	0.10	0		0
ID6	0.12	0.17	0.12	0.17	0		0
ID2	0.33	0.17	0.10	0	0	0	0
MMRd Lynch							
ID21	0.18	0.31	0.38	0.33	0.50	1	0.50
ID15	0.22	0.12	0.04	0.07	0	0	0
ID17	0.18	0.50	0.50	0.50	0		
MMRd non-Lynch							
ID11	0.38	0.52	0.51	0.49	0.63	0.90	0.51
ID3	0.32	0.22	0.23	0.17	0		0
Other							
ID5	0.50	0.70	0.53	0.47	0.35		0.40
ID13	0.28	0.11	0.25	0.25	0	0	0.50
ID18	0.37	0.24	0.17	0.08	0.05	0	0.13
ID4	0.18	0.16	0.06	0	0	0	0
ID7	0.09	0	0	0	0		0
ID12	0.32	0.44	0.58	0.63	0.67	0.64	0.73
ID22	0.32	0.33	0.18	0.07	0	0	0
ID14	0.50	0.46	0.28	0.14	0	0	
ID1	0.08	0.05	0.03	0	0	0	0
ID16	0.43	0.32	0.11	0.04	0	0	0
ID8	0.13	0.17	0.16	0.18	0.40	0.50	0.25
ID9	0.14	0.11	0.08	0.17	0		0
ID10	0.29	0.20	0.18	0.14	0.12	0.17	0.17
Cohort summary							
Evaluable pairs, n	21	21	21	21	21	14	19
Median CN Jaccard (bootstrap 95% CI)	0.28 (0.18–0.32)	0.20 (0.17–0.32)	0.17 (0.11–0.25)	0.14 (0.07–0.18)	0.00 (0.00–0.05)	0.00 (0.00–0.41)	0.00 (0.00–0.25)
Spearman ρ vs ±0.4	0.54	0.82	1	0.84	0.60	0.63	0.80

CN Jaccard index (state-concordant altered genes divided by genes altered in at least one tumor) recomputed for each pair with symmetric gain/loss thresholds on the median-centered log2 fold change of the 514 panel genes, and with the copy-number caller's native gain/loss calls. Empty cells, no gene altered in either tumor at that threshold (index not defined). Medians and bootstrap 95% CIs (10,000 resamples of patients, percentile method) are computed over evaluable pairs; Spearman ρ compares the pair ranking at each setting with the main analysis (±0.4).

Supplementary Table 5 | Mutational signature analysis (SigMA) of the 42 endometrial and ovarian tumors, by molecular subgroup.

Patient	Tumor				SigMA likelihood						COSMIC v3.5 refit (POLmut)	
	Site	SigMA tumor-type model	SNVs, n	Dominant process	Clock-like	Signature 3 (HRD)	APOBEC	Signature 18	MSI	POLE	COSMIC v3.5 signatures (% of SNVs)	Cosine similarity
POLmut												
ID2	Endometrium	Uterus	340	POLE	1.00	<0.01	<0.01	—	<0.01	1.00	SBS10d 84%; SBS5 11%; SBS1 4%	0.984
ID2	Ovary	Ovary	211	POLE	<0.01	<0.01	—	1.00	<0.01	1.00	SBS10d 70%; SBS52 15%; SBS5 11%; SBS1 4%	0.990
ID6	Endometrium	Uterus	940	POLE	1.00	<0.01	<0.01	—	<0.01	1.00	SBS10a 44%; SBS10b 23%; SBS5 18%; SBS28 11%; SBS1 4%	0.991
ID6	Ovary	Ovary	352	POLE	<0.01	<0.01	—	1.00	<0.01	1.00	SBS10a 50%; SBS28 30%; SBS5 19%	0.994
ID19	Endometrium	Uterus	710	Clock-like	1.00	<0.01	<0.01	—	0.98	0.02	SBS10b 44%; SBS15 33%; SBS10a 16%; SBS1 6%	0.985
ID19	Ovary	Ovary	808	MSI	<0.01	<0.01	—	1.00	1.00	<0.01	SBS10b 39%; SBS15 23%; SBS10a 21%; SBS5 10%; SBS1 7%	0.982
MMRd Lynch												
ID15	Endometrium	Uterus	106	MSI	1.00	<0.01	<0.01	—	1.00	0		
ID15	Ovary	Ovary	43	MSI	0.99	0.01	—	<0.01	1.00	0		
ID17	Endometrium	Uterus	61	MSI	0.91	0.09	<0.01	—	1.00	0		
ID17	Ovary	Ovary	36	Clock-like	0.85	0.15	—	0	0.88	0		
ID21	Endometrium	Uterus	96	MSI	1.00	<0.01	<0.01	—	1.00	0		
ID21	Ovary	Ovary	61	MSI	1.00	<0.01	—	<0.01	1.00	0		
MMRd non-Lynch												
ID3	Endometrium	Uterus	22	MSI	0.77	0.22	0.01	—	1.00	0		
ID3	Ovary	Ovary	28	MSI	0.37	0.62	—	0.01	1.00	0		
ID11	Endometrium	Uterus	76	MSI	0.83	0.17	<0.01	—	1.00	0		
ID11	Ovary	Ovary	50	MSI	0.35	0.64	—	<0.01	1.00	0		
Other												
ID1	Endometrium	Uterus	15	MSI	0.44	0.53	0.03	—	1.00	0		
ID1	Ovary	Ovary	4	NC								
ID4	Endometrium	Uterus	36	Clock-like	0.44	0.45	0.11	—	0.01	<0.01		
ID4	Ovary	Ovary	28	HRD (Signature 3)	<0.01	<0.01	—	1.00	<0.01	<0.01		
ID5	Endometrium	Uterus	16	Clock-like	0.25	0.71	0.04	—	0.97	0		
ID5	Ovary	Ovary	14	Clock-like	0.31	0.69	—	0	0.31	0		
ID7	Endometrium	Uterus	14	HRD (Signature 3, low confidence)	0.07	0.84	0.09	—	<0.01	0		
ID7	Ovary	Ovary	8	HRD (Signature 3, low confidence)	0.29	0.41	—	0.30	0.10	0		
ID8	Endometrium	Uterus	9	Clock-like	0.83	0.08	0.09	—	0.93	0		
ID8	Ovary	Ovary	12	HRD (Signature 3)	0.34	0.63	—	0.04	0.02	0		
ID9	Endometrium	Uterus	12	Clock-like	0.09	0.84	0.07	—	0.03	0		

Patient	Tumor				SigMA likelihood						COSMIC v3.5 refit (POLmut)	
	Site	SigMA tumor-type model	SNVs, n	Dominant process	Clock-like	Signature 3 (HRD)	APOBEC	Signature 18	MSI	POLE	COSMIC v3.5 signatures (% of SNVs)	Cosine similarity
ID9	Ovary	Ovary	10	HRD (Signature 3)	0.11	0.89	—	0	0.02	0		
ID10	Endometrium	Uterus	33	HRD (Signature 3)	<0.01	0.94	0.06	—	<0.01	0		
ID10	Ovary	Ovary	17	HRD (Signature 3)	0.11	0.89	—	0	0.01	0		
ID12	Endometrium	Uterus	6	APOBEC	0.10	0.75	0.14	—	0.37	0		
ID12	Ovary	Ovary	3	NC								
ID13	Endometrium	Uterus	6	Clock-like	0.25	0.63	0.12	—	0.20	0		
ID13	Ovary	Ovary	9	HRD (Signature 3, low confidence)	0.19	0.58	—	0.23	0.08	0		
ID14	Endometrium	Uterus	16	Clock-like	0.77	0.15	0.07	—	0.69	0.01		
ID14	Ovary	Ovary	13	Clock-like	0.26	0.74	—	0	0.35	0		
ID16	Endometrium	Uterus	17	MSI	0.44	0.50	0.06	—	1.00	0		
ID16	Ovary	Ovary	9	Clock-like	0.41	0.39	—	0.20	0.02	0		
ID18	Endometrium	Uterus	11	HRD (Signature 3)	0.02	0.94	0.04	—	0.33	0		
ID18	Ovary	Ovary	9	HRD (Signature 3)	0.13	0.83	—	0.04	0.03	0		
ID22	Endometrium	Uterus	4	NC								
ID22	Ovary	Ovary	2	NC								

Dominant mutational process assigned by SigMA (COSMIC v2-based reference) from the broader single-nucleotide variant (SNV) set used for signature analysis (see Methods), with the uterus tumor-type model for endometrial tumors and the ovary model for ovarian tumors (MSK-IMPACT 410-gene platform setting). SNVs, number of SNVs analyzed. Likelihoods are SigMA likelihood scores for each candidate process; APOBEC is part of the uterus model only and Signature 18 of the ovary model only (—, not part of the model). SigMA's POLE category corresponds to COSMIC v2 Signature 10 and was interpreted as polymerase-proofreading-associated (see Methods). HRD, homologous recombination deficiency; MSI, microsatellite instability; NC, not classified (fewer than 5 SNVs). For the POLmut tumors, the same SBS96 profiles were refitted to COSMIC v3.5 reference signatures with SigProfilerAssignment (v1.1.3), which distinguishes POLE-associated (SBS10a/b) from POLD1-associated (SBS10c/d) polymerase-proofreading signatures; signatures contributing ≥0.5% of substitutions are listed, with the cosine similarity between observed and reconstructed profiles.