Supplemental Tables

Table S1 Demographics from the OTTA cohorts representing the test set and excluded cases

			MAY	UKO	HOP
Testing set (N=524)	N		428	86	10
	Age	Mean (Range) years	61.9 (21-93)	61.5 (32-90)	50.2 (38-67)
	Type	HGSC	292 (68%)	44 (51%)	0
		EC	77 (18%)	11 (13%)	9 (90%)
		CCC	30 (7%)	16 (19%)	1 (10%)
		MC	14 (3%)	8 (9%)	0
		LGSC	15 (3%)	7 (8%)	0
	Stage	I/II	94 (22%)	44 (51%)	9 (90%)
		III/IV	333 (78%)	42 (49%)	1 (10%)
	Outcome	Median follow time up for censored patients, (range) in months	52 (1.8 – 140)	56 (43-121)	N/A
		N of deaths	251	33	NA
		5-year survival rate	43%	59%	NA
Excluded cases based on missing IHC (N=117)*	N		96	15	6
	Type	HGSC	66 (69%)	10 (66%)	0
		EC	11 (11%)	1 (7%)	0
		CCC	6 (6%)	0	0
		MC	5 (5%)	2 (13%)	0
		LGSC	5 (5%)	1 (7%)	0
		Mixed	3 (3%)	0	3 (50%)
		other	0	1 (7%)	1 (17%)
		SC ungraded	0	0	2 (33%)
Excluded cases based on COSP incompatible original pathology	N		20	18	33

(N=71)**					
	Type	SC ungraded	3 (15%)	6 (33%)	26 (79%)
		Mixed	14 (70%)	2 (11%)	3 (9%)
		Other	0	7 (39%)	4 (12%)
		Undifferentiated	1 (5%)	1 (6%)	0
		Unknown	2 (10%)	2 (11%)	0

* Cases without the original diagnosis of one of the five major types
* Cases with incomplete immunostaining data on at least one of ten markers tested
N/A not available

Table S2 Antibodies, details of immunohistochemical protocols and scoring cut-off

Marker	Supplier	Clone	Antigen retrieval	Primary dilution	Amplification step	Categorized as Negative	Categorized as Negative	Background information
ARID1A	Abgent	3H2	CC1-std	1:50	UltraMap anti-Ms HRP 16min	Retained staining in ≥ 10% of tumor cells	Reduced staining in < 10% of tumor cells	ARID1A is part of a chromatin remodelling complex mutated in EC and CCC, with subsequent loss of expression.
DKK1	R&D Systems	Poly	Prot2-8m	1:25	UltraMap anti-Rb HRP 16min	Absence of staining	Any staining ≥ 1% of tumor cells	Dickkopf-related protein 1 is an inhibitor of the Wnt signalling pathway, which is altered in a subset of EC.
HNF1B	Sigma	Poly	CC1-std	1:100	Universal Secondary	Absence or focal in <50% of tumor cells	Diffuse staining ≥ 50% of tumor cells*	Hepatocyte nuclear factor 1B is a CCC cell lineage marker.
MDM2	Zymed	IF2	CC1-std	1:50	UltraMap anti-Ms HRP 16min	Absence of staining	Any staining ≥ 1% of tumor cells	MDM2 is involved in ubiquitation of wild type TP53.
CDKN2A/p16	mtm laboratories	E6H4	CC1-std	1:2	UltraMap anti-Ms HRP 16min	Absence or patchy in <90% of tumor cells	Block staining ≥ 90% of tumor cells	The cyclin dependent kinase inhibitor 2A is overexpressed in highly proliferative tumors as futile attempt to stop cell cycle.
TP53	Dako	DO-7	CC1-std	1:400	Universal secondary	Wild type pattern with nuclear staining between ≥ 1% and < 50%	Complete absence of staining or or diffuse staining in ≥ 50% of tumor	The tumor suppressor gene TP53 is ubiquitously mutated in HGSC.

								cells
PGR	Ventana	1E2	CC1-std	1:1	Universal secondary	Absence of staining	Any staining ≥ 1% of tumor cells	Hormone receptor highly expressed in EC.
TFF3	Abnova	3D9	CC2-std	1:50	Universal secondary	Absence or focal in <50% of tumor cells	Diffuse staining ≥ 50% of tumor cells*	Trefoil factor 3 is a marker of mucinous gastrointestinal epithelium and therefore a marker for MC.
VIM	Zymed	V9	CC2-mild	1:50	Universal secondary	Absence or focal in <50% of tumor cells	Diffuse staining ≥ 50% of tumor cells*	Vimentin is an intermediate filament expressed in mesenchymal cells as well as normal endometrium and a subset of EC.
WT1	Dako	6F-H2	CC1-std	1:50	Universal secondary	Absence of staining	Any staining ≥ 1% of tumor cells	Wilms tumor gene 1 is very sensitive and specific serous cell lineage marker.

Std-standard

* Changes to the scoring categories in comparison to TB_COSPv1, in which any staining ≥ 1% of tumor cells was considered positive.

Table S3 Training set revision of the COSP model – Areas under the curve (AUC) by histology and model

	A_COSP*	TB_COSPv1*	TB_COSPv2
HGSC	0.981	0.982	0.999
EC	0.978	0.991	0.999
CCC	0.994	0.995	0.999
MC	0.993	0.999	0.999
LGSC	0.991	0.981	0.998

* Previously published (24) A_COSP, archival based calculator for ovarian carcinoma subtype probability, TB_COSPv2, tumor bank based calculator for ovarian carcinoma subtype probability version 2; N=253 tumor bank cohort; HGSC-high-grade serous carcinoma, EC-endometrioid carcinoma, CCC-clear cell carcinoma, MC-mucinous carcinoma, LGSC-low-grade serous carcinoma

Table S4 Test for heterogeneity for marker expression between training and testing set

Marker	HGSC			LGSC			EC			CCC			MC		
	TR	TE	p	TR	TS	p	TR	TS	p	TR	TS	p	TR	TS	p
ARID1A	2.3	1.8	0.68	11.1	13.8	0.84	22.6	22.5	0.99	31.2	60.5	0.012	0	4.7	0.59
CDKN2A	58.3	64.6	0.16	0	17.2	0.18	6.5	19.1	0.097	9.4	4.6	0.42	16.7	19.0	0.89
DKK1	0	12.6	**<0.0001**	0	0		41.9	61.8	0.054	0	18.6	0.0098	0	28.6	0.14
HNF1B	0.6	0.6	0.99	0	10.3	0.31	0	13.5	0.031	87.5	72.1	0.10	16.7	42.9	0.24
MDM2	2.3	16.4	**<0.0001**	44.4	58.6	0.45	35.5	61.2	**0.0040**	75.0	58.1	0.13	0	0	
PGR	30.3	31.3	0.82	44.4	68.9	0.18	77.5	77.5	0.99	0	0		0	14.3	0.32
TFF3	1.1	0.6	0.49	0	31.0	0.055	33.3	43.8	0.26	0	2.3	0.38	83.3	66.7	0.43
TP53 0	30.9	27.8	0.43	11.1	13.8	0.83	3.2	11.2	0.31	9.4	14.0	0.43	16.7	19.1	0.87
TP53 2	62.9	62.9		0	3.4		6.5	10.1		3.1	0		33.3	40.8	
VIM	8.6	3.8	0.023	33.3	20.7	0.43	48.4	23.6	0.0095	9.4	2.3	0.18	0	0	
WT1	92.0	94.7	0.22	100	100		3.2	15.7	0.069	0	0		0	19.4	0.25

TR training set. TE testing set. Bold: significant p-value <0.005 after adjusting for multiple comparison (Bonferroni)

Table S5 Pairwise agreement of histological types in the testing set by classification method for A_COSP

		A_COSP							Cohen's κ (95% CI)
		All	HGSC	EC	CCC	MC	LGSC	Concordance Rate	
Original type	All	**524**	361	84	61	15	3	75%	0.516 (0.451-0.581)
	HGSC	336	**301**	19	13	2	1	90%	
	EC	97	39	**47**	9	2	0	48%	
	CCC	47	6	6	**34**	1	0	73%	
	MC	22	4	6	3	**9**	0	41%	
	LGSC	22	11	6	2	1	**2**	9%	
		A_COSP							Cohen's κ (95% CI)
		All	HGSC	EC	CCC	MC	LGSC	Concordance Rate	
TB_COSPv2	All	**524**	361	84	61	15	3	88%	0.739 (0.686-0.792)
	HGSC	342	**331**	1	10	0	0	97%	
	EC	89	5	**73**	8	3	0	82%	
	CCC	43	0	6	**36**	1	0	84%	
	MC	21	4	4	2	**11**	0	52%	
	LGSC	29	21	0	5	0	**3**	10%	

HGSC-high-grade serous carcinoma, EC-endometrioid carcinoma, CCC-clear cell carcinoma, MC-mucinous carcinoma, LGSC-low-grade serous carcinoma

Table S6 Univariate Cox model in the testing set comparing A_COPS and TB_COSPv2.

		A_COSP	TB_COSPv2
Histological type*	HGSC (Reference) p-value overall	1.00, p<0.0001	1.00, p<0.001
	EC	0.43 (0.28-0.64), p<0.001	0.35 (0.22 -0.52), p<0.001
	CCC	0.57 (0.37-0.85), p=0.0047	0.56 (0.33-0.88), p=0.010
	MC	0.52 (0.18-1.30), p=0.10	0.80 (0.41-1.40), p=0.46
	LGSC	instable	0.59 (0.33-0.97), p=0.038

HGSC-high-grade serous carcinoma, EC-endometrioid carcinoma, CCC-clear cell carcinoma, MC-mucinous carcinoma, LGSC-low-grade serous carcinoma. Significant p-value highlighted in bold.

Table S7 Five-year survival estimates for four different type assignments as defined in the text within histological types

	Original type		TB_COSPv2		Agreement between original type and TB_COSPv2		Agreement between 2 out of 3 methods of original type, TB_COSPv2 and WT1-assisted core review	
	No/No of events	5y-OS (SE)	No/No of events	5y-OS (SE)	No/No of events	5y-OS (SE)	No/No of events	5y-OS (SE)
HGSC	334/ 214	39% (2.9)	337/ 216	36% (2.9)	286/ 185	36% (3.2)	339/ 219	36%/ 2.9
EC	88/ 35	59% (5.8)	83/ 25	71% (5.4)	43/ 7	87% (5.5)	60/ 14	80%/ 5.5
CCC	46/ 18	59% (8.2)	42/ 18	66% (7.4)	28/ 9	70% (8.8)	44/ 20	56%/ 8.2
LGSC	22/ 10	37% (14.3)	29/ 14	62% (9.6)	8/ 2	70% (18.2)	21/ 7	67%/ 11.1
MC	22/ 7	71% (9.9)	21/11	57% (11.9)	8/2	73% (16.5)	17/ 6	61%/ 12.9

5y-OS - five year survival rate; SE – standard error; HGSC-high-grade serous carcinoma, EC-endometrioid carcinoma, CCC-clear cell carcinoma, MC-mucinous carcinoma, LGSC-low-grade serous carcinoma

Table S8 Demographics of endometrioid carcinomas in the test set classified by different methods

	Original type	TB_COSPv2	Agreement between original type and TB_COSPv2	Majority of original type, TB_COSPv2 and WT1-assisted core review	Reference (21)
No	97	88	49	54	139
Age (Mean)	58.0	57.1 (0.58)	56.8 (p=0.53)	57.5 (0.77)	54.2
FIGO Stage III or IV	46%	37% (0.19)	20% (p=0.0022)	27% (p=0.011)	5%
Grade 3	50%	43% (0.65)	26% (p-0.050)	40% (p=0.46)	N/A
WT1 positivity	40%	16% (0.0002)	8% (p<0.0001)	6% (p<0.0001)	4%
5y-OS	59%	71% (p=0.31)	87% (p=0.011)	80% (p=0.10)	87%

5y-OS – five year survival rate. N/A not available. P-value refer to pair wise comparison with original type.

Table S9 Prediction of type in test set among cases with unclear original diagnosis (N=71)

		Original type						
		Unknown	Mixed	Other	Undifferentiated	Serous carcinoma ungraded	TOTAL	5y-OS
TB_COSPv2	HGSC	1	10	10	2	28	51	39%
	EC	2	6	0	0	0	8	71%
	LGSC	0	0	0	0	7	7	100%
	CCC	0	2	1	0	0	3	67%
	MC	1	1	0	0	0	2	0%
	TOTAL	4	19	11	2	35	71	
	5y-OS	25%	65%	28%	100%	38%		

HGSC-high-grade serous carcinoma, EC-endometrioid carcinoma, CCC-clear cell carcinoma, MC-mucinous carcinoma, LGSC-low-grade serous carcinoma. 5y-OS-five year overall survival rate.