

SUPPLEMENTARY MATERIALS

The Genetic Landscape of Metaplastic Breast Cancers and Uterine Carcinosarcomas

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Supplementary Methods

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SUPPLEMENTARY METHODS

Whole-exome sequencing analysis

DNA samples from each the histologically distinct components of each of the 11 metaplastic breast cancers (MBCs) and six uterine carcinosarcomas (UCSs) and their respective normal samples were subjected to whole-exome sequencing (WES) at MSKCC's Integrated Genomics Operation (IGO) following validated protocols (1,2). Sequencing data of the separately microdissected components, as well as of the 35 bulk MBCs (Ng et al, 2017)(3) and 57 UCSs (The Cancer Genome Atlas, TCGA)(4) were analyzed as previously described (1,2). In brief, somatic single nucleotide variants (SNVs) were identified using MuTect (v.1.1.4) (5), and small insertions and deletions (indels) were detected using a combination of callers (i.e. VarScan2 (v2.3.6)(6), Strelka (v3.1.1)(7), Lancet (8), Platypus (9) and Scalpel (10)) as previously described (1). SNVs and indels outside the intersection of the two WES capture designs (i.e. Ng et al (3) and TCGA (4)) were filtered out, as were SNVs and indels for which the variant allele fraction (VAF) in the tumor sample was <5 times the VAF of the paired normal tissue, SNVs and indels found at >5% global minor allele frequency of dbSNP (build 146) or found at >1% global allele frequency in ExAC or gnomAD (11), as previously described (1,12).

Fraction of the genome altered

Allele specific copy number aberrations (CNAs), tumor purity and ploidy were obtained from the WES data using FACETS (13). The fraction of the genome altered was computed from the CNAs obtained from FACETS. Segments with an absolute copy number above or below the integer ploidy or were affected by copy neutral loss of heterozygosity were considered altered. The footprint of genome covered by these segments was reported as a function of the total footprint of genome covered by the WES capture design, as described (12).

Clonal relatedness

To infer the clonal relatedness between the histologically distinct components of each MBC and UCS, we defined the "clonality index" (CI) as the probability of two lesions sharing mutations not expected to have co-occurred by chance based on a previously validated method (14,15). Briefly, all somatic mutations were included and at least one non-synonymous mutation was required to be shared in two samples being compared. Given that this analysis is potentially confounded by the presence of highly recurrent somatic mutations, the CI provides an adjustment for the presence and frequency of a given somatic mutation, including synonymous and non-synonymous, in the triple-negative breast cancer (TNBC) dataset from TCGA (n=123)(16), given that all MBCs included in this study were TNBCs, the 35 MBCs from Ng et al. (3), and the 57 UCSs retrieved from TCGA (4).

Adopting previous approach (14,15), we defined $CI = -\log_{10} \prod_{m=1}^M P(X)_m$. Given the repertoire of mutations of two samples, the probability of observing a given mutation in both samples is defined by the binomial probability $P(X) = C_n^k p^k (1-p)^{n-k}$, $n=2$, $k=2$, where p is the frequency of a given mutation in the combined 158 TNBCs and MBCs for the analysis of the 11 multicomponent MBCs, or the 55 non-hypermutated UCSs cases from TCGA for the analysis of the 6 multicomponent UCSs, and n is the number of shared mutations between a pair of lesions or the average number of mutations found in the two samples in the target regions divided by the size of the target regions. Thus, the probability of observing a given set of M identical mutations in the two samples is given by $\prod_{m=1}^M P(X)_m$. To objectively define a cut-off for clonal relatedness among the MBC cases, we used the mutational data from the 123 TNBCs from TCGA (16) and the 35 MBCs from Ng et al. (3). As the positive control (i.e. clonally related), we randomly selected 40%, 60% and 80% of the set of mutations from the 158 unrelated cases in duplicate to simulate heterogeneity between biologically related samples. As the negative control (i.e. unrelated), we randomly selected an equivalent number of pairs (i.e. $3 \times 158 = 474$) of unrelated cases from TCGA. To define the optimum cut-offs, the R package 'ROCR' was used to maximize accuracy. To avoid over-fitting of data, the above procedures were repeated 100 times to define the median and 95% confidence interval of the optimum cut-off. The median optimum cut-off was 18.78 (95% confidence interval 18.71-18.86), the median accuracy was 82.3% (95% confidence interval 80.1%-83.8%), the median sensitivity was 78.9% (95% confidence interval 75.9%-81.9%), and the median specificity was 85.7% (95% confidence interval 85.3%-86.0%).

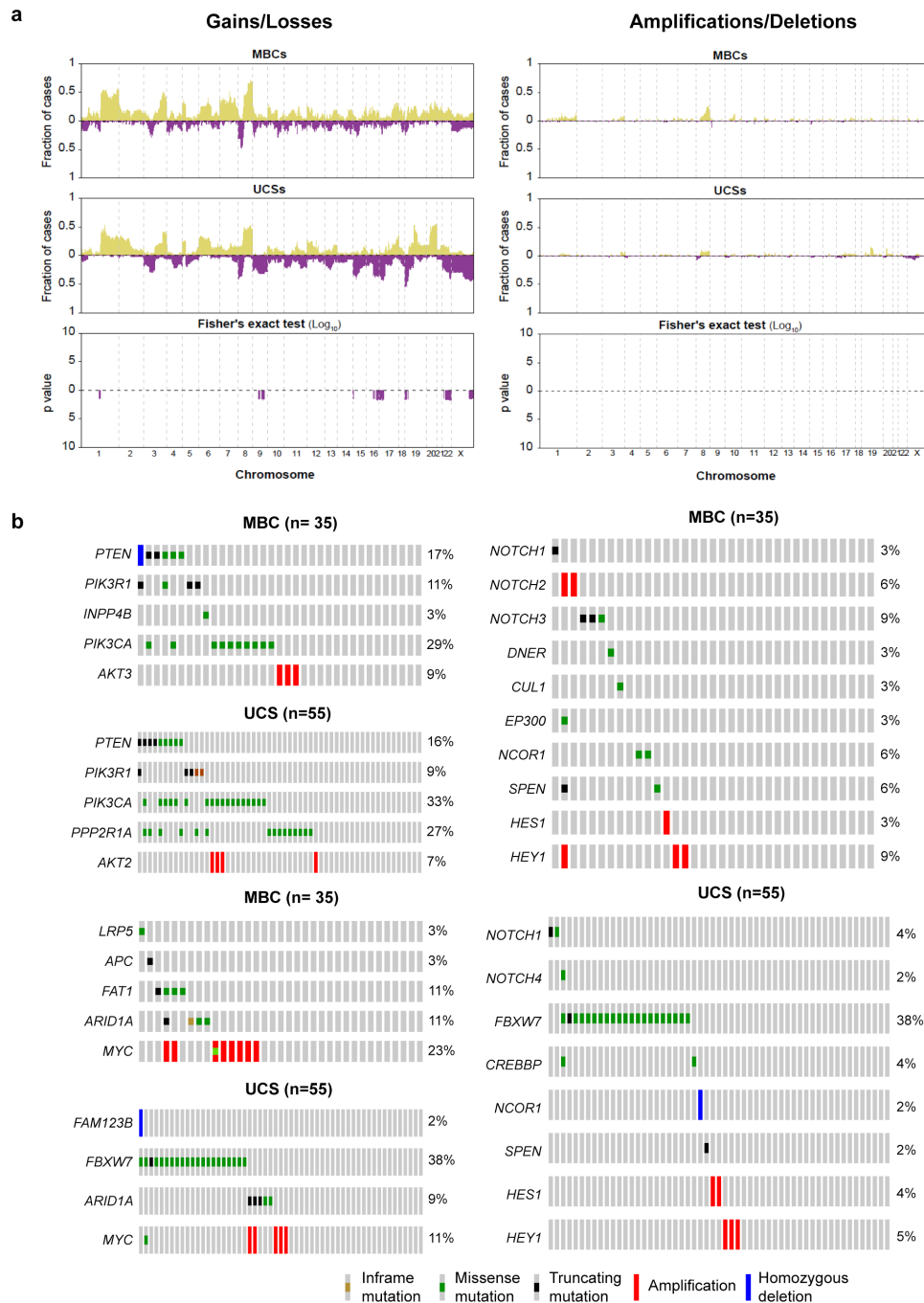
A similar analysis was performed to define a cut-off for clonal relatedness among the UCS cases, using the mutational data from the 55 non-hypermutated UCSs from TCGA (4). The median optimum cut-off was 15.3 (95% confidence interval 15.0-15.6), the median accuracy was 93.1% (95% confidence interval 91.9%-94.4%), the median sensitivity was 89.1% (95% confidence interval 86.8%-91.4%), and the median specificity was 97.1% (95% confidence interval 96.7%-97.6%).

Supplementary References

1. Pareja F, Brandes AH, Basili T, Selenica P, Geyer FC, Fan D, et al. Loss-of-function mutations in ATP6AP1 and ATP6AP2 in granular cell tumors. *Nat Commun.* 2018;9:3533.
2. Geyer FC, Li A, Papanastasiou AD, Smith A, Selenica P, Burke KA, et al. Recurrent hotspot mutations in HRAS Q61 and PI3K-AKT pathway genes as drivers of breast adenomyoepitheliomas. *Nat Commun.* 2018;9:1816.
3. Ng CKY, Piscuoglio S, Geyer FC, Burke KA, Pareja F, Eberle CA, et al. The Landscape of Somatic Genetic Alterations in Metaplastic Breast Carcinomas. *Clin Cancer Res.* 2017;23:3859-70.

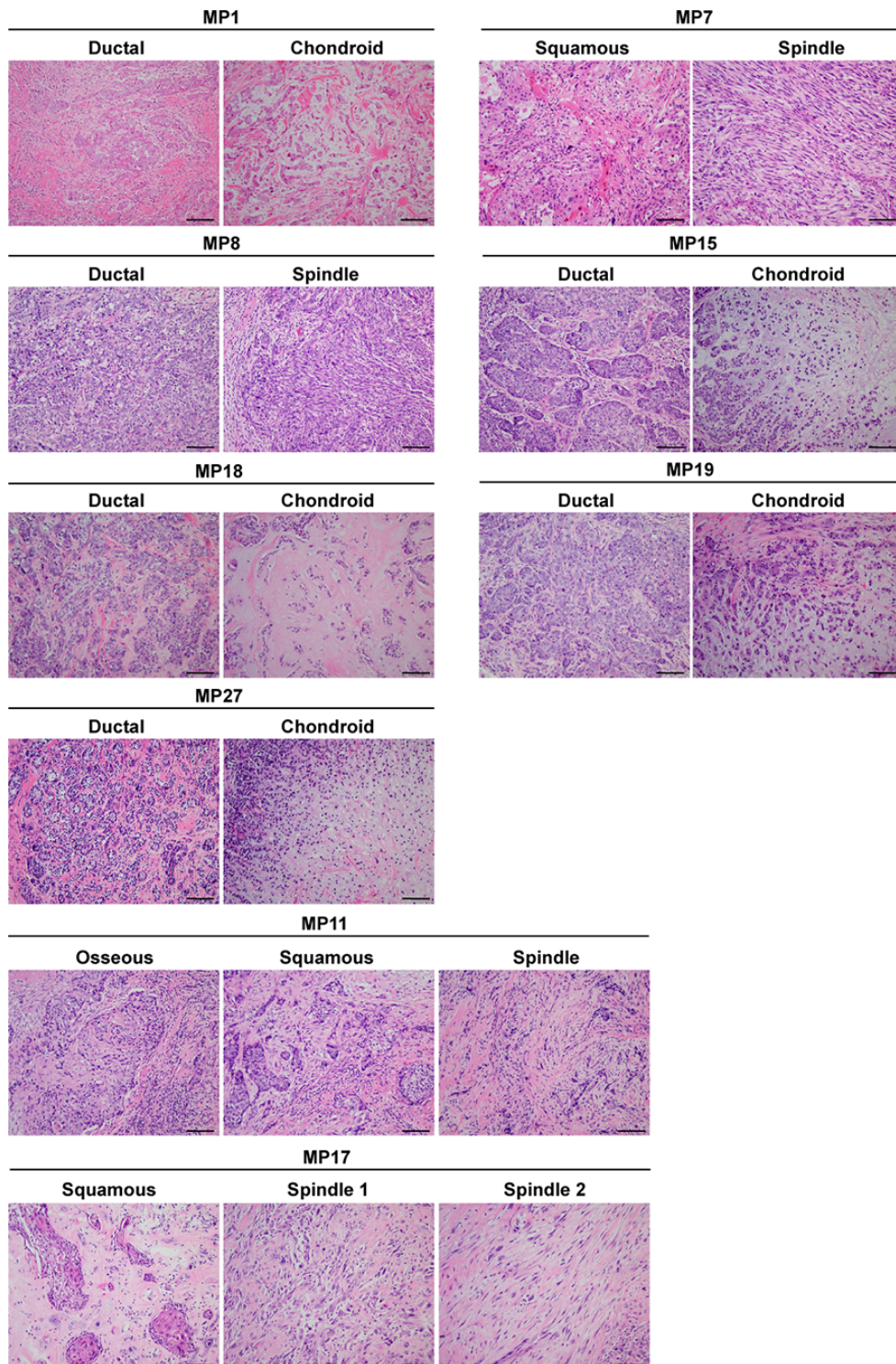
4. Cherniack AD, Shen H, Walter V, Stewart C, Murray BA, Bowlby R, et al. Integrated Molecular Characterization of Uterine Carcinosarcoma. *Cancer Cell*. 2017;31:411-23.
5. Cibulskis K, Lawrence MS, Carter SL, Sivachenko A, Jaffe D, Sougnez C, et al. Sensitive detection of somatic point mutations in impure and heterogeneous cancer samples. *Nat Biotechnol*. 2013;31:213-9.
6. Koboldt DC, Zhang Q, Larson DE, Shen D, McLellan MD, Lin L, et al. VarScan 2: somatic mutation and copy number alteration discovery in cancer by exome sequencing. *Genome Res*. 2012;22:568-76.
7. Saunders CT, Wong WS, Swamy S, Becq J, Murray LJ, Cheetham RK. Strelka: accurate somatic small-variant calling from sequenced tumor-normal sample pairs. *Bioinformatics*. 2012;28:1811-7.
8. Narzisi G, Corvelo A, Arora K, Bergmann EA, Shah M, Musunuri R, et al. Genome-wide somatic variant calling using localized colored de Bruijn graphs. *Commun Biol*. 2018;1:20.
9. Rimmer A, Phan H, Mathieson I, Iqbal Z, Twigg SRF, Consortium WGS, et al. Integrating mapping-, assembly- and haplotype-based approaches for calling variants in clinical sequencing applications. *Nat Genet*. 2014;46:912-8.
10. Fang H, Bergmann EA, Arora K, Vacic V, Zody MC, Iossifov I, et al. Indel variant analysis of short-read sequencing data with Scalpel. *Nat Protoc*. 2016;11:2529-48.
11. Lek M, Karczewski KJ, Minikel EV, Samocha KE, Banks E, Fennell T, et al. Analysis of protein-coding genetic variation in 60,706 humans. *Nature*. 2016;536:285-91.
12. Weigelt B, Bi R, Kumar R, Bleuca P, Mandelker DL, Geyer FC, et al. The Landscape of Somatic Genetic Alterations in Breast Cancers From ATM Germline Mutation Carriers. *J Natl Cancer Inst*. 2018;110:1030-4.
13. Shen R, Seshan VE. FACETS: allele-specific copy number and clonal heterogeneity analysis tool for high-throughput DNA sequencing. *Nucleic Acids Res*. 2016;44:e131.
14. Schultheis AM, Ng CK, De Filippo MR, Piscuoglio S, Macedo GS, Gatus S, et al. Massively Parallel Sequencing-Based Clonality Analysis of Synchronous Endometrioid Endometrial and Ovarian Carcinomas. *J Natl Cancer Inst*. 2016;108:djv427.
15. Lee JY, Schizas M, Geyer FC, Selenica P, Piscuoglio S, Sakr RA, et al. Lobular Carcinomas In Situ Display Intralesion Genetic Heterogeneity and Clonal Evolution in the Progression to Invasive Lobular Carcinoma. *Clin Cancer Res*. 2019;25:674-86.
16. Ciriello G, Gatza ML, Beck AH, Wilkerson MD, Rhie SK, Pastore A, et al. Comprehensive Molecular Portraits of Invasive Lobular Breast Cancer. *Cell*. 2015;163:506-19.

Supplementary Figure S1



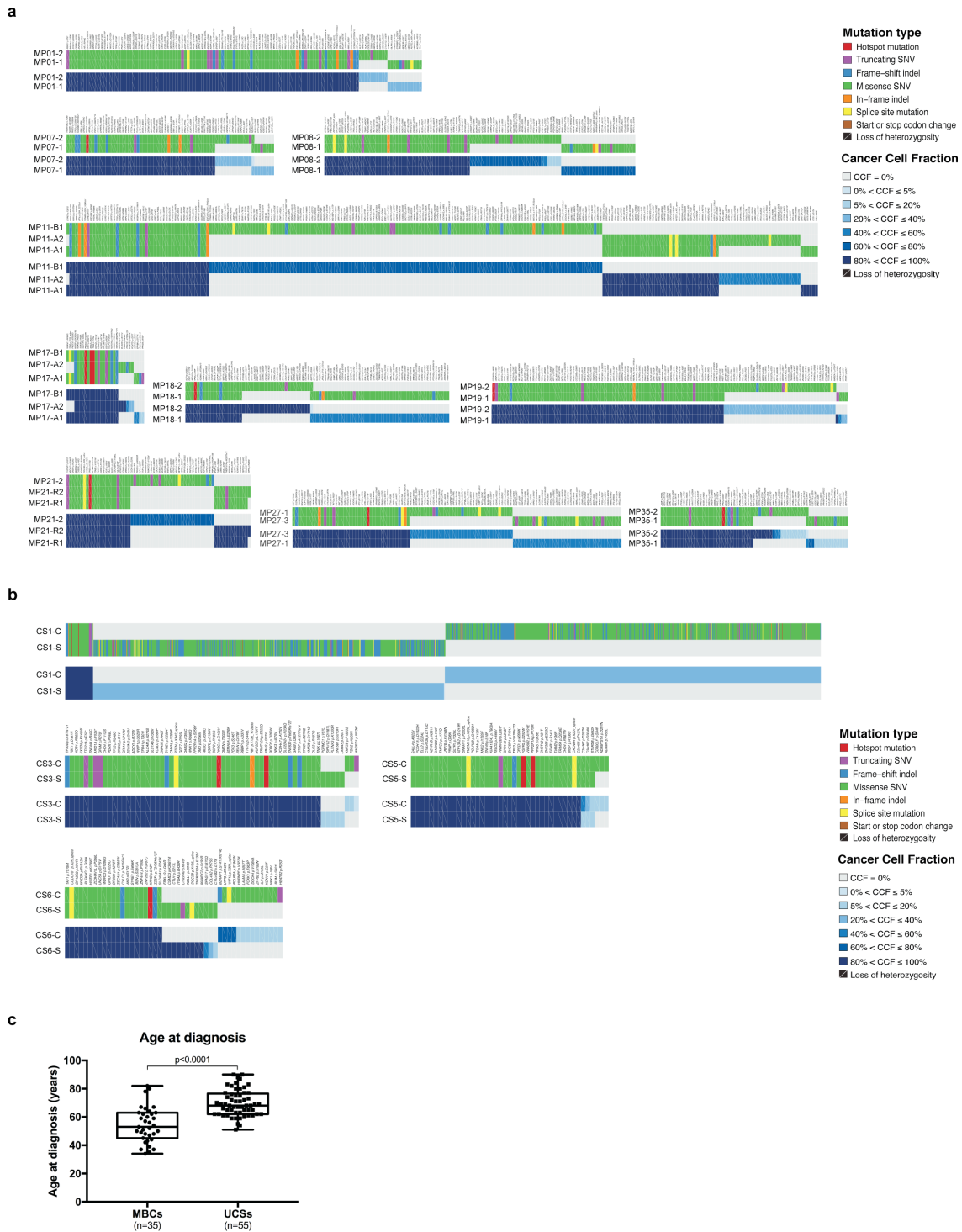
Supplementary Figure S1. Copy number alterations and somatic mutations affecting selected signaling pathways in metaplastic breast cancers and uterine carcinosarcomas. (a) Comparisons of the frequencies of copy number alterations (gains and losses, left; amplifications and homozygous deletions, right) metaplastic breast cancers (MBCs, n=35, top) and uterine carcinosarcomas (UCSs, n=55, middle). Fisher's exact test is shown in the bottom. **(b)** Genetic alterations in key pathways. Oncoprint of altered genes of the canonical PI3K/AKT/mTOR, Wnt and Notch pathways in metaplastic breast cancers (MBC, n=35) and uterine carcinosarcomas (UCSs, n=55). Cases are shown in columns and genes in rows. Somatic mutations and copy number alterations are color-coded according to the legend.

Supplementary Figure S2



Supplementary Figure S2. Representative micrographs of the histologic components of the metaplastic breast cancers subjected to bulk whole-exome sequencing as well as to whole-exome sequencing of the distinct microdissected components. Please note that for MP21 micrographs were not available.

Supplementary Figure S3



Supplementary Figure S3. Clonal decomposition of the epithelial and mesenchymal components of the metaplastic breast carcinomas and uterine carcinosarcomas. Clonal frequency heatmaps of mutations in the epithelial and mesenchymal histologic components of (a) MP1, MP7, MP8, MP11, MP17, MP18, MP19, MP21, MP27, MP35 and of (b) CS1, CS3, CS5, and CS6. Mutations are shown grouped by their clonal structure as inferred by PyClone. (c) Age at diagnosis of patients with metaplastic breast cancer (MBC, median 53 years, range 34-82, n=35) and with uterine carcinosarcoma (UCS, median 68 years, range 51-90, n=55). Mann-Whitney *U* test.

Supplementary Table S1. Clinico-pathologic information of the 35 metaplastic breast cancers re-analyzed from Ng et al (Clin Cancer Res 2017), 57 uterine carcinosarcomas from Cherniack et al (TCGA, Cancer Cell 2017), 11 metaplastic breast cancers with separately analyzed histologic components (this study), and 6 uterine carcinosarcomas with separately analyzed histologic components (this study).

METAPLASTIC BREAST CANCERS (BULK WHOLE-EXOME SEQUENCING)												
Sample ID	Diagnosis	Matrix producing	Predominant Cellular Type	Histologic grade*	ER**	PR	HER2	Triple-negative phenotype	Age at diagnosis (years)	Tumor size (cm)	pT stage	pN stage
META31	Carcinoma with mesenchymal elements	Yes	Chondroid	2	-	-	-	Yes	59	1.2	T1c	N0
META30	Carcinoma with mesenchymal elements	No	Chondroid	3	-	-	-	Yes	44	0.7	T1b	N0
META39	Carcinoma with mesenchymal elements	No	Spindle	3	-	-	-	Yes	45	5.5	T3	N0
MP140	Spindle cell carcinoma	No	Squamous	3	-	-	-	Yes	42	4	T2	N0
META42	Carcinoma with squamous metaplasia	No	Squamous	3	-	-	-	Yes	48	3.1	T2	N0
META52	Carcinoma with mesenchymal elements	No	Chondroid	3	-	-	-	Yes	59	3.3	T2	N0
META45	Carcinoma with mesenchymal elements	Yes	Chondroid	3	-	-	-	Yes	50	9	T3	N1b
META57	Spindle cell carcinoma	No	Spindle	3	-	-	-	Yes	56	2.3	T2	N0
META61	Spindle cell carcinoma	No	Spindle	2	-	-	-	Yes	67	1.8	T1c	N1m
MP1	Carcinoma with mesenchymal elements	Yes	Chondroid	3	-	-	-	Yes	26	1.4	T1c	N0
MP11	Carcinoma with squamous metaplasia	No	Squamous	3	-	-	-	Yes	37	2.2	T2	N0
MP15	Carcinoma with mesenchymal elements	Yes	Chondroid	3	-	-	-	Yes	63	2.3	T2	N1m
MP17	Spindle cell carcinoma	No	Spindle	3	-	-	-	Yes	66	1.4	T3	N1a
MP18	Carcinoma with mesenchymal elements	Yes	Chondroid	3	-	-	-	Yes	39	1.7	T1c	N0
MP19	Carcinoma with mesenchymal elements	Yes	Spindle	3	-	-	-	Yes	62	1.3	T1c	N0
MP21	Spindle cell carcinoma	No	Spindle	3	-	-	-	Yes	37	2.4	T2	N0
MP27	Carcinoma with mesenchymal elements	Yes	Chondroid	3	-	-	-	Yes	67	1.1	T1c	N0
MP7	Spindle cell carcinoma	No	Spindle	3	-	-	-	Yes	51	2.5	T2	N0
MP8	Spindle cell carcinoma	No	Spindle	3	-	-	-	Yes	34	2.9	T2	N0
MTC01	Spindle cell carcinoma	No	Spindle	3	-	-	-	Yes	67	3.6	T2	N0
MTC03	Spindle cell carcinoma	No	Spindle	3	-	-	-	Yes	43	3.2	T2	N0
MTC04	Carcinoma with mesenchymal elements	Yes	Chondroid	3	-	-	-	Yes	48	2.3	T2	N0
MTC05	Carcinoma with mesenchymal elements	Yes	Chondroid	2	-	-	-	Yes	49	1.1	T1b	N0
MTC07	Carcinoma with mesenchymal elements	Yes	Chondroid	3	-	-	-	Yes	60	2.2	T2	N0
MTC10	Carcinoma with mesenchymal elements	No	Chondroid	3	-	-	-	Yes	63	4	T2	N0
MTC12	Carcinoma with squamous metaplasia	No	Squamous	2	-	-	-	Yes	62	3.5	T2	N0
MTC13	Carcinoma with mesenchymal elements	Yes	Chondroid	2	-	-	-	Yes	47	4	T2	N0
MTC14	Carcinoma with mesenchymal elements	Yes	Spindle	3	-	-	-	Yes	67	3.1	T2	N0
MTC19	Spindle cell carcinoma	No	Spindle	3	-	-	-	Yes	60	5	T2	N0
MTC16	Carcinoma with squamous metaplasia	No	Squamous	3	-	-	-	Yes	44	2	T2	N0
MTC17	Carcinoma with squamous metaplasia	No	Squamous	3	-	-	-	Yes	52	7.5	T3	N2
MTC18	Carcinoma with squamous metaplasia	No	Squamous	3	+ (1% weak) + (20% weak)	-	-	No	62	5.2	T3	N0
MTC19	Carcinoma with mesenchymal elements	Yes	Chondroid	3	-	-	-	Yes	64	3	T2	N0
MTC20	Carcinoma with squamous metaplasia	No	Squamous	3	-	-	-	Yes	78	3	T2	N0
MTC23	Carcinoma with squamous metaplasia	No	Squamous	3	-	-	-	No	49	12	T3	N2

UTERINE CARCINOSARCOMAS (BULK WHOLE-EXOME SEQUENCING)												
Sample ID	Histological Type	Clinical Stage	Age at diagnosis (years)	Frozen Sarcoma (%)	Frozen Carcinoma (%)	Serous (%)	Endometrioid (%)	Undifferentiated Sarcoma (%)	L leiomyosarcoma (%)	Heterologous cartilage (%)	Heterologous rhabdomyosarcoma (%)	Histologic classification
TCGA-NS-A49B	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IA	65	N/A	N/A	0	15	25	0	0	0	Serous-like
TCGA-NS-A49A	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIC2	63	98	2	5	0	0	0	0	0	Serous-like
TCGA-NS-A49D	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIA	68	98	2	0	0	0	0	0	0	Serous-like
TCGA-NS-A49E	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IA	68	98	2	0	40	0	0	0	0	Endometrioid-like
TCGA-NS-A49J	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIB	61	70	30	40	0	60	0	0	0	Serous-like
TCGA-NS-A49M	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIB	62	62	38	0	20	60	0	0	0	Serous-like
TCGA-NS-A49N	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIB	71	40	60	0	30	70	0	0	0	Serous-like
TCGA-NS-A49Z	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIC2	67	90	10	50	0	50	0	0	0	Serous-like
TCGA-NS-A49S	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IB	65	50	50	0	0	50	0	0	0	Serous-like
TCGA-NS-A49T	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIC1	69	80	20	80	0	20	0	0	0	Serous-like
TCGA-NS-A49U	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIC2	64	70	30	60	0	40	0	0	0	Serous-like
TCGA-NS-A49V	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IA	62	100	0	20	0	70	0	0	0	Serous-like
TCGA-NS-A49E	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIB	62	90	10	0	0	70	0	0	0	Serous-like
TCGA-NS-A49F	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IB	69	60	40	0	0	20	0	0	0	Serous-like
TCGA-NS-A49V	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IA	59	80	20	0	0	80	0	0	0	Serous-like
TCGA-NS-A49C	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage II	67	60	40	0	0	70	0	0	0	Serous-like
TCGA-NS-A49D	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIA	81	60	40	20	20	60	0	0	0	Endometrioid-like
TCGA-NS-A49E	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIC	84	30	70	0	0	30	0	40	0	Serous-like
TCGA-NS-A49F	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IB	71	70	30	0	0	70	0	0	0	Endometrioid-like
TCGA-NS-A49G	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIB	77	60	40	30	0	70	0	0	0	Serous-like
TCGA-NS-A49H	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIC	69	N/A	N/A	0	30	0	0	30	0	Endometrioid-like
TCGA-NS-A49I	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIB	67	N/A	N/A	0	40	0	0	60	0	Serous-like
TCGA-NS-A49J	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIB	72	100	N/A	0	0	0	0	0	0	Serous-like
TCGA-NS-A49K	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IA	67	N/A	N/A	0	0	0	0	0	0	Serous-like
TCGA-NS-A49L	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IA	71	60	40	25	10	70	0	0	0	Endometrioid-like
TCGA-NS-A49M	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IA	62	50	50	30	0	70	0	0	0	Serous-like
TCGA-NS-A49N	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IB	73	60	40	0	0	60	0	0	0	Serous-like
TCGA-NS-A49P	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIC1	68	100	N/A	15	0	80	0	0	0	Serous-like
TCGA-NS-A49Q	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IB	69	30	70	0	0	70	0	0	0	Serous-like
TCGA-NS-A49R	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIC2	88	N/A	N/A	15	0	85	0	0	0	Serous-like
TCGA-NS-A49S	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIC2	76	100	N/A	10	0	88	0	0	0	Serous-like
TCGA-NS-A49T	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IB	75	60	40	60	0	40	0	10	0	Serous-like
TCGA-NS-A49U	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIC2	77	40	60	0	0	70	0	0	0	Serous-like
TCGA-NS-A49V	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage II	70	N/A	N/A	0	0	60	0	10	0	Serous-like
TCGA-NS-A49W	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IA	65	60	40	0	0	60	0	0	0	Serous-like
TCGA-NS-A49X	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIC	61	80	20	0	0	10	0	0	85	Serous-like
TCGA-NS-A49Y	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IA	69	30	70	0	0	0	0	0	0	Serous-like
TCGA-NS-A49Z	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IA	68	30	70	30	0	70	0	0	0	Serous-like
TCGA-NS-A49A	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIB	72	80	20	0	0	80	0	0	0	Serous-like
TCGA-NS-A49B	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IA	61	100	0	0	0	0	0	0	90	Serous-like
TCGA-NS-A49C	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIB	69	100	0	20	0	80	0	0	0	Serous-like
TCGA-NS-A49D	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIB	62	70	30	0	0	70	0	0	0	Endometrioid-like
TCGA-NS-A49E	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIB	69	70	30	0	0	70	0	0	0	Endometrioid-like
TCGA-NS-A49F	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIC1	75	0	0	20	0	80	10	0	0	Endometrioid-like
TCGA-NS-A49G	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIB	60	70	30	0	0	80	10	0	0	Serous-like
TCGA-NS-A49H	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIC	67	70	30	45	0	60	0	0	0	Endometrioid-like
TCGA-NS-A49I	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IC	80	0	10	20	0	20	0	20	0	None
TCGA-NS-A49J	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IB	83	0	30	80	0	20	0	0	0	None
TCGA-NS-A49K	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIA	77	100	0	1	0	99	0	0	0	Serous-like
TCGA-NS-A49L	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IA	59	0	100	0	0	0	0	0	0	Serous-like
TCGA-NS-A49M	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IV	61	50	50	70	0	30	0	0	0	Serous-like
TCGA-NS-A49N	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage II	59	50	0	0	0	30	0	0	0	Endometrioid-like
TCGA-NS-A49O	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIC2	60	90	10	20	0	60	20	0	0	Endometrioid-like
TCGA-NS-A49P	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IIB	63	100	0	30	0	60	0	0	10	Serous-like
TCGA-NS-A49Q	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IC	74	0	0	60	0	40	0	0	0	Endometrioid-like
TCGA-NS-A49R	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IA	67	0	0	40	0	60	0	0	0	Endometrioid-like
TCGA-NS-A49S	Uterine Carcinosarcoma (MMMT, Heterologous Type)	Stage IB	55	100	0	0	0	90	0	0	0	Serous-like

METAPLASTIC BREAST CANCERS: TWO THREE MICRODISSECTED COMPONENTS: WHOLE EXOME SEQUENCING						
Case ID	Component	Component subtype	ER/PR/HER2**	Histologic Grade*	Age at diagnosis (years)	Stage
MP01	MP01-1	Ductal	-/-/-	3	50	IC
MP01	MP01-2	Ductal	-/-/-	3	51	II
MP07	MP07-1	Spindle	-/-/-	3	51	II
MP08	MP08-1	Spindle	-/-/-	3	54	II
MP08	MP08-2	Ductal	-/-/-	3	54	II
MP11	MP11-A1	Squamous	-/-/-	3	37	II
MP11	MP11-A2	Spindle	-/-/-	3	37	II
MP11	MP11-B1	Chondroid	-/-/-	3	37	II
MP15	MP15-1	Chondroid	-/-/-	3	63	II
MP15	MP15-2	Ductal	-/-/-	3	63	II
MP17	MP17-A1	Spindle	-/-/-	3	66	III
MP17	MP17-A2	Spindle	-/-/-	3	66	III
MP18	MP18-1	Squamous	-/-/-	3	39	IC
MP18	MP18-2	Ductal	-/-/-	3	39	IC
MP19	MP19-1	Chondroid	-/-/-	3	52	IC
MP19	MP19-2	Ductal	-/-/-	3	52	IC
MP21	MP21-R0	Spindle	-/-/-	3	37	II
MP21	MP21-R2	Ductal	-/-/-	3	37	II
MP27	MP27-1	Chondroid	-/-/-	3	57	IC
MP27	MP27-2	Ductal	-/-/-	3	57	IC
MP27	MP27-3	Ductal	-/-/-	3	57	IC
MP27	MP27-4	Ductal	-/-/-	3	52	II

UTERINE CARCINOSARCOMAS: TWO MICRODISSECTED COMPONENTS: WHOLE EXOME SEQUENCING					
Case	Component	Component subtype	Histology	Age at diagnosis (years)	Stage
C51	C51-C	Carcinoma	(chondrosarcoma)	84	IB
C51	C51-S	Carcinoma	(chondrosarcoma)	84	IB
C53	C53-S	Carcinoma	Heterologous	68	IA
C54	C54-C	Carcinoma	Heterologous	75	IIA
C58	C58-C	Carcinoma	Heterologous	88	IIIC
C58	C58-S	Carcinoma	Heterologous	79	IIIC
C58	C58-C	Sarcoma	Heterologous	82	IIIC
C58	C58-S	Sarcoma	Heterologous	82	IIIC

* ER, estrogen receptor expression; PR, progesterone receptor expression; HER2, overexpression/amplification according to the Nottingham grading system

Supplementary Table S3. DAVID pathway analysis in 35 metaplastic breast cancers from Ng et al (Clin Cancer Res 2017) and 55 non-hypermethylated uterine carcinosarcomas from Cherniack et al (TCGA, 2017).

DAVID pathway analysis in metaplastic breast carcinomas					
Database gene set ID	Description Term	Number of genes in gene set	Number of genes in overlap	P value	
KEGG_PATHWAY_hsa05200	Pathways in cancer	393	45	3.34E-21	
KEGG_PATHWAY_hsa05202	Transcriptional misregulation in cancer	168	27	5.12E-16	
KEGG_PATHWAY_hsa04116	p53 signaling pathway	87	14	9.32E-10	
KEGG_PATHWAY_hsa04181	Cell cycle	124	17	5.34E-09	
KEGG_PATHWAY_hsa02030	PI3K-Akt signaling pathway	345	27	1.62E-08	
KEGG_PATHWAY_hsa04012	Central carbon metabolism in cancer	64	11	7.44E-07	
KEGG_PATHWAY_hsa04068	ERB signaling pathway	87	12	1.62E-06	
KEGG_PATHWAY_hsa04008	FoxO signaling pathway	134	14	4.52E-06	
KEGG_PATHWAY_hsa04006	HP1-1 signaling pathway	98	11	3.72E-05	
KEGG_PATHWAY_hsa04510	Focal adhesion	206	15	1.05E-04	
KEGG_PATHWAY_hsa04550	Signaling pathways regulating pluripotency of stem cells	140	12	1.69E-04	
KEGG_PATHWAY_hsa04370	Jak-STAT signaling pathway	145	11	9.41E-04	
KEGG_PATHWAY_hsa04319	Wnt signaling pathway	138	19	0.0024965	
KEGG_PATHWAY_hsa04520	Adherens junction	71	7	0.0037188	
KEGG_PATHWAY_hsa04390	Hippo signaling pathway	151	10	0.0045419	
KEGG_PATHWAY_hsa00310	Lysine degradation	6	2	0.0045992	
KEGG_PATHWAY_hsa04015	Rap1 signaling pathway	210	12	0.0047454	
KEGG_PATHWAY_hsa04150	mTOR signaling pathway	58	6	0.0073511	
KEGG_PATHWAY_hsa04611	Platelet activation	130	8	0.0186611	
KEGG_PATHWAY_hsa04014	Ras signaling pathway	228	11	0.0210506	
KEGG_PATHWAY_hsa04370	VEGF signaling pathway	81	5	0.0294807	
KEGG_PATHWAY_hsa04210	Apoptosis	62	5	0.0415144	
KEGG_PATHWAY_hsa04690	Natural killer cell mediated cytotoxicity	122	7	0.0440307	
KEGG_PATHWAY_hsa04690	CTCF: First Multivalent Nuclear Factor	25	12	4.59E-09	
KEGG_PATHWAY_hsa04690	Role of BRCA1, BRCA2 and ATM in Cancer Susceptibility	8	2	4.65E-05	
KEGG_PATHWAY_hsa04690	Cell Cycle: G1/S Check Point	30	9	5.36E-05	
KEGG_PATHWAY_hsa04690	Cytidine and Cell Cycle Regulation	25	8	1.16E-04	
KEGG_PATHWAY_hsa04690	Influence of Ras and Rho proteins on G1 to S Transition	27	11	0.0001144	
KEGG_PATHWAY_hsa04690	Cell Cycle: G2/M Checkpoint	25	7	9.21E-04	
KEGG_PATHWAY_hsa04690	p53 Signaling Pathway	17	6	9.34E-04	
KEGG_PATHWAY_hsa04690	ATM Signaling Pathway	21	6	0.0024965	
KEGG_PATHWAY_hsa04690	Role of ERBB2 in Signal Transduction and Oncology	23	6	0.004035	
KEGG_PATHWAY_hsa04690	Inhibition of Cellular Proliferation by Gleevec	23	6	0.004035	
KEGG_PATHWAY_hsa04690	TPO Signaling Pathway	6	24	0.0045992	
KEGG_PATHWAY_hsa04690	Phospholipase C Signaling Pathway	9	4	0.0075159	
KEGG_PATHWAY_hsa04690	IL7 Signaling Transduction	17	5	0.0079592	
KEGG_PATHWAY_hsa04690	Growth Hormone Signaling Pathway	27	6	0.0091448	
KEGG_PATHWAY_hsa04690	PTEN dependent cell cycle arrest and apoptosis	18	5	0.0094855	
KEGG_PATHWAY_hsa04690	IL2 Receptor Beta Chain in T Cell Activation	39	7	0.0098287	
KEGG_PATHWAY_hsa04690	VEGF: Hypoxia, and Angiogenesis	6	11	0.0101314	
KEGG_PATHWAY_hsa04690	mTOR Signaling Pathway	26	5	0.042099	
KEGG_PATHWAY_hsa04690	NOTCH1 Intracellular Domain Regulates Transcription	47	7	1.26E-04	
KEGG_PATHWAY_hsa04690	Constitutive Signaling by NOTCH1 PEST Domain Mutants	57	7	3.72E-04	
KEGG_PATHWAY_hsa04690	Constitutive Signaling by NOTCH1 HD+PEST Domain Mutants	57	7	3.72E-04	
KEGG_PATHWAY_hsa04690	PI3K events in ERBB2 signaling	16	5	1.21E-04	
KEGG_PATHWAY_hsa04690	Activation of anterior HOX genes in hindbrain development during early embryogenesis	122	12	8.58E-05	
KEGG_PATHWAY_hsa04690	PI3K activates Akt signaling	81	8	4.13E-04	
KEGG_PATHWAY_hsa04690	Constitutive Signaling by Aberrant PI3K in Cancer	61	7	5.38E-04	
KEGG_PATHWAY_hsa04690	Deactivation of the beta-catenin transactivating complex	42	6	0.008144	
KEGG_PATHWAY_hsa04690	RAF/MEK kinase cascade	116	9	7.42E-04	
KEGG_PATHWAY_hsa04690	Transcriptional regulation of white adipocyte differentiation	19	7	0.0021621	
KEGG_PATHWAY_hsa04690	Resolution of Disjunct Synaptic Junction Intermediates	13	5	0.0021621	
KEGG_PATHWAY_hsa04690	GPVI-mediated activation cascade	56	6	0.0024394	
KEGG_PATHWAY_hsa04690	RMTs methylate histone arginines	77	6	0.0092177	
KEGG_PATHWAY_hsa04690	Signaling by GPCR in disease	27	4	0.0101314	
KEGG_PATHWAY_hsa04690	Synthesis of PIPs at the plasma membrane	35	4	0.0207352	
KEGG_PATHWAY_hsa04690	AXIN misassembles mutants destabilize the destruction complex	14	3	0.0225016	
KEGG_PATHWAY_hsa04690	Truncations of AMER1 destabilize the destruction complex	14	3	0.0225016	
KEGG_PATHWAY_hsa04690	SUMOylation of transcription factors	17	3	0.0324509	
KEGG_PATHWAY_hsa04690	Constitutive Signaling by Ligand-Responsive EGFR Cancer Variants	19	3	0.0403312	
KEGG_PATHWAY_hsa04690	Factors involved in mesoplasia development and patient production	112	3	0.0403312	
KEGG_PATHWAY_hsa04690	Pre-NOTCH Transcription and Translation	29	6	1.09E-04	
KEGG_PATHWAY_hsa04690	Notch-4/5 transcription pathway	12	3	0.0168823	

DAVID pathway analysis in uterine carcinosarcomas					
Database gene set ID	Description Term	Number of genes in gene set	Number of genes in overlap	P value	
KEGG_PATHWAY_hsa05200	Pathways in cancer	393	49	5.34E-20	
KEGG_PATHWAY_hsa05202	Transcriptional misregulation in cancer	168	27	3.16E-21	
KEGG_PATHWAY_hsa02030	Central carbon metabolism in cancer	64	16	7.47E-11	
KEGG_PATHWAY_hsa04012	Signaling pathways regulating pluripotency of stem cells	140	20	1.40E-09	
KEGG_PATHWAY_hsa04012	ERB signaling pathway	87	16	7.19E-09	
KEGG_PATHWAY_hsa04151	PI3K-Akt signaling pathway	345	27	1.35E-06	
KEGG_PATHWAY_hsa02030	Central carbon metabolism in cancer	64	16	7.47E-11	
KEGG_PATHWAY_hsa04012	ERB signaling pathway	87	16	7.19E-09	
KEGG_PATHWAY_hsa04014	Ras signaling pathway	226	21	2.20E-06	
KEGG_PATHWAY_hsa04008	FoxO signaling pathway	134	16	2.48E-06	
KEGG_PATHWAY_hsa04110	Cell cycle	124	15	4.91E-06	
KEGG_PATHWAY_hsa04006	HP1-1 signaling pathway	98	13	1.03E-05	
KEGG_PATHWAY_hsa04510	Focal adhesion	206	18	3.31E-05	
KEGG_PATHWAY_hsa04690	Adherens junction	71	5	0.0021621	
KEGG_PATHWAY_hsa04015	Rap1 signaling pathway	210	17	1.46E-04	
KEGG_PATHWAY_hsa04370	VEGF signaling pathway	61	9	1.98E-04	
KEGG_PATHWAY_hsa04319	Wnt signaling pathway	138	19	0.0024965	
KEGG_PATHWAY_hsa04682	B cell receptor signaling pathway	69	9	4.69E-04	
KEGG_PATHWAY_hsa04690	Jak-STAT signaling pathway	145	13	4.80E-04	
KEGG_PATHWAY_hsa04611	Platelet activation	130	8	5.71E-04	
KEGG_PATHWAY_hsa05231	Choline metabolism in cancer	101	10	0.0014574	
KEGG_PATHWAY_hsa04210	Apoptosis	62	7	0.00602	
KEGG_PATHWAY_hsa04350	TGF-beta signaling pathway	84	8	0.0030263	
KEGG_PATHWAY_hsa04611	Platelet activation	130	10	0.0079302	
KEGG_PATHWAY_hsa04116	p53 signaling pathway	67	7	0.0097781	
KEGG_PATHWAY_hsa04062	Chemokine signaling pathway	22	168	0.0101312	
KEGG_PATHWAY_hsa04010	MAPK signaling pathway	255	14	0.0190157	
KEGG_PATHWAY_hsa04690	CTCF: First Multivalent Nuclear Factor	25	10	5.62E-06	
KEGG_PATHWAY_hsa04690	Role of ERBB2 in Signal Transduction and Oncology	9	23	9.21E-09	
KEGG_PATHWAY_hsa04690	PDGF Signaling Pathway	28	9	1.29E-04	
KEGG_PATHWAY_hsa04690	IL7 Signaling Transduction	17	7	2.65E-04	
KEGG_PATHWAY_hsa04690	TPO Signaling Pathway	24	8	0.0021621	
KEGG_PATHWAY_hsa04690	Tumor Suppressor Ar Inhibits Ribosomal Biogenesis	18	7	3.79E-04	
KEGG_PATHWAY_hsa04690	EGF Signaling Pathway	27	8	6.75E-04	
KEGG_PATHWAY_hsa04690	VEGF: Hypoxia, and Angiogenesis	6	11	0.0101314	
KEGG_PATHWAY_hsa04690	Role of EAS in Neuronal Survival	18	6	0.0030032	
KEGG_PATHWAY_hsa04690	Influence of Ras and Rho proteins on G1 to S Transition	27	7	0.0030989	
KEGG_PATHWAY_hsa04690	Role of BRCA1, BRCA2 and ATM in Cancer Susceptibility	22	6	0.0036163	
KEGG_PATHWAY_hsa04690	Ras Signaling Pathway	23	6	0.0093148	
KEGG_PATHWAY_hsa04690	Chromatin Remodeling by hSWI/SNF ATP-dependent Complexes	17	5	0.0150159	
KEGG_PATHWAY_hsa04690	p53 Signaling Pathway	17	5	0.0150159	
KEGG_PATHWAY_hsa04690	Telomeres, Telomerase, Cellular Aging, and Immortality	18	5	0.0184481	
KEGG_PATHWAY_hsa04690	Growth Hormone Signaling Pathway	27	6	0.0185223	
KEGG_PATHWAY_hsa04690	IL2 Receptor Beta Chain in T Cell Activation	39	7	0.0212442	
KEGG_PATHWAY_hsa04690	ERK1/2 Mapk Signaling pathway	30	6	0.0284197	
KEGG_PATHWAY_hsa04690	ATM Signaling Pathway	21	5	0.0314884	
KEGG_PATHWAY_hsa04690	Downstream signal transduction	29	9	1.57E-07	
KEGG_PATHWAY_hsa04690	NOTCH1 Intracellular Domain Regulates Transcription	47	9	3.82E-06	
KEGG_PATHWAY_hsa04690	Constitutive Signaling by NOTCH1 HD+PEST Domain Mutants	57	9	3.52E-05	
KEGG_PATHWAY_hsa04690	Constitutive Signaling by NOTCH1 PEST Domain Mutants	57	9	3.52E-05	
KEGG_PATHWAY_hsa04690	PI3K activates Akt signaling	81	10	0.0030263	
KEGG_PATHWAY_hsa04690	Activation of anterior HOX genes in hindbrain development during early embryogenesis	122	12	8.58E-05	
KEGG_PATHWAY_hsa04690	Deactivation of the beta-catenin transactivating complex	42	6	3.72E-04	
KEGG_PATHWAY_hsa04690	PI3K events in ERBB2 signaling	16	5	1.21E-04	
KEGG_PATHWAY_hsa04690	SHC1 events in ERBB2 signaling	19	5	7.24E-04	
KEGG_PATHWAY_hsa04690	PI3K activation	61	9	0.0021621	
KEGG_PATHWAY_hsa04690	VEGFR3 mediated cell proliferation	21	5	0.0010791	
KEGG_PATHWAY_hsa04690	RAF/MEK kinase cascade	116	10	0.0011349	
KEGG_PATHWAY_hsa04690	Signaling by SCF: K11	37	6	0.0012979	
KEGG_PATHWAY_hsa04690	Downregulation of SMAD2/3-SMAD4 transcriptional activity	23	5	0.0022269	
KEGG_PATHWAY_hsa04690	Homologous DNA Pairing and Strand Exchange	15	5	0.0022269	
KEGG_PATHWAY_hsa04690	Downregulation of ERBB2-ERBB3 signaling	23	4	0.0022727	
KEGG_PATHWAY_hsa04690	RMTs methylate histone lysines	64	7	0.0022727	
KEGG_PATHWAY_hsa04690	Transcriptional regulation of pluripotent stem cells	28	5	0.0022660	
KEGG_PATHWAY_hsa04690	Cyclin E associated events during G1/S transition	14	4	0.003346	
KEGG_PATHWAY_hsa04690	Formation of the beta-catenin/TCF transactivating complex	88	6	0.003346	
KEGG_PATHWAY_hsa04690	Pre-NOTCH Transcription and Translation	29	6	0.0037238	
KEGG_PATHWAY_hsa04690	GRB1 events in ERBB2 signaling	5	3	0.0047627	
KEGG_PATHWAY_hsa04690	Formation of Serine/Threonine Associated Helicostromatin Foci (SAHF)	16	4	0.0048903	
KEGG_PATHWAY_hsa04690	GRB2 events in ERBB2 signaling	16	4	0.0048903	
KEGG_PATHWAY_hsa04690	Regulation of gene expression by hypoxia-inducible factor	10	3	0.0190989	
KEGG_PATHWAY_hsa04690	Signaling to RAS	10	3	0.0190989	
KEGG_PATHWAY_hsa04690	Signaling by Jun	11	3	0.023979	
KEGG_PATHWAY_hsa04690	Formation of annular gap junctions	11	3	0.023979	
KEGG_PATHWAY_hsa04690	Gap junction degradation	12	3	0.0284197	
KEGG_PATHWAY_hsa04690	SUMOylation of DNA damage response and repair proteins	77	6	0.0287762	
KEGG_PATHWAY_hsa04690	RNA Polymerase II transcription elongation	54	5	0.0322269	
KEGG_PATHWAY_hsa04690	mRNAP events	13	3	0.0322269	
KEGG_PATHWAY_hsa04690	AKT phosphatases targets in the cytosol	13	3	0.0322269	
KEGG_PATHWAY_hsa04690	Notch-4/5 transcription pathway	13	3	0.0322269	
KEGG_PATHWAY_hsa04690	APC truncation mutants have impaired AXIN binding	14	3	0.0379733	
KEGG_PATHWAY_hsa04690	Truncations of AMER1 destabilize the destruction complex	14	3	0.0379733	
KEGG_PATHWAY_hsa04690	AXIN misassembles mutants destabilize the destruction complex	14	3	0.0379733	
KEGG_PATHWAY_hsa04690	SHC1 events in ERBB4 signaling	4	3	0.0379733	
KEGG_PATHWAY_hsa04690	SHC2 DNA damage checkpoint	84	6	0.0397302	

Supplementary Table S4. Genetic alterations affecting homologous recombination genes in metaplastic breast carcinomas and uterine carcinosarcomas.

Sample name	Gene	Mutation	Effect	Chromosome	Position	Reference allele	Alternate allele	Sequencing depth at position	Loss of heterozygosity	Clinvar	Mutation status	Somatic homozygous deletion
META33	BRCA1	Q74*	Nonsense mutation	17	41256966	G	A	57	TRUE	Pathogenic	Germline	-
META39	BRCA2	Y3225fs	Frame_Shift_Ins	13	32972321	T	TA	156	-	Pathogenic	Germline	-
META39	RBBP8	R100W	Missense mutation	18	20548818	C	T	67	TRUE	Pathogenic	Germline	-
META52	RAD54B	S240A	Missense mutation	8	95419730	A	C	135	-	-	Somatic	-
MP1	BRCA2	S1982fs	Frame_Shift_Del	13	32914437	GT	G	173	-	Pathogenic	Germline	-
MP1	BRCA2	E2226Sfs*6	Frame_Shift_Del	13	32915166	CAG	C	507	-	Pathogenic	Somatic	-
MP11	EME1	S411T	Missense_Mutation	17	48456548	G	C	769	TRUE	-	Somatic	-
MP11	BRCA1	G1777fs	Frame_Shift_Ins	17	41209079	T	TG	169	TRUE	Pathogenic	Germline	-
MP15	BRIP1	A349P	Missense mutation	17	59878709	C	G	183	-	Pathogenic	Germline	-
MP19	BRCA1	L639*	Nonsense mutation	17	41245632	A	T	126	TRUE	Pathogenic	Germline	-
MP21	BRCA1	G1800Fs	Frame_Shift_Del	17	41201208	TG	T	84	TRUE	Pathogenic	Germline	-
MP27	SLX4	A1358G	Missense mutation	16	3639566	G	C	212	-	-	Somatic	-
MP27	POLQ	T948fs	Frame_Shift_Del	3	121208934	AT	A	68	-	-	Germline	-
MP8	BRCA1	Q23fs	Frame_Shift_Del	17	41276044	ACT	A	71	TRUE	Pathogenic	Germline	-
MTC04	EME1	N233K	Missense mutation	17	48453268	T	A	713	TRUE	-	Somatic	-
MTC06	BRCA1	E1346Fs	Frame_Shift_Del	17	41243512	CT	C	111	TRUE	Pathogenic	Germline	-
MTC14	BRIP1	D674G	Missense mutation	17	59853838	T	C	386	TRUE	-	Somatic	-
MP15	BRCA2	-	-	13	-	-	-	-	-	-	-	13q13.1
UCS11	WRN	-	-	8	-	-	-	-	-	-	-	8p12
UCS11	USP11	-	-	X	-	-	-	-	-	-	-	Xp11.23
UCS12	FANCA	-	-	16	-	-	-	-	-	-	-	16q24.3

Supplementary Table S5. Number of shared and unique mutations, mutational signatures and clonal relatedness index of the histologically distinct components of 11 metaplastic breast cancers and 6 uterine carcinosarcomas subjected to whole-exome sequencing.

Case ID	Shared non-synonymous somatic mutations carcinoma and mesenchymal components (n)	Shared non-synonymous somatic mutations between mesenchymal components (n)	Carcinoma unique non-synonymous somatic mutations (n)	Mesenchymal unique non-synonymous somatic mutations (n)	Mutational signature (dominant/secondary)	SigMA (dominant/secondary)	Clonal relatedness index
MP1-1	131	N/A	14	18	NP	Aging/APOBEC	66
MP1-2					NP	APOBEC/HRD	66
MP7-1	54	N/A	18	9	NP	Aging/HRD	48
MP7-2					NP	Aging/HRD	48
MP8-1	78	N/A	42	44	3 (HRD)/Sig. 22	HRD/Aging	66
MP8-2					3 (HRD)/13 (APOBEC)	HRD/Aging	66
MP11-A1	62	54	N/A	17	NP	HRD/Aging	66
MP11-A2				41	3 (HRD)/13 (APOBEC)	HRD/Aging	66
MP11-B				185	N/A	3 (HRD)/26 (MSI)	HRD/Aging
MP15-1	87	N/A	46	16	NP	HRD/Aging	66
MP15-2					3 (HRD)/7 (UV)	HRD/Aging	66
MP17-A1	17	20	N/A	4	NP	NP	19/25
MP17-A2				3	NP	NP	19/25
MP17-B1				2	N/A	NP	NP
MP18-1	29	N/A	35	62	3 (HRD)/1 (Aging)	HRD/Aging	66
MP18-2					3 (HRD)/13 (APOBEC)	HRD/Aging	66
MP19-1	109	N/A	17	38	NP	HRD/Aging	66
MP19-2					3 (HRD)/Sig. 24	HRD/Aging	66
MP21-R1	36	18	N/A	31	3 (HRD)/Sig. 11	HRD/Aging	66
MP21-R2				2	NP	NP	66
MP21-2				4	N/A	NP	NP
MP27-1	54	N/A	47	48	3 (HRD)/1 (Aging)	HRD/Aging	66
MP27-3					1 (Aging)/3 (HRD)	HRD/Aging	66
MP35-1	48	N/A	19	18	NP	Aging/HRD	33
MP35-2					NP	Aging/HRD	33
CS1-C	81	N/A	1047	865	6 (MSI)/15 (MSI)	MSI/Aging	57
CS1-S					6 (MSI)/15 (MSI)	MSI/Aging	57
CS3-C	67	N/A	3	6	NP	NP	47
CS3-S					NP	Aging/HRD	47
CS4-C	51	N/A	19	41	1 (Aging)/7 (UV)	Aging	30
CS4-S					3 (HRD)/1 (Aging)	Aging	30
CS5-C	50	N/A	4	1	NP	NP	30
CS5-S					NP	NP	30
CS6-C	25	N/A	19	17	NP	APOBEC/HRD	18
CS6-S					NP	Aging/HRD	18
CS8-C	67	N/A	21	20	3 (HRD)/1 (Aging)	APOBEC/HRD	57
CS8-S					8 (HRD)/Sig. 29	Aging/HRD	57

N/A, not applicable; NP, not performed (mutational signatures using DeconstructSigs could only be defined in samples ≥ 20 single nucleotide variants (SNVs); SigMA signatures could only be defined for samples ≥ 5 SNVs).