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BRIEF COMMUNICATION

Prognostic and Therapeutic Relevance of Molecular Subtypes in High-Grade Serous Ovarian Cancer

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Molecular classification of high-grade serous ovarian cancer (HGSOC) using transcriptional profiling has proven to be complex and difficult to validate across studies. We determined gene expression profiles of 174 well-annotated HGSOCs and demonstrate prognostic significance of the prespecified TCGA Network gene signatures. Furthermore, we confirm the presence of four HGSOC transcriptional subtypes using a de novo classification. Survival differed statistically significantly between de novo subtypes (log rank, *P* = .006) and was the best for the immunoreactive-like subtype, but statistically significantly worse for the proliferative- or mesenchymal-like subtypes (adjusted hazard ratio = 1.89, 95% confidence interval = 1.18 to 3.02, *P* = .008, and adjusted hazard ratio = 2.45, 95% confidence interval = 1.43 to 4.18, *P* = .001, respectively). More prognostic information was provided by the de novo than the TCGA classification (Likelihood Ratio tests, *P* = .003 and *P* = .04, respectively). All statistical tests were two-sided. These findings were replicated in an external data set of 185 HGSOCs and confirm the presence of four prognostically relevant molecular subtypes that have the potential to guide therapy decisions.

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Ovarian cancer (OC) is the second most common gynecologic malignancy in the United States (1). Despite radical surgery and initial high response rates to platinum- and taxane-based chemotherapy, most patients experience a relapse, with a median progression-free survival of only 18 months (2). Thus novel therapies are urgently needed to improve outcomes. However, the success of new drug development in OC will strongly depend on biomarkers able to identify women likely to benefit from a given new therapy. Large-scale genomic studies of high-grade serous OC (HGSOC), the most common histological subtype, have identified novel molecular subtypes that are associated with distinct biology (3,4). A gene expression analysis of high-grade serous and endometrioid OCs as part of the Australian Ovarian Cancer Study identified distinct molecular subtypes that have been designated with neutral descriptors (C1, C2, C4, and C5) (3). The four molecular subtypes were validated in a Cancer Genome Atlas Research (TCGA) Network study and were termed "immunoreactive," "differentiated," "proliferative," and "mesenchymal" on the basis of gene expression in the clusters (4). Surprisingly, however, survival time did not differ statistically significantly for the TCGA subtypes in the 489 tumor samples studied (4). This result was unexpected, because considerable variation in outcome can be observed in HGSOC patients matched for stage and the amount of residual tumor following primary debulking surgery, suggesting that molecular determinants of survival may nonetheless be very important (5). Thus the TCGA Network recently modified their molecular classification of HGSOC by integrating the original TCGA subtype gene signatures with pure prognostic gene expression signatures, thus creating a combined classifier that may allow a more robust survival classification and enrichment strategy for new treatment approaches (6). Gene expression–based outcome predictors have had the greatest impact in breast cancer, where gene expression–based assays were developed with the potential to guide therapy decisions (7). We hypothesize that expression-based classifiers in HGSOC may also be able to predict outcome and recognize categories of patients that are more likely to respond to particular therapies. However, a common unambiguous requirement for broader acceptance of a molecular signature is validation in independent patients.

Gene expression profiles were established using Agilent Whole Human Genome 4x44K Expression Arrays. An unsupervised method (non-negative matrix factorization) was devised to build a de novo classification. The accuracy of the model was evaluated using signatures developed by the TCGA. Both classifiers were validated in an external data set. The -2 Log Likelihood (L) functions were calculated and Likelihood ratio (LR) tests were used to assess the prognostic information provided by each classification beyond clinical parameters (age, FIGO stage, grade, and residual tumor after primary debulking surgery). Subgroup assignments were compared by use of the chi-square test. Overall survival (OS) is depicted according to the method of Kaplan and Meier, and the curves were compared with use of the log-rank test. For univariate and multivariable (adjusted for age, FIGO stage, grade, and residual tumor after primary debulking surgery) survival analysis, a Cox proportional hazards regression model was used, and hazard ratios (HRs) and associated 95% confidence intervals (CIs) were estimated. Proportionality of the model was checked by adding time interactions to the model and using cumulative Martingale residuals and the Kolmogorov test. All statistical tests were two-sided, and a *P* value of less than .05 was considered statistically significant.

To confirm the presence of four HGSOC expression subtypes, we first

applied the prespecified TCGA Network gene signatures to a cohort of 174 well-annotated HGSOCs from Mayo Clinic (4,6). All patients signed an Institutional Review Board approved consent for biobanking, clinical data extraction, and molecular analysis. Evaluation of patient and disease characteristics of this study cohort demonstrates that the group is representative of the general HGSOC population (Supplementary Table 1, available online) (5). With our complete long-term follow-up, only 12% of patients were alive at the time of last follow-up, as compared with 53% of patients in the published TCGA data set (4,6). In the original TCGA clinical data set, the HGSOC molecular subtypes were not prognostically relevant (log rank, P = .26) (Figure 1A). However, when the TCGA Network gene signatures were applied to the Mayo Clinic cohort, a statistically significant difference in OS was observed (log rank, P = .004) (Figure 1B). The longest survival was seen for the immunoreactive subtype. Patients whose tumor samples express the proliferative signature (unadjusted HR = 1.50, 95% CI = 0.96 to 2.34, P = .08; adjusted HR = 1.52, 95% CI = 0.96 to 2.42, P = .07) or the mesenchymal signature (unadjusted HR = 2.12, 95% CI = 1.35 to 3.34, P = .001; adjusted HR = 1.84, 95% CI = 1.15 to 2.94, P = .01) had shorter survival (Table 1) when compared with the immunoreactive subtype (Figure 1B).

Next we performed a de novo analysis of the Mayo Clinic cohort. We selected 1850 genes (2040 probe sets) with the highest variability across patients using median absolute deviation. Subclasses were computed by applying a consensus NMF clustering method, which confirmed the presence of four stable clusters (Figure 2A). Differentially expressed marker genes were determined by significance analysis of microarrays, and subtype names were chosen based on similarity of signature genes to prior nomenclature: immunoreactive-like, differentiated-like, proliferative-like, and mesenchymal-like. The composition of each subtype and differentially expressed marker genes are depicted in Figure 2B and described in the Supplementary Materials (Supplementary Table 2, available online). OS differed statistically significantly between these subtypes, and the best survival was seen for the immunoreactive-like subtype (log rank, P = .006) (Table 1; Figure 2C). Compared with the immunoreactive-like subtype, patients whose tumor samples express the proliferative-like signature (unadjusted HR = 1.68, 95% CI = 1.06 to 2.65, P = .03; adjusted HR = 1.89, 95% CI = 1.18 to 3.02, P = .008) or the mesenchymal-like signature (unadjusted HR = 2.40, 95% CI = 1.43 to 4.02, P = .001; adjusted HR = 2.45, 95% CI = 1.43 to 4.18, P = .001) had statistically significantly worse survival (Table 1; Figure 2C).

Multivariable Cox regression analysis showed that the de novo classification was a stronger independent factor in predicting disease outcome when compared with the TCGA classification (Table 1). Although both approaches identified four stable clusters, which were each associated with specific molecular characteristics and independently associated with patient survival, there was overlap of only 667 genes between the 1850 most variable genes in our current study and the 1500 genes used by the TCGA Network (Supplementary Figure 1, available online). This may be in part because of the fact that the TCGA normalized and standardized expression data from three platforms to integrate three expression values to a unified expression value, leaving 8596 genes for further analysis (4). In contrast, we used one platform (containing 41 000 sequence probes corresponding to 30 936 EntrezGene IDs and 19 596 unique genes), did not have issues with shared features, and thus were not required to reduce the number of probes used for our analysis. In addition to statistical significance testing of adjusted hazard ratios, we also performed likelihood ratio tests to assess the prognostic information provided beyond clinical parameters by each molecular classification. The de novo classification added prognostic information beyond that achieved solely by clinical variables (change in -2 Log L: 14.0, LR test, P = .003). The TCGA classification similarly added prognostic information (change in -2 Log L: 8.2, LR test, P = .04), albeit to a lesser degree.

Next we validated the de novo classification in an external data set of 185 HGSOC case patients, published by Bonome and colleagues, who have been molecularly profiled using the Affymetrix human U133A microarray (8). A minimized gene set was derived from the prototypic samples using a Prediction Analysis of Microarray (PAM) classification strategy (9) to validate the four de novo subtypes in the Bonome data set (Figure 3A; Supplementary Materials, available online). OS differed statistically significantly between these subtypes in the Bonome cohort (log rank, P = .005) (Figure 3A). Again, the best survival was seen for the immunoreactive-like subtype. Compared with this subtype, patients whose tumor samples express the proliferative-like signature (unadjusted HR = 1.62, 95% CI = 0.94 to 2.80, P = .08; adjusted HR = 1.40, 95% CI = 0.80 to 2.44, P = .24) or the mesenchymal-like signature (unadjusted HR = 2.63, 95% CI = 1.52 to 4.56, P < .001; adjusted HR = 2.36, 95% CI = 1.21 to 4.17, P = .003) had worse survival (Table 1; Figure 3A). When comparing the de novo with the TCGA classification in the external set, likelihood ratio tests suggested that the de novo classification (change in -2 Log L: 8.9, LR test, P = .03) provided slightly more prognostic information with better differentiation of high and intermediate risk groups when compared with the TCGA classification (change in -2 Log L: 7.4, LR test, P = .06) (Figure 3, A and B). In both cohorts, more patients were assigned to the differentiated-like subtype and fewer to the immunoreactive-, proliferative- or mesenchymal-like subtypes using the de novo classification when compared with the TCGA classification (Supplementary Tables 3 and 4, available online). Because of limited clinical follow-up information, the original TCGA data set did not appear to be suitable for a comparison of the classifiers prognostic performance, as neither established prognostic factors (eg, suboptimal debulking) nor molecular signatures were able to demonstrated prognostic relevance in multivariate analyses (Supplementary Table 5, available online).

Consensus NMF also demonstrated stable clustering of HGSOC into two or three subgroups (Figure 2A). However, unlike clustering based on four subgroups, neither two nor three subgroups had prognostic relevance (Supplementary Figure 2, available online). In fact, a comparison of group assignments by cross tabulation suggests that the expression matrix of the immunoreactive- and mesenchymal-like groups are merged when three clusters are depicted (Supplementary Table 6, available online). Moreover, the differentiated-like and proliferative-like

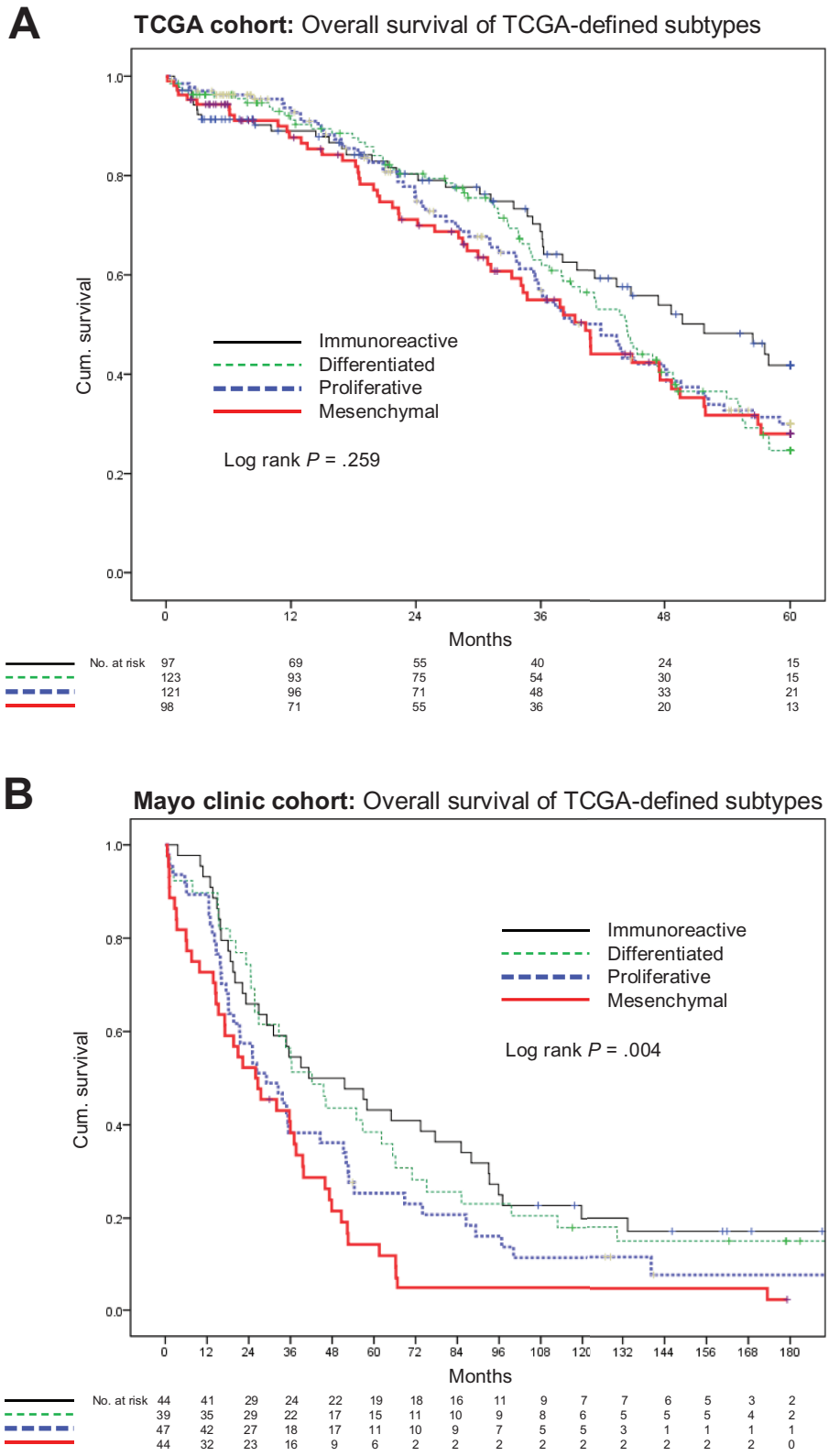

Figure 1. Survival per molecular subtype. Kaplan Meier curves for (**A**) TCGA classification in the original cohort of 489 patients with high-grade serous ovarian cancer and (**B**) for the TCGA classification applied to 174 patients with high-grade serous ovarian cancer from Mayo Clinic with long-term clinical follow-up. For the original TCGA data set, survival was capped at 60 months. All statistical tests were two-sided.

subtypes appear to merge into one subgroup when only two NMF clusters are depicted (Supplementary Table 6, available online). These findings may reflect a commonality in the biological underpinnings between subgroups but could also be explained by the fact that individual tumors may express multiple subtype signatures.

Table 1. Uni- and multivariable analyses of the prognostic relevance of the TCGA classification and the de novo molecular classification in the Mayo Clinic and Bonome cohort of patients diagnosed with high-grade serous papillary ovarian cancer

Classification	Events	Median survival in months (95% CI)	Estimated survival in % (95% CI)		Univariate analysis		Multivariable analysis*	
			3-year	5-year	HR (95% CI)	Wald test, *P*	HR (95% CI)	Wald test, *P*
Mayo Clinic Cohort, N = 174								
TCGA classification								
Immunoreactive	36/44	46.4 (23.0 to 85.1)	54.6 (38.8 to 67.8)	43.2 (28.4 to 57.1)	1.00 (ref.)		1.00 (ref.)	
Differentiated	33/39	42.1 (25.7 to 65.4)	56.4 (39.6 to 70.2)	38.5 (23.5 to 53.2)	1.10 (0.69 to 1.77)	.683	1.11 (0.69 to 1.81)	.663
Proliferative	42/47	29.0 (18.2 to 44.5)	38.3 (24.6 to 51.8)	25.4 (14.0 to 38.4)	1.50 (0.96 to 2.34)	.078	1.52 (0.96 to 2.42)	.074
Mesenchymal	42/44	26.3 (14.5 to 37.1)	38.3 (24.1 to 52.3)	14.4 (5.9 to 26.5)	2.12 (1.35 to 3.34)	.001	1.84 (1.15 to 2.94)	.011
De novo classification								
Immunoreactive-like	35/42	54.3 (29.2 to 85.2)	57.1 (40.9 to 70.4)	47.6 (32.1 to 61.6)	1.0 (ref.)		1.0 (ref.)	
Differentiated-like	51/61	32.7 (21.4 to 46.2)	47.5 (34.6 to 59.4)	31.2 (20.1 to 42.9)	1.30 (0.84 to 2.00)	.233	1.25 (0.80 to 1.95)	.329
Proliferative-like	40/43	32.5 (19.7 to 44.5)	39.5 (25.1 to 53.6)	23.0 (11.8 to 36.4)	1.68 (1.06 to 2.65)	.027	1.89 (1.18 to 3.02)	.008
Mesenchymal-like	27/28	27.0 (14.6 to 39.5)	38.7 (21.0 to 56.1)	11.6 (3.0 to 26.8)	2.40 (1.43 to 4.02)	.001	2.45 (1.43 to 4.18)	.001
Bonome Cohort, N = 185								
TCGA classification								
Immunoreactive	24 / 43	61.8 (43.7 to 103.6)	73.7 (57.5 to 84.5)	53.8 (35.5 to 69.0)	1.00 (ref.)		1.00 (ref.)	
Differentiated	30 / 42	47.3 (34.7 to 67.6)	65.4 (48.6 to 77.9)	42.9 (26.9 to 58.0)	1.41 (0.82 to 2.41)	.215	1.39 (0.80 to 2.42)	.239
Proliferative	38 / 51	42.0 (27.8 to 56.0)	53.1 (38.2 to 66.0)	33.0 (20.1 to 46.6)	1.44 (0.86 to 2.41)	.160	1.30 (0.77 to 2.19)	.328
Mesenchymal	34 / 44	29.4 (19.1 to 47.4)	44.3 (29.1 to 58.4)	31.8 (17.7 to 46.8)	2.12 (1.26 to 3.60)	.005	2.08 (1.21 to 3.56)	.008
De novo classification								
Immunoreactive-like	24 / 42	68.2 (47.4 to 103.6)	75.5 (59.2 to 86.0)	59.2 (41.0 to 73.5)	1.00 (ref.)		1.00 (ref.)	
Differentiated-like	45 / 65	46.0 (32.9 to 64.1)	59.3 (45.9 to 70.5)	39.2 (26.2 to 52.0)	1.46 (0.89 to 2.40)	.137	1.43 (0.87 to 2.36)	.159
Proliferative-like	28 / 37	42.0 (23.6 to 64.8)	56.4 (39.0 to 70.6)	35.7 (20.5 to 51.3)	1.62 (0.94 to 2.80)	.082	1.40 (0.80 to 2.44)	.239
Mesenchymal-like	29 / 36	28.4 (20.6 to 44.2)	40.2 (24.0 to 55.8)	22.9 (10.1 to 38.8)	2.63 (1.52 to 4.56)	<.001	2.36 (1.21 to 4.17)	.003

* Multivariable analysis using Cox proportional hazards regression model, two-sided Wald test: Mayo Cohort accounting for age (TCGA: $P = .05$; de novo: $P = .02$), FIGO stage (TCGA: $P = .009$; de novo: $P = .005$), grade (TCGA: $P = .40$; de novo: $P = .22$), suboptimal debulking (TCGA: $P < .001$; de novo: $P < .001$); Bonome Cohort accounting for age (TCGA: $P = .001$; de novo: $P = .001$), FIGO stage (TCGA: $P = .47$; de novo: $P = .59$), grade (TCGA: $P = .73$; de novo: $P = .97$), suboptimal debulking (TCGA: $P = .002$; de novo: $P = .002$). Three patients who had both age and stage data missing and two who had a missing de novo score were excluded. CI = confidence interval; HR = hazard ratio, SE = standard error.

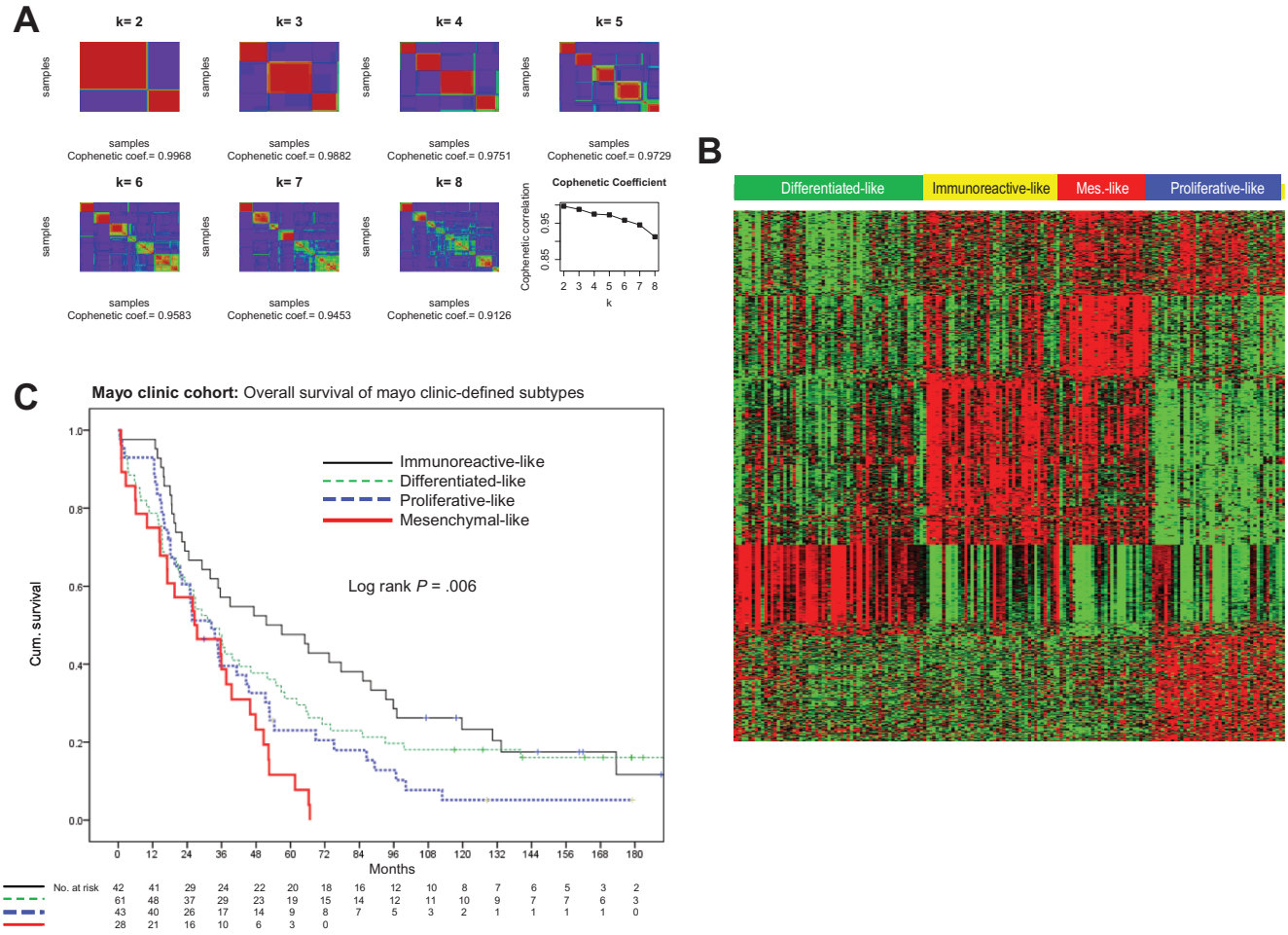

Figure 2. Subclasses were computed by applying a consensus NMF clustering method, which confirmed the presence of four stable clusters. **A**) Consensus matrices and sample correlation matrices are shown for k = 2 to k = 8, using the 1850 genes (2040 probe sets) with the highest variability across patients using median absolute deviation. **B**) Differentially expressed marker genes were determined by significance analysis of microarrays, and subtype names were chosen based on prior nomenclature and the expression of signature genes: immunoreactive-like, differentiated-like, proliferative-like, and mesenchymal-like. Using the gene class signatures, 174 samples and the 1000 most differentially expressed genes were ordered based on subtype assignments. Each column represents a sample; each row represents a gene set. **C**) Kaplan Meier curves for molecular subtypes among 174 Mayo Clinic high-grade serous ovarian cancers for overall survival is shown. The *P* value was calculated using a two-sided log rank test. Differentially expressed marker genes were determined by significance analysis of microarrays, and subtype names were chosen based on prior nomenclature and the expression of signature genes: immunoreactive-like, differentiated-like, proliferative-like, and mesenchymal-like.

To better understand to what extent individual tumor samples can be assigned to multiple subtypes, single-sample GSEA scores were calculated for all 174 tumor samples. The gene set activation scores for each individual sample (columns) are depicted in Figure 4A. When using binary scores, 40% of the 174 tumor samples could be assigned to two subtypes and 2% to three subtypes (Figure 4B). These findings confirm previous observations (6) that HGSOC does not consist of mutually exclusive expression subtypes and suggest that an individual tumor sample can be represented by multiple signatures at different levels of activation. However, the assignment of an individual sample to multiple signatures is less pronounced in the current study compared with the degree seen in the TCGA cohort, where 82% of the 489 tumor samples were assigned to at least two subtypes and 44% to at least three subtypes (6).

The likelihood that the efficacy of a treatment modality may be higher in one or two groups and may not be seen in all prognostic groups is briefly illustrated by the following example. An enrichment of genes and signaling pathways associated with immune response was most characteristic of the immunoreactive-like subtype. This subtype was specifically characterized by high expression levels of MHC class I and II genes that enable the immune system to detect the presence of antigens, thereby creating humoral immunity and aiding cytotoxic T cells. Of note, interferon regulatory factor 7 (IRF7) and programmed cell death ligand 1 (PD-L1/CD274) were also among the genes differentially expressed in the immunoreactive-like subtype. These genes have been associated with immune tolerance as increased expression has been described to cause immune evasion of the tumor by the impairment of effector T cells (10,11). Immune modulatory antibodies may be able to increase the activity of cytotoxic T cells and specifically show clinical efficacy in this subtype (12,13).

In summary, the present microarray-based expression study demonstrates that HGSOC is both a clinically diverse and molecularly heterogeneous disease comprising subtypes with distinct gene

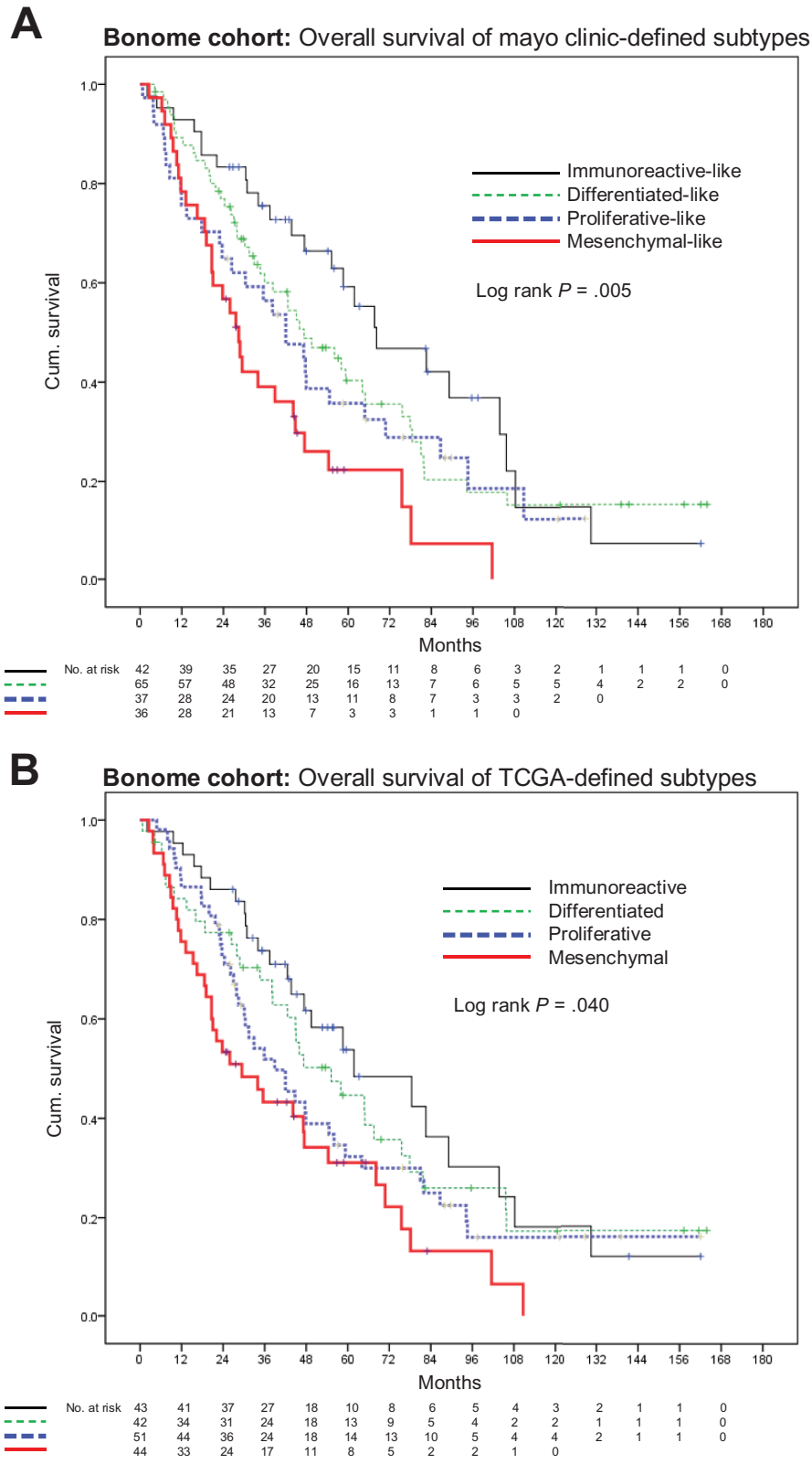

Figure 3. Kaplan Meier curves for (**A**) the de novo Mayo Clinic molecular classification and (**B**) for the TCGA classification applied to 185 high-grade serous ovarian cancers (Bonome cohort) and overall survival (OS) for each subtype. *P* values were calculated using the two-sided log-rank test.

expression patterns that are each associated with statistically significantly different clinical outcomes. Our findings also confirm that a dimensional approach where molecular subtypes lie on a spectrum with partly overlapping causes may be more suitable for classification of HGSOC rather than one of complete mutual exclusivity.

Our study, however, is not without limitations in that the sample size is small, the study retrospective in nature, and the assay used is limited to the use of fresh

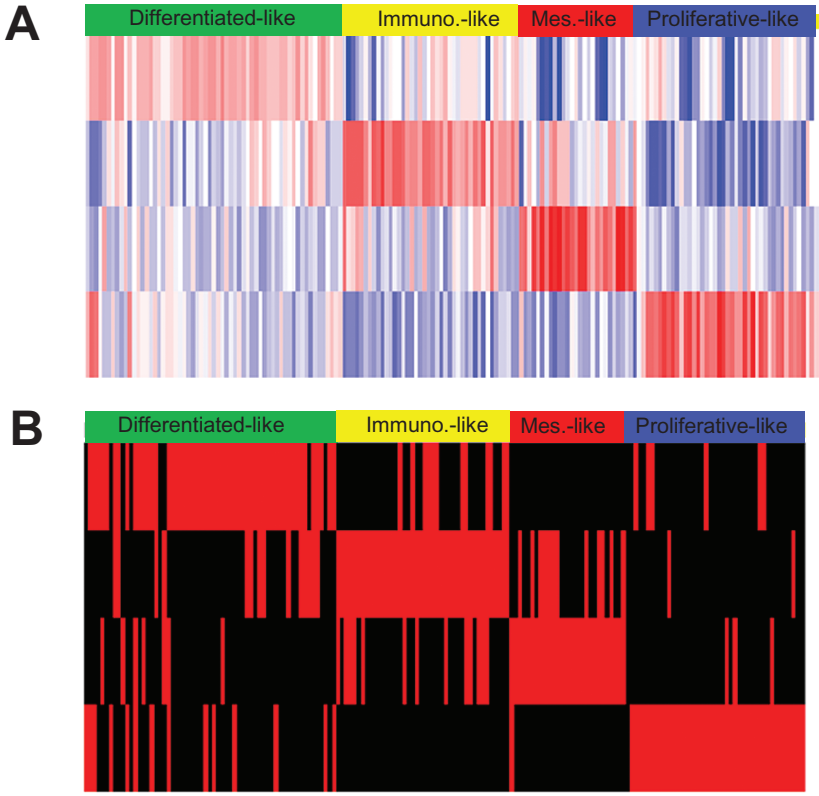

Figure 4. HGSOC signature ssGSEA scores. ssGSEA scores for 174 HGSOC tumor samples were generated using described gene expression signatures: differentiated-like, immunoreactive-like, mesenchymal-like, and proliferative-like. **A**) Raw gene set activation scores. Each column represents one sample; each row represents one gene signature. **B**) Binary scores indicating whether a tumor sample activates the gene signature. Each column represents one sample; each row represents one gene signature. **Red** = activated; **black** = not activated.

frozen tissue. Moreover, we were not able to define the predictive role of each subtype. Thus, before either classification can be converted to clinical use, further validation of their prognostic importance is required, and associations between subtype signatures and treatment responses will need to be assessed, preferably using samples from controlled randomized clinical trials using assays that can be performed on the available formalin fixed paraffin embedded tissues such as whole-genome DASL or NanoString, which both allow gene expression profiling of low-abundance and partially degraded RNA (14,15). Only these studies will allow us to ultimately determine which subtype signatures are most appropriate to select patients for a given therapy.

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Notes

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