Large-scale meta-analysis of cancer microarray data identifies common transcriptional profiles of neoplastic transformation and progression

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Many studies have used DNA microarrays to identify the gene expression signatures of human cancer, yet the critical features of these often unmanageably large signatures remain elusive. To address this, we developed a statistical method, comparative meta-profiling, which identifies and assesses the intersection of multiple gene expression signatures from a diverse collection of microarray data sets. We collected and analyzed 40 published cancer microarray data sets, comprising 38 million gene expression measurements from >3,700 cancer samples. From this, we characterized a common transcriptional profile that is universally activated in most cancer types relative to the normal tissues from which they arose, likely reflecting essential transcriptional features of neoplastic transformation. In addition, we characterized a transcriptional profile that is commonly activated in various types of undifferentiated cancer, suggesting common molecular mechanisms by which cancer cells progress and avoid differentiation. Finally, we validated these transcriptional profiles on independent data sets.

To identify genes potentially important in cancer, scientists have compared the global gene expression profiles of cancer tissue and corresponding normal tissue (1–11). Such analyses usually generate hundreds of genes differentially expressed in cancer relative to normal tissue, making it difficult to distinguish the genes that play a critical role in the neoplastic phenotype from those that represent epiphenomena or are spuriously differentially expressed. Another common experimental design is to compare cancer samples based on their degree of progression, as determined by histological grade, invasiveness, or metastatic potential (2, 11–22). For example, it is known that high-grade undifferentiated-appearing cancers tend to behave more aggressively than their low-grade counterparts, often leading to poorer patient outcomes. To understand the mechanisms by which this progression occurs, many studies have compared the global gene expression profiles of undifferentiated and well differentiated cancers of the same origin. But again, like the "cancer vs. normal" studies, these analyses can also yield hundreds of differentially expressed genes. Thus, it remains a critical problem to elucidate the essential transcriptional features of neoplastic transformation and progression both to direct future research and to define candidate therapeutic targets.

A logical approach for identifying the essential features of a process, given a large set of possibilities observed in a variety of independent systems, is to search for the intersection of observed possibilities across the set of systems, because it is expected that the essential features will be overrepresented and the system-specific, epiphenomenal, and spurious features will be underrepresented. Given the multitude of studies that have attempted to capture the cancer type-specific gene expression programs of neoplastic transformation and progression, we sought to define cancer type-independent, and likely essential, transcriptional features of these important processes. It was initially unclear to us whether such essential features might exist. The complexity in the cellular and molecular origins of cancer might lead one to suspect largely distinct transcriptional programs for independent cancer types, whereas the observation of common phenotypes and behaviors among distinct cancer types might suggest similar transcriptional programs.

In this report, we attempt to identify common transcriptional programs of neoplastic transformation and progression across a wide range of cancer types. To establish a framework for such analysis, we adopted and modified a method, termed meta-analysis of microarrays, which was previously used to validate analogous prostate cancer microarray studies against one another (25). This method avoids many of the pitfalls that complicate the comparison of disparate microarray data sets by comparing statistical measures of differential expression generated independently from each data set rather than actual gene expression measurements. Here, we present a similar method, termed comparative meta-profiling, aimed not at validating analogous data sets, but at comparing and assessing the intersection of many cancer type-specific gene expression data sets, with the goal of identifying cancer type-independent, and likely essential, transcriptional profiles of neoplastic transformation and progression.

Methods

Data Collection, Processing, and Storage. Microarray data sets were downloaded from public web sites or provided by the authors upon request. Data are available at www.oncomine.org/meta. Data were of two general types, two channel ratio data and single channel intensity data, and were usually provided in single composite file format. All available data were included in processing and analysis, except for negative single channel intensity values. All data sets were log transformed and median centered per array, and the standard deviations were normalized to one per array. Studies were named by the following convention: FirstAuthor_TissueTypeProfiled (e.g., Dhanasekaran_Prostate). To facilitate multistudy analysis, microarray features were mapped to Unigene Build 159. Data and initial data analyses were stored in an ORACLE 8.1 relational database.

Initial Data Analysis. For each of the 40 microarray data sets present in the database, we reviewed the samples profiled. Thirty-four studies had at least four samples corresponding to both classes of one analysis of interest and were further analyzed. Analyses of interest included: cancer versus respective normal tissue, high grade (undifferentiated) cancer versus low grade (differentiated cancer) cancer, poor outcome (metastases, recurrence, or cancer-specific death) cancer versus good outcome (long-term or recurrence-free survival) cancer, metastasis versus primary cancer, and subtype 1 versus subtype 2. After the assignment of samples to classes, each gene was assessed for differential expression with Student's *t* test

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using TOTAL ACCESS STATISTICS 2002 (FM, Vienna, VA). *t* tests were conducted both as two-sided for differential expression analysis and one-sided for overexpression analysis. To account for multiple hypothesis testing, *Q* values (26) (estimated false discovery rates) were calculated as

$$Q = (\text{estimated no. of false positives})/(\text{no. of called positives at a given } P \text{ value})$$

$$Q = (P \times n)/i,$$

where *P* is *P* value, *n* is the total number of genes, and *i* is the sorted rank of *P* value.

Meta-Profiling. The purpose of meta-profiling is to address the hypothesis that a selected set of differential expression signatures shares a significant intersection of genes (a meta-signature), thus inferring a biological relatedness. The automated method proceeds as follows: (*i*) a set of *S* similar differential expression analyses are selected for meta-profiling; (*ii*) an overexpression direction (e.g., cancer > normal) and a significance threshold (*T*) are chosen to define differential expression signatures from the selected analyses ($T_{\text{DEFAULT}} = 0.10$); (*iii*) genes are sorted by the number of signatures in which they are present; (*iv*) the number of genes present in each possible number of signatures is tallied (N_0, N_1, $N_2 \ldots N_S$); (*v*) random permutations are performed (steps *iii* and *iv*) in which the actual *Q* values are randomly assigned to genes per study, so that the genes in each signature change at random, but the number of genes in each signature remain the same. This simulation generates a tally of the number of genes present in each possible number of random signatures ($E_0, E_1, E_2 \ldots E_S$); (*vi*) the significance of intersection among the true signatures is assessed by the minimum meta-false discovery rate ($mFDR_{\text{MIN}}$) calculated as

$$mFDR_{\text{MIN}} = \text{MINIMUM}([E_i + 1]/[N_i]) \text{ for } i = 0 \text{ to } S.$$

(*vii*) If $mFDR_{\text{MIN}} < 0.10$, a meta-signature is defined as those genes that are significantly differentially expressed ($Q < T$) in at least *j* of *S* analyses, where *j* is equal to *i* when $mFDR_{\text{MIN}}$ was defined; (*viii*) if no meta-signature is defined by using T_{DEFAULT}, steps *ii* through *vii* are repeated as *T* is systematically lowered by 50% at each iteration until either a meta-signature is defined or the number of genes in two or more signatures reaches 0, in which case the result is negative. This assures that a meta-signature is not missed because of an overly liberal *Q* value threshold. The meta-profiling algorithm was implemented in PERL.

Class Prediction. To assess the classification accuracy of the meta-signatures, a leave-one-out voting classifier was applied. To predict the class of a particular sample, that sample was removed from the data set, and the remaining samples were used to calculate the two class means for each gene in the signature. The left out sample's gene expression values were compared to the class means. The class mean in which the left out sample's value was closest to received a vote. The votes were tallied, and the prediction was defined as the class with the most votes. A Fisher's exact test was used to assess the significance of the classification. The meta-signatures and class prediction results were visualized by using TREEVIEW (27) (http://rana.lbl.gov/eisensoftware.htm).

Results and Discussion

Data and Primary Analysis. As of May 1, 2003, we cataloged information on 152 cancer microarray studies by searching the literature. This catalog and the results from this report are available to explore via our companion web resource, ONCOMINE (www.oncomine.org/meta). Of these published studies, 40 data sets were publicly available and compiled; in total, 37,901,459 gene measurements from 3,762 microarray experiments. Most data sets were of two general formats, either single-channel intensity data, usually corresponding to Affymetrix microarrays, or dual-channel ratio data, usually corresponding to spotted cDNA microarrays, and in the majority of cases, a single composite data file was provided by the study authors and incorporated into our database.

Although many sophisticated analytical and statistical approaches have been applied to microarray normalization and differential expression analysis, we sought a single approach that would be simple in application yet robust to the heterogeneous data formats, experimental platforms, and experimental designs. We first applied a global normalization procedure to all data sets (see *Methods*). Second, by studying the samples profiled in each of the 40 data sets, we defined potential two class differential expression analyses relevant to the processes of neoplastic transformation and progression. These included cancer versus respective normal tissue, high-grade (undifferentiated) cancer versus low-grade (differentiated cancer) cancer, poor outcome (metastases, recurrence, or cancer-specific death) cancer versus good outcome (long-term or recurrence-free survival) cancer, metastatic cancer versus primary cancer, and cancer subtype 1 (e.g., estrogen receptor positive) versus subtype 2 (e.g., estrogen receptor negative) and were identified in 34 data sets (Fig. 4, which is published as supporting information on the PNAS web site). Based on these classifications, we conducted 81 sets of analyses by defining two classes of samples, calculating a Student's *t* statistic, *P* value (false positive rate), and *Q* value (false discovery rate) for each microarray feature (see *Methods*) (26). The majority of cancer vs. normal (36 of 40), differentiation (8 of 11), metastases vs. primary (3 of 3), and cancer subtype (15 of 16) analyses identified large sets of differentially expressed genes ($Q < 0.10$), whereas only 3 of 11 outcome analyses did, two of which compared poor outcome breast cancer with favorable outcome (14, 15), and one which compared poor outcome diffuse large B cell lymphoma with favorable outcome (28). Fig. 4 summarizes the 81 analyses and the number of significant differentially expressed genes identified in each at varying significance thresholds. These data can be analyzed with our companion web resource, ONCOMINE (www.oncomine.org/meta).

Comparative Meta-Profiling Method. Because it is generally agreed that microarray data from distinct experimental platforms, often using distinct reference samples, are not directly comparable, we developed a method that instead compares statistical measures (*Q* values) generated independently from each data set (25). To compare statistical measures across data sets, our method requires that analogous hypotheses have been tested in each data set (e.g., genes differentially expressed between normal tissue and cancer tissue). To identify and assess the intersection of multiple differential expression signatures, so-called meta-signatures, we applied our automated method, comparative meta-profiling (Fig. 1, see *Methods*). The method is as follows: (*i*) a set of analogous differential expression analyses are selected for meta-profiling, (*ii*) a direction and significance threshold are set to define differential expression signatures from the precomputed differential expression analyses (e.g., overexpressed in cancer relative to normal, $Q < 0.10$), (*iii*) genes are sorted based on the number of signatures in which they are present, and (*iv*) a meta-signature is defined if there are significantly more genes intersecting a given number of signatures than would be expected by chance, as defined by a random simulation. A statistical measure, the minimum meta-false discovery rate ($mFDR_{\text{MIN}}$) is used to assess the degree of intersection among gene expression signatures (see *Methods*).

Meta-Signature of Neoplastic Transformation. We began by meta-profiling 36 neoplastic transformation signatures from 21 data sets (overexpressed in cancer relative to respective normal tissue, $Q < 0.10$), which span 12 tissue types including breast, prostate, colon, lung, liver, brain, ovary, pancreas, uterus, salivary gland, bladder, and B lymphocytes. We hypothesized that if a meta-signature

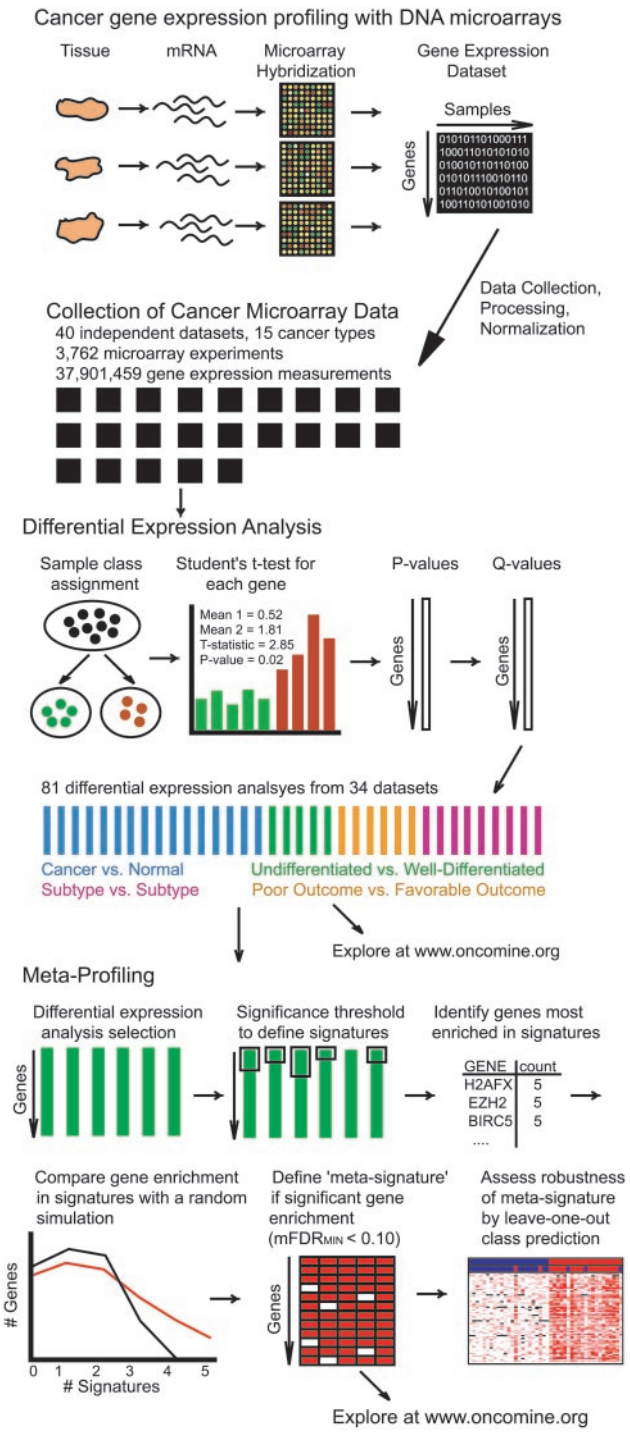

Fig. 1. Comparative meta-profiling flow diagram (see *Methods* for details).

existed, the genes in the signature would reflect essential transcriptional features of cancer, independent of tissue of origin or initial transforming mechanism. At the significance threshold of $Q < 0.10$, 183 genes were present in at least 10 of 36 signatures, 67 genes in at least 12 signatures, and one gene in 18 signatures. In a random simulation, in which genes were randomly assigned to signatures while maintaining the number of genes in each signature, no genes were present in 10 or more signatures, indicating that the 183 genes present in at least 10 signatures represented a statistically significant multicancer-type meta-signature ($mFDR_{MIN} = 0.0055$). Fig. 2*A* depicts the 67 genes present in at least 12 cancer vs. normal signatures. Many of these genes have previously been associated with cancer; however, often associations have only been made with one specific type of cancer or in cell lines, and not with cancer in general. As defined by the Gene Ontology Consortium (29) (www.geneontology.org), the meta-signature contains genes involved in the cell cyle (CDKN3, CKS2, E2F5, PTMA, PLK, CCT4), invasion (MMP9), transcriptional regulation (E2F5, SOX4, HDAC1, CBX3, SMARCA4), protein folding (HSPD1, HSPE1, CCT4), and the proteasome (PSMA1, PSMC4, PSME2). The genes in this signature can be further explored with ONCOMINE (www.oncomine.org/meta).

To assess the universality of the meta-signature, the top 67 genes were used to predict cancer vs. normal status in 39 analyses using a leave-one-out voting classifier (see *Methods* and Table 1, which is published as supporting information on the PNAS web site). The signature was a significant predictor ($P < 0.05$) in 29 of 39 analyses (from 19 of 21 data sets), and was marginally predictive ($P < 0.10$) in 3 of 39 analyses (from 3 of 21 data sets) (Fig. 2*B*). The seven analyses in which the profile was not an accurate classifier were from a single multicancer data set (30). This data set was the largest in the database, providing 13 of the 39 cancer vs. normal analyses, of which six were predicted significantly. For each of the seven analyses that were not predicted significantly, there was a similar (i.e., same cancer type) analysis from an independent study that was predicted significantly. Taken together, 20 of 21 data sets suggest that the genes in this cancer meta-signature are differentially overexpressed in most, if not all, available cancer types relative to the normal tissue from which they arose.

The existence of a general cancer meta-signature may not be entirely surprising, because all cancer types share the common features of unregulated cell proliferation and invasion, and it would follow that the genes that are essential to these processes would be highly expressed in multiple cancer types. On the other hand, however, it is interesting that a small number of genes are almost universally activated, given the vast array of transforming mechanisms that are known to initiate cancer and the variety of tissue types represented in this analysis. Activation of these genes may represent convergence on the essential transcriptional features of neoplastic transformation. From a clinical standpoint, pharmacological agents that target these essential features of cancer might have broad application. For example, TOP2A, a gene present in 18 cancer vs. normal signatures representing 10 types of cancer, encodes the enzyme topoisomerase II, which is critical for DNA replication and is targeted by numerous chemotherapeutic agents (31). Furthermore, agents targeting the proteasome complex, of which three members were identified in the meta-signature, have also shown promise. These agents are in clinical trials and have been shown to induce apoptosis and sensitize cancer cells to traditional tumoricidal agents (32). The widespread activation of genes that encode successfully targeted proteins suggests that other genes in the meta-signature may play equally critical roles in carcinogenesis, and may serve as novel therapeutic targets.

Meta-Signature of Undifferentiated Cancer. We next sought to identify meta-signatures that characterize cancer progression as defined by histological, pathological, or clinical criteria, similar in concept to a report that identified a metastasis signature common to multiple types of primary tumors (19). As described above, only 3 of 10 outcome-based analyses identified significant differentially expressed genes, and two were of the same cancer type, making it infeasible to attempt to define an outcome meta-signature. However, 8 of 11 differentiation analyses, spanning seven types of cancer, identified significant differential expression signatures (differentially expressed in undifferentiated cancers relative to well differentiated cancers of the same origin, $Q < 0.10$). Undifferentiated cancers of different tissue types all fail to recapitulate their normal tissue architecture, instead maintaining a disordered state

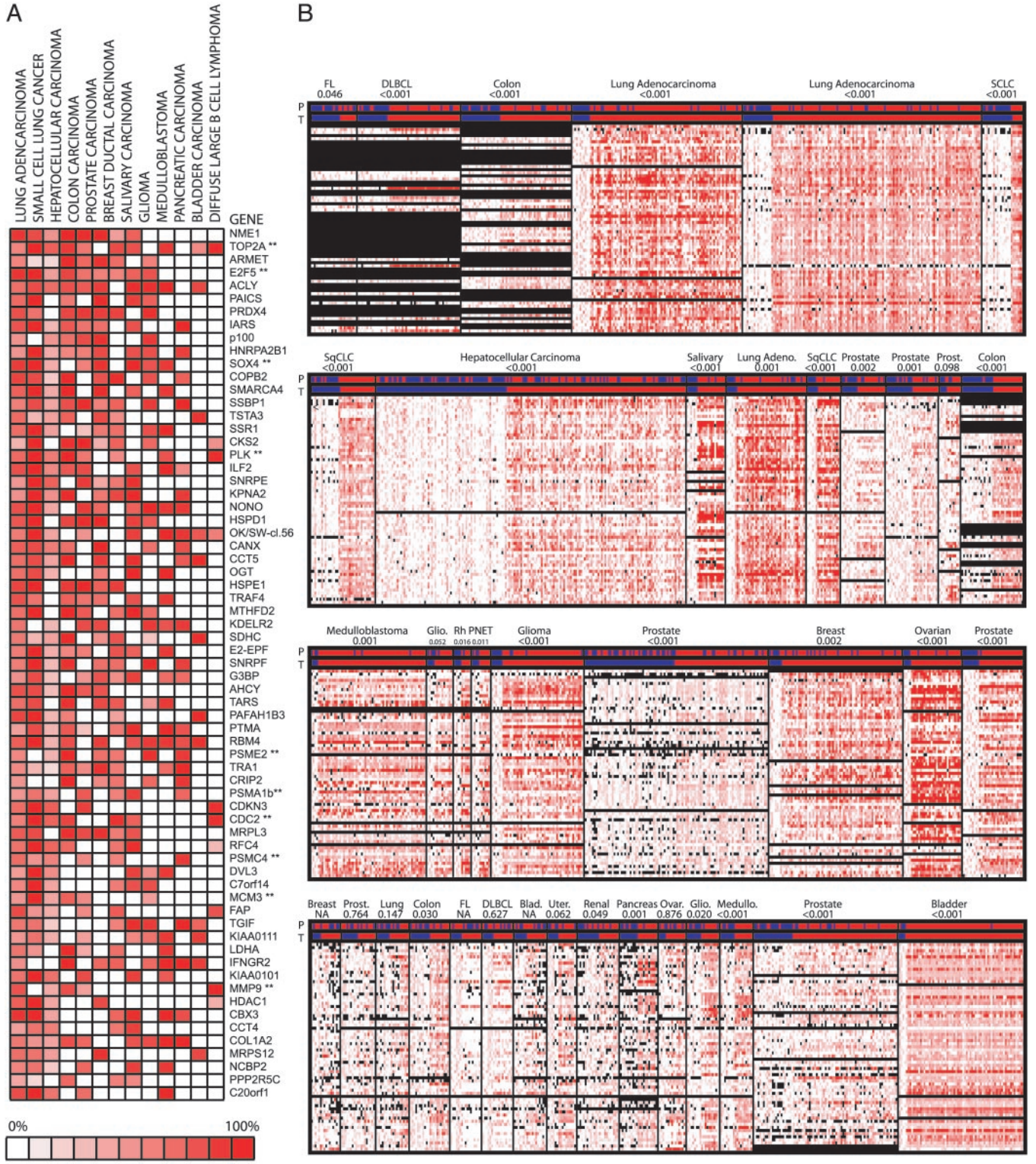

Fig. 2. Meta-signature of neoplastic transformation. (*A*) Sixty-seven genes overexpressed in cancer relative to normal tissue counterpart in at least 12 of 39 ''cancer vs. normal'' signatures. Twelve distinct cancer types were selected for the figure. White boxes signify either not present or not significant. Red boxes signify significant overexpression in cancer relative to normal tissue ($Q < 0.10$), the shade of red indicating the percentage of cancer samples that had an expression value greater than the 90th percentile of normal samples. (*B*) The signature significantly predicts ''cancer vs. normal'' status in 32 of 39 analyses. The two bars above each heat map represent the predicted class (P) and the true class (T): red signifies cancer and blue signifies normal tissue. Fisher's exact test was used to assess the significance of classification. In the heat maps, black signifies data not available, white signifies less than or equal to the normal class mean expression level, and red signifies the degree of overexpression relative to the mean normal class expression level. FL, follicular lymphoma; DLBCL, diffuse large B cell lymphoma; SCLC, small cell lung cancer; SqCLC, squamous cell lung cancer; adeno., adenocarcinoma; Prost., prostate; Glio., glioblastoma; Rh, rhabdomyosarcoma; PNET, primitive neuroectodermal tumor.

of increased cellular proliferation and invasion. Furthermore, undifferentiated cancers are associated with aggressive behavior and poor patient outcomes. Thus, we hypothesized that if an undifferentiated meta-signature existed, it might suggest common transcriptional mechanisms by which cancer cells avoid differentiation, or dedifferentiate. Meta-profiling was performed on seven "undifferentiated vs. well differentiated" signatures spanning six cancer types (overexpressed in undifferentiated cancers relative to well differentiated cancers, $Q < 0.10$). Sixty-nine genes were present in at least four of seven signatures, whereas just one gene was significant in four of seven signatures by chance ($mFDR_{MIN} = 0.030$). Twenty-four genes were present in five signatures, and six genes were present in six of seven signatures, whereas zero genes were significant in five or more by chance, thus defining an undifferentiated meta-signature common to multiple types of cancer. Fig. 3 displays the 69 genes present in at least four of seven signatures. Interestingly, a fraction of genes in this meta-signature overlap with the meta-signature of neoplastic transformation. These genes are predominantly associated with proliferation (TOP2A, MCM3, CDC2, RFC4, etc.), the overlap likely owing to the parallel increase in proliferation in cancer relative to normal tissues and in undifferentiated cancer relative to differentiated cancer. Of note, three genes unique to the undifferentiated meta-signature have a demonstrated role in chromatin remodeling and broad spectrum transcriptional regulation, including the polycomb group protein EZH2, which is involved in transcriptional memory (33), and the histone variant proteins, H2AFX and H2AFZ, which are known to control the euchromatin–heterochromatin transition (34). The ability of these genes to modulate the expression of tens or hundreds of genes suggests that they may play a role in maintaining the undifferentiated cellular state of high-grade cancer. Interestingly, our group recently found EZH2 to be involved in the metastatic progression of prostate cancer (13) and in the invasive breast cancer phenotype (35), and another recent study demonstrated amplification of the EZH2 gene locus in several primary tumor types (36). Other genes present in the meta-signature whose function suggests a role in the undifferentiated phenotype include MELK, a kinase with a demonstrated role in early mammalian embryogenesis (37), and BIRC5 (survivin), an inhibitor of apoptosis (IAP family), which may allow undifferentiated cancer cells to overcome apoptotic checkpoints favoring aberrant progression through mitosis (38). The genes in this signature can be further explored with ONCOMINE (www.oncomine.org/meta).

To assess the generality of the undifferentiated meta-signature, a leave-one-out voting classifier was used to predict "high grade vs. low grade" status in all 11 differentiation analyses (Table 2 and Fig. 5, which are published as supporting information on the PNAS web site). The meta-signature was a significant predictor in six of the seven analyses in which differentially expressed genes were originally identified ($P < 0.001$). The one analysis that was not predicted accurately was Singh_Prostate ($P = 0.75$). In the four remaining analyses, in which no significant differentially expressed genes were originally identified, the meta-signature was a significant predictor in one analysis (Welsh_Ovarian, $P = 0.005$), marginally predictive in two analyses (Dhanaskearan_Prostate, Welsh_Prostate, $P < 0.15$), and not predictive in one analysis (Garber_Lung, $P =$ not applicable). Taken together, it appears that this meta-signature is common to undifferentiated breast cancer, lung cancer, ovarian cancer, bladder cancer, and medulloblastoma, and may be marginally associated with undifferentiated prostate cancer.

Independent Data Set Validation of Meta-Signatures. To confirm the validity and biological relevance of the meta-signatures, we tested their discriminative power on 12 independent data sets that became recently available and were collected after the initial discovery of the metasignatures (28, 39–49) (see supporting information). To validate the universal cancer meta-signature, we analyzed nine independent data sets representing nine distinct cancer types, three of which were not represented in the original analysis [adrenocortical carcinoma (40), pilocytic astrocytoma (41), meningioma (39)]. Table 3, which is published as supporting information on the PNAS web site, shows that in seven of the nine data sets, including all three data sets representing new cancer types, the metasignature significantly discriminated between cancer and respective normal tissue (Fisher's Exact Test, $P < 0.05$). In the two other data sets,

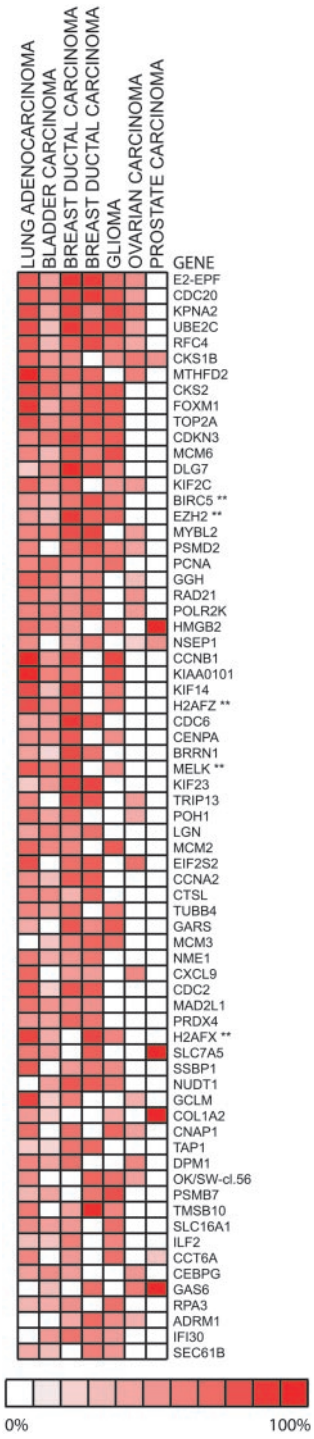

Fig. 3. Meta-signature of undifferentiated cancer. Sixty-nine genes that are overexpressed in undifferentiated cancer relative to well differentiated cancer ($Q < 0.10$) in at least four of seven signatures representing six types of cancer. See Fig. 2 legend for description.

LaTulippe_Prostate (45) and Rosenwald_Lymphoma (28), the metasignature made many more correct than incorrect predictions; however, the discrimination did not reach statistical significance ($P = 0.085$ and 0.115, respectively).

To assess the discriminative power of the undifferentiated meta-signature, we identified five independent data sets that included low- and high-grade cancer samples (Table 4, which is published as supporting information on the PNAS web site). In three of five data sets [Katua_Astrocytoma (44), Schaner_Ovarian (48), and Sotiriou_Breast (49)] the meta-signature significantly discriminated between low- and high-grade cancer samples (Table 1, all $P < 0.01$), whereas in the remaining two data sets the signature was not predictive ($P > 0.5$). In these two data sets [Mutter_Endometrium (46), Powell_Lung (47)], no genes were found to be significantly differentially expressed between high- and low-grade cancers ($Q < 0.10$) and only a small number of cases defined each class (low grade: $n = 4$, high grade: $n = 3$). Similar to the results in the training set, this signature seems to perform well in data sets that identified significant gene expression differences, but poorly in those that do not. It is unclear whether this represents cancer types for which the undifferentiated meta-signature is not present, or if it was not detected because of technical issues in particular data sets. Regardless, the signature appears to define a wide variety of undifferentiated cancer types both in the training and test sets and likely points to common transcriptional mechanisms by which cancer cell avoid differentiation. In summary, this validation on independent microarray data sets confirms that the meta-signatures represent common gene expression programs that may be important to the processes of neoplastic transformation and progression.

In conclusion, the systematic collection of public microarray data (see www.oncomine.org/meta) combined with the comparative meta-profiling framework generated a useful platform for drawing conclusions that span multiple microarray data sets and importantly, multiple cancer types. By integrating microarray data and analysis from a number of cancer types, we characterized a meta-signature of neoplastic transformation, defining a transcriptional program that is almost always activated in cancer, regardless of cell of origin. This universal activation suggests that these genes may be essential to carcinogenesis, and likely represent the convergence of a number of transforming mechanisms in a variety of cellular contexts. Furthermore, universal overexpression suggests that these genes may serve as attractive therapeutic targets. Interestingly, topoisomerase II and the proteasome complex, both members of the meta-signature, have been targeted therapeutically with some degree of success. We also identified a meta-signature of cancer progression, demonstrating that various types of high-grade cancer share common transcriptional features, including the overexpression of specific chromatin remodeling and transcriptional memory genes that may play a role in the cancer cells' ability to avoid differentiation. Finally, this work provides a simple, scalable framework for comparing and assessing the intersection of multiple gene expression signatures from disparate data sets. This approach will be increasingly useful as the mass of published transcriptome data continues to grow.

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Table 1. Universal meta-signature training data sets

Study Name	Class 1 Description	Class 2 Description	*n*	Accuracy	*P* value	
Alizadeh_Lymphoma	Blood B-Cells	Follicular Lymphoma	26	0.731	0.062553	
Alizadeh_Lymphoma	Blood B-Cells	Diffuse Large B-Cell Lymphoma	58	0.828	1.18E-05	**
Alon_Colon	Normal Colon	Colon Adenocarcinoma	62	0.839	1.41E-07	
Beer_Lung	Normal Lung	Lung Adenocarcinoma	96	0.875	5.73E-08	**
Bhattacharjee_Lung	Normal Lung	Lung Adenocarcinoma	135	0.867	9.54E-09	**
Bhattacharjee_Lung	Normal Lung	Lung Carcinoid	37	0.838	5.04E-05	**
Bhattacharjee_Lung	Normal Lung	Small Cell Lung Carcinoma	23	0.870	0.000832	**
Bhattacharjee_Lung	Normal Lung	Squamous Cell Lung Carcinoma	37	0.892	6.68E-07	**
Chen_Liver	Normal Liver	Hepatocellular Carcinoma	180	0.689	1.25E-07	**
Frierson_Salivary	Normal Salivary Gland	Salivary Adenoid Cystic Carcinoma	22	0.909	0.000375	**
Garber_Lung	Normal Lung	Lung Adenocarcinoma	46	0.804	0.004717	**
Garber_Lung	Normal Lung	Sqamous Cell Lung Carcinoma	19	0.895	0.002912	**
Luo_Prostate	Benign Prostatic Hyperplasia	Prostate Cancer	25	0.800	0.003258	**
LuoJH_Prostate	Normal Prostate	Prostate Cancer	30	0.800	0.001407	**
Magee_Prostate	Normal Prostate	Prostate Cancer	12	0.750	0.151515	
Notterman_Colon	Normal Colon	Colon Adenocarcinoma	36	0.972	2.09E-09	**
Perou_Breast	Normal Breast	Breast Cancer	63	0.857	0.00554	**
Pomeroy_Brain	Normal Cerebellum	Medulloblastoma	64	0.938	0.001849	*
Pomeroy_Brain	Normal Cerebellum	Glioblastoma	14	0.786	0.094905	
Pomeroy_Brain	Normal Cerebellum	Rhabdomyosarcoma	9	0.889	0.039683	*
Pomeroy_Brain	Normal Cerebellum	Primitive Neuroectodermal Tumor	10	0.900	0.033333	*
Rickman_Brain	Normal Neocortex of temporal lobe	Glioma	51	0.922	1.17E-05	**
Singh_Prostate	Nontumor Prostate	Prostate Cancer	102	0.667	0.000621	**
Sorlie_Breast	Normal Breast	Breast Ductal Carcinoma	74	0.797	0.007927	**
Welsh_Ovarian	Normal Ovary	Ovarian Carcinoma	32	0.906	0.000973	**
Welsh_Prostate	Normal Prostate	Prostate Cancer	34	0.971	1.91E-07	**
Ramaswamy_Multi	Normal Breast	Breast Adenocarcinoma	16	0.375	0.230769	
Ramaswamy_Multi	Normal Prostate	Prostate Cancer	19	0.474	0.570017	
Ramaswamy_Multi	Normal Lung	Lung Adenocarcinoma	18	0.667	0.167421	
Ramaswamy_Multi	Normal Colon	Colon Tumor	22	0.727	0.040248	*
Ramaswamy_Multi	Normal Gerrminal Center	Follicular Lymphoma	17	0.294	0.088235	
Ramaswamy_Multi	Normal Gerrminal Center	Diffuse Large B-Cell Lymphoma	17	0.471	0.515837	
Ramaswamy_Multi	Normal Bladder	Bladder Cancer	18	0.500	0.647813	
Ramaswamy_Multi	Normal Uterus	Uterine Cancer	16	0.750	0.091908	
Ramaswamy_Multi	Normal Kidney	Renal Cell Carcinoma	23	0.696	0.060237	
Ramaswamy_Multi	Normal Pancreas	Pancreatic Adenocarcinoma	21	0.857	0.001718	**
Ramaswamy_Multi	Normal Ovary	Ovarian Carcinoma	15	0.533	0.661538	

Ramaswamy_Multi	Normal Whole Brain and Normal Cerebellum	Glioblastoma	18	0.778	0.030646	*
Ramaswamy_Multi	Normal Whole Brain and Normal Cerebellum	Medulloblastoma	18	0.889	0.001508	**
Dhanasekaran_Prostate	BPH and Normal Prostate	Prostate Cancer	81	0.815	2.64E-07	**
Dyrskjot_Bladder	Normal Bladder	Bladder Cancer	71	0.972	0.000277	**
Median			25	0.814815	0.002912	

The classification accuracy and statistical significance of the universal meta-signature in the training data sets. The class of each sample was predicted using a leave-one-out voting classifier (see *Methods*). *n* is the total number of samples that were predicted. Accuracy is the fraction of total samples that were classified correctly. *P* values were generated using Fisher's exact test. Significant *P* values ($P < 0.05$) are marked with an asterisk and highly significant *P* values ($P < 0.01$) are marked with double asterisks.

Table 2. Undifferentiated meta-signature training data sets

Study Name	Class 1 Description	Class 2 Description	*n*	Accuracy	*P* value	
Beer_Lung	Lung Adenocarcinoma: Well Differentiated	Lung Adenocarcinoma: Poorly Differentitated	44	0.886	1.94E-07	**
Garber_Lung	Lung Adenocarcinoma: Grade 2	Lung Adenocarcinoma: Grade 3	29	0.345	0.098672	
Rickman_Brain	Glioma: Grade 1	Glioblastoma: Grade 4	40	0.850	4.42E-06	**
Schwartz_Ovarian	Ovarian Carcinoma: Grade 1	Ovarian Carcinoma: Grade 3	75	0.773	0.000174	**
Singh_Prostate	Prostate Cancer: Gleason 6	Prostate Cancer: Gleason 8,9	19	0.421	0.627193	
Sorlie_Breast	Breast Adenocarcinoma: Grade 1	Breast Adenocarcinoma: Grade 3	42	0.810	0.000401	**
VantVeer_Breast	Breast Adenocarcinoma: Grade 1	Breast Adenocarcinoma: Grade 3	90	0.833	1.08E-06	**
Welsh_Ovarian	Ovarian Carcinoma: Well Differentiated	Ovarian Carcinoma: Poorly Differentiated	17	0.824	0.00905	**
Welsh_Prostate	Prostate Cancer: Gleason 6	Prostate Cancer: Gleason 8,9	15	0.667	0.181818	
Dyrskjot_Bladder	Bladder Cancer: Grade 2	Bladder Cancer: Grade 3	67	0.731	0.00013	**
Dhanasekaran_Prostate	Prostate Cancer: Gleason 6	Prostate Cancer: Gleason 8	35	0.629	0.110949	
Median			40	0.773333	0.000401	

The classification accuracy and statistical significance of the undifferentiated meta-signature in the training data sets. The class of each sample was predicted using a leave-one-out voting classifier (see *Methods*). *n* is the total number of samples that were predicted. Accuracy is the fraction of total samples that were classified correctly. *P* values were generated using Fisher's exact test. Highly significant *P* values ($P < 0.01$) are marked with double asterisks.

Table 3. Universal meta-signature test data sets

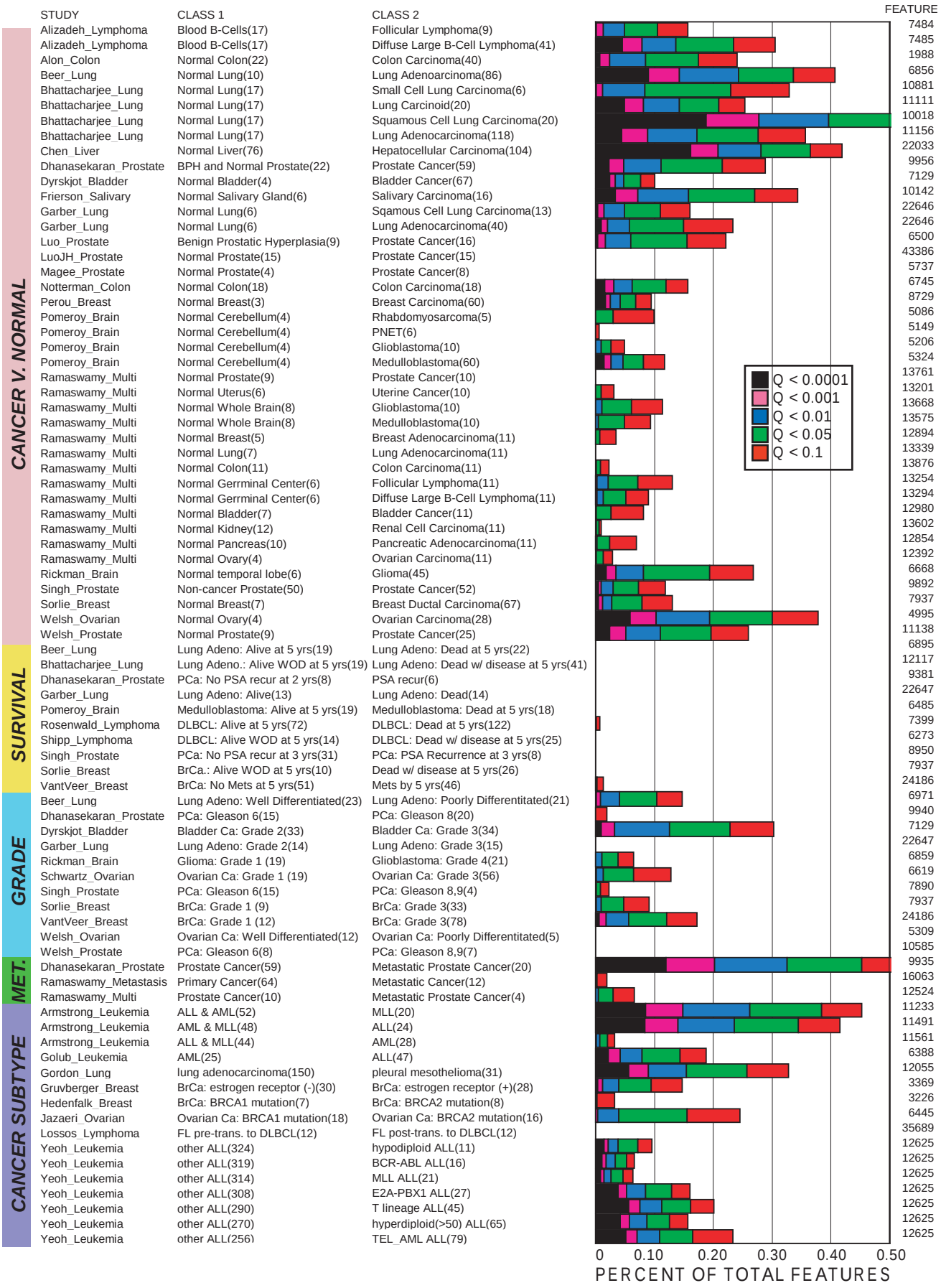
Study Name	Class 1 Description	Class 2 Description	*n*	Accuracy	*P* value	
Giordano_Adrenal	Adrenocortical Adenoma, Macronodular Hyperplasia, Normal Adrenal Cortex	Adrenocorticoal Carcinoma	19	0.895	0.000595	**
Gutmann_Astrocytoma	Normal White Matter	Pilocytic Astrocytoma	11	0.909	0.024242	*
Higgins_Renal	Normal Kidney	Clear Renal Cell Carcinoma	29	1.000	0.000274	**
Iacobuzio_Pancreas_II	Normal Pancreas	Pancreatic Adenocarcinoma	17	0.882	0.009858	**
LaTulippe_Prostate	Non-neoplastic Prostate	Primary Prostate Carcinoma	26	0.846	0.084615	
Mutter_Endometrium	Normal Endometrium	Endometrioid Adenocarcinoma	14	0.929	0.010989	*
Powell_Lung	Non-Malignant Lung	Lung Adenocarcinoma	22	0.864	0.000953	**
Rosenwald_Lymphoma	Normal Blood CD19+ B-Cells, Normal Germinal Center B-Cells	Diffuse Large B-Cell Lymphoma	284	0.718	0.116676	
Watson_Brain	Non-neoplastic Meningium	Meningioma	18	0.944	0.019608	*
Median			19	0.894737	0.010989	

The classification accuracy and statistical significance of the universal meta-signature in the test data sets. The class of each sample was predicted using a leave-one-out voting classifier (see *Methods*). *n* is the total number of samples that were predicted. Accuracy is the fraction of total samples that were classified correctly. *P* values were generated using Fisher's exact test. Significant *P* values ($P < 0.05$) are marked with an asterisk and highly significant *P* values ($P < 0.01$) are marked with double asterisks.

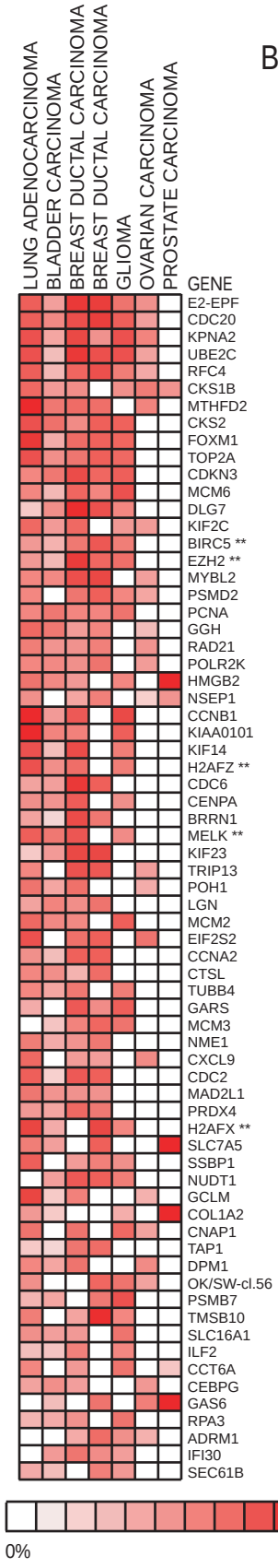
Table 4. Undifferentiated meta-signature test data sets

Study Name	Class 1 Description	Class 2 Description	*n*	Accuracy	*P* value	
Khatua_Astrocytoma	Grade: Low	Grade: High	13	0.923	0.004662	**
Mutter_Endometrium	Grade: 1	Grade: 3	7	0.571	0.714286	
Powell_Lung	Grade: Well	Grade: Poor	7	0.571	0.714286	
Schaner_Ovarian	Low Grade	High Grade	41	0.732	0.006625	**
Sotiriou_Breast_II	Low Grade	High Grade	61	0.738	0.000365	**
Median			13	0.731707	0.006625	

The classification accuracy and statistical significance of the undifferentiated meta-signature in the test data sets. The class of each sample was predicted using a leave-one-out voting classifier (see *Methods*). *n* is the total number of samples that were predicted. Accuracy is the fraction of total samples that were classified correctly. *P* values were generated using Fisher's exact test. Highly significant *P* values ($P < 0.01$) are marked with double asterisks.


CANCER V. NORMAL
SURVIVAL
GRADE
MET.
CANCER SUBTYPE
STUDY
CLASS 1
CLASS 2
FEATURE
Alizadeh_Lymphoma Blood B-Cells(17) Follicular Lymphoma(9) 7484
Alizadeh_Lymphoma Blood B-Cells(17) Diffuse Large B-Cell Lymphoma(41) 7485
Alon_Colon Normal Colon(22) Colon Carcinoma(40) 1988
Beer_Lung Normal Lung(10) Lung Adenoarcinoma(86) 6856
Bhattacharjee_Lung Normal Lung(17) Small Cell Lung Carcinoma(6) 10881
Bhattacharjee_Lung Normal Lung(17) Lung Carcinoid(20) 11111
Bhattacharjee_Lung Normal Lung(17) Squamous Cell Lung Carcinoma(20) 10018
Bhattacharjee_Lung Normal Lung(17) Lung Adenocarcinoma(118) 11156
Chen_Liver Normal Liver(76) Hepatocellular Carcinoma(104) 22033
Dhanasekaran_Prostate BPH and Normal Prostate(22) Prostate Cancer(59) 9956
Dyrskjot_Bladder Normal Bladder(4) Bladder Cancer(67) 7129
Frierson_Salivary Normal Salivary Gland(6) Salivary Carcinoma(16) 10142
Garber_Lung Normal Lung(6) Sqamous Cell Lung Carcinoma(13) 22646
Garber_Lung Normal Lung(6) Lung Adenocarcinoma(40) 22646
Luo_Prostate Benign Prostatic Hyperplasia(9) Prostate Cancer(16) 6500
LuoJH_Prostate Normal Prostate(15) Prostate Cancer(15) 43386
Magee_Prostate Normal Prostate(4) Prostate Cancer(8) 5737
Notterman_Colon Normal Colon(18) Colon Carcinoma(18) 6745
Perou_Breast Normal Breast(3) Breast Carcinoma(60) 8729
Pomeroy_Brain Normal Cerebellum(4) Rhabdomyosarcoma(5) 5086
Pomeroy_Brain Normal Cerebellum(4) PNET(6) 5149
Pomeroy_Brain Normal Cerebellum(4) Glioblastoma(10) 5206
Pomeroy_Brain Normal Cerebellum(4) Medulloblastoma(60) 5324
Ramaswamy_Multi Normal Prostate(9) Prostate Cancer(10) 13761
Ramaswamy_Multi Normal Uterus(6) Uterine Cancer(10) 13201
Ramaswamy_Multi Normal Whole Brain(8) Glioblastoma(10) 13668
Ramaswamy_Multi Normal Whole Brain(8) Medulloblastoma(10) 13575
Ramaswamy_Multi Normal Breast(5) Breast Adenocarcinoma(11) 12894
Ramaswamy_Multi Normal Lung(7) Lung Adenocarcinoma(11) 13339
Ramaswamy_Multi Normal Colon(11) Colon Carcinoma(11) 13876
Ramaswamy_Multi Normal Gerrminal Center(6) Follicular Lymphoma(11) 13254
Ramaswamy_Multi Normal Gerrminal Center(6) Diffuse Large B-Cell Lymphoma(11) 13294
Ramaswamy_Multi Normal Bladder(7) Bladder Cancer(11) 12980
Ramaswamy_Multi Normal Kidney(12) Renal Cell Carcinoma(11) 13602
Ramaswamy_Multi Normal Pancreas(10) Pancreatic Adenocarcinoma(11) 12854
Ramaswamy_Multi Normal Ovary(4) Ovarian Carcinoma(11) 12392
Rickman_Brain Normal temporal lobe(6) Glioma(45) 6668
Singh_Prostate Non-cancer Prostate(50) Prostate Cancer(52) 9892
Sorlie_Breast Normal Breast(7) Breast Ductal Carcinoma(67) 7937
Welsh_Ovarian Normal Ovary(4) Ovarian Carcinoma(28) 4995
Welsh_Prostate Normal Prostate(9) Prostate Cancer(25) 11138
Beer_Lung Lung Adeno: Alive at 5 yrs(19) Lung Adeno: Dead at 5 yrs(22) 6895
Bhattacharjee_Lung Lung Adeno.: Alive WOD at 5 yrs(19) Lung Adeno: Dead w/ disease at 5 yrs(41) 12117
Dhanasekaran_Prostate PCa: No PSA recur at 2 yrs(8) PSA recur(6) 9381
Garber_Lung Lung Adeno: Alive(13) Lung Adeno: Dead(14) 22647
Pomeroy_Brain Medulloblastoma: Alive at 5 yrs(19) Medulloblastoma: Dead at 5 yrs(18) 6485
Rosenwald_Lymphoma DLBCL: Alive at 5 yrs(72) DLBCL: Dead at 5 yrs(122) 7399
Shipp_Lymphoma DLBCL: Alive WOD at 5 yrs(14) DLBCL: Dead w/ disease at 5 yrs(25) 6273
Singh_Prostate PCa: No PSA recur at 3 yrs(31) PCa: PSA Recurrence at 3 yrs(8) 8950
Sorlie_Breast BrCa.: Alive WOD at 5 yrs(10) Dead w/ disease at 5 yrs(26) 7937
VantVeer_Breast BrCa: No Mets at 5 yrs(51) Mets by 5 yrs(46) 24186
Beer_Lung Lung Adeno: Well Differentiated(23) Lung Adeno: Poorly Differentitated(21) 6971
Dhanasekaran_Prostate PCa: Gleason 6(15) PCa: Gleason 8(20) 9940
Dyrskjot_Bladder Bladder Ca: Grade 2(33) Bladder Ca: Grade 3(34) 7129
Garber_Lung Lung Adeno: Grade 2(14) Lung Adeno: Grade 3(15) 22647
Rickman_Brain Glioma: Grade 1 (19) Glioblastoma: Grade 4(21) 6859
Schwartz_Ovarian Ovarian Ca: Grade 1 (19) Ovarian Ca: Grade 3(56) 6619
Singh_Prostate PCa: Gleason 6(15) PCa: Gleason 8,9(4) 7890
Sorlie_Breast BrCa: Grade 1 (9) BrCa: Grade 3(33) 7937
VantVeer_Breast BrCa: Grade 1 (12) BrCa: Grade 3(78) 24186
Welsh_Ovarian Ovarian Ca: Well Differentiated(12) Ovarian Ca: Poorly Differentitated(5) 5309
Welsh_Prostate PCa: Gleason 6(8) PCa: Gleason 8,9(7) 10585
Dhanasekaran_Prostate Prostate Cancer(59) Metastatic Prostate Cancer(20) 9935
Ramaswamy_Metastasis Primary Cancer(64) Metastatic Cancer(12) 16063
Ramaswamy_Multi Prostate Cancer(10) Metastatic Prostate Cancer(4) 12524
Armstrong_Leukemia ALL & AML(52) MLL(20) 11233
Armstrong_Leukemia AML & MLL(48) ALL(24) 11491
Armstrong_Leukemia ALL & MLL(44) AML(28) 11561
Golub_Leukemia AML(25) ALL(47) 6388
Gordon_Lung lung adenocarcinoma(150) pleural mesothelioma(31) 12055
Gruvberger_Breast BrCa: estrogen receptor (-)(30) BrCa: estrogen receptor (+)(28) 3369
Hedenfalk_Breast BrCa: BRCA1 mutation(7) BrCa: BRCA2 mutation(8) 3226
Jazaeri_Ovarian Ovarian Ca: BRCA1 mutation(18) Ovarian Ca: BRCA2 mutation(16) 6445
Lossos_Lymphoma FL pre-trans. to DLBCL(12) FL post-trans. to DLBCL(12) 35689
Yeoh_Leukemia other ALL(324) hypodiploid ALL(11) 12625
Yeoh_Leukemia other ALL(319) BCR-ABL ALL(16) 12625
Yeoh_Leukemia other ALL(314) MLL ALL(21) 12625
Yeoh_Leukemia other ALL(308) E2A-PBX1 ALL(27) 12625
Yeoh_Leukemia other ALL(290) T lineage ALL(45) 12625
Yeoh_Leukemia other ALL(270) hyperdiploid(>50) ALL(65) 12625
Yeoh_Leukemia other ALL(256) TEL_AML ALL(79) 12625
Q < 0.0001
Q < 0.001
Q < 0.01
Q < 0.05
Q < 0.1
0
0.10
0.20
0.30
0.40
0.50
PERCENT OF TOTAL FEATURES

A



B

	STUDY	CLASS1	CLASS2	P-VAL
A	Beer_Lung	Well Differentiated Lung Adeno.	Poorly Differentitated	<0.001
B	Garber_Lung	Grade 2 Lung Adenocarcinoma	Grade 3	NA
C	Rickman_Brain	Grade 1 Medulloblastoma	Grade 4	<0.001
D	Schwartz_Ovarian	Grade 1 Ovarian Carcinoma	Grade 3	<0.001
E	Singh_Prostate	Gleason 6 Prostate Cancer	Gleason 8,9	0.750
F	Sorlie_Breast	Grade 1 Breast Carcinoma	Grade 3	<0.001
G	VantVeer_Breast	Grade 1 Breast Carcinoma	Grade 3	<0.001
H	Welsh_Ovarian	Well Differentiated Ovarian Ca.	Poorly Differentitated	0.005
I	Welsh_Prostate	Gleason 6 Prostate Cancer	Gleason 8,9	0.143
J	Dyrskjot_Bladder	Grade 2 Bladder Cancer	Grade 3	<0.001
K	Dhanasekaran_Prostate	Gleason 6 Prostate Cancer	Gleason 8	0.118