	Beer			GSE8894			GSE3141		
	coef	pval	threshold	coef	pval	threshold	coef	pval	threshold
ASSEMBLY_OF_THE_PRE_REPLICATIVE_COMPLEX	0.520099	0.000415	0.386737	1.21574	0.000892	0.861136	0.710268	0.046145	0.55635
CYCLIN_E_ASSOCIATED_EVENTS_DURING_G1_S_TRANSITION_	0.42974	0.003513	0.247331	0.792707	0.027953	0.547786	0.716713	0.044535	0.213168
DNA_STRAND_ELONGATION	0.71499	1.00E-06	1.274833	1.071312	0.003607	1.391335	0.716089	0.04458	1.193017
FACILITATIVE_NA_INDEPENDENT_GLUCOSE_TRANSPORTERS	0.354506	0.01565	0.168691	0.763299	0.033131	-0.24277	1.184847	0.001134	-0.27284
G1_S_SPECIFIC_TRANSCRIPTION	0.830124	0	0.890295	0.944739	0.00934	1.179604	0.702067	0.049373	0.167741
G2_M_CHECKPOINTS	0.705606	2.00E-06	0.816311	0.904154	0.011586	1.161367	0.709231	0.04604	1.045875
GLUCOSE_TRANSPORT	0.770402	0	0.678839	0.700776	0.049534	0.284518	0.913949	0.010858	-0.28531
INTERACTIONS_OF_VPR_WITH_HOST_CELLULAR_PROTEINS	0.545955	0.000228	0.742698	0.841117	0.019373	0.558675	0.830168	0.019384	0.185536
M_G1_TRANSITION	0.552641	0.000178	0.513903	1.032637	0.00431	0.877324	0.733152	0.039056	0.637421
METABOLISM_OF_NUCLEOTIDES	0.415754	0.004697	0.674579	0.987276	0.006085	0.720526	0.701953	0.048824	0.607988
PHOSPHORYLATION_OF_THE_APC_C	0.688238	3.00E-06	0.487527	0.897167	0.013935	0.775273	0.743429	0.035953	0.891884
POL_SWITCHING	0.765461	0	0.759954	1.298079	0.000486	1.169592	0.742413	0.038171	0.909319
PROCESSING_OF_CAPPED_INTRONLESS_PRE_MRNA	0.44213	0.002712	0.238756	1.199786	0.001042	0.637821	0.715653	0.043672	0.673775
PYRIMIDINE_METABOLISM	0.496914	0.000737	0.670047	0.865313	0.015118	0.505466	0.76726	0.030959	0.15402
RECRUITMENT_OF_NUMA_TO_MITOTIC_CENTROSOMES	0.591678	6.10E-05	0.478313	0.850128	0.01803	1.178261	0.740686	0.038929	0.960324
REGULATION_OF_MITOTIC_CELL_CYCLE	0.657655	9.00E-06	0.47527	0.888198	0.013234	0.760152	0.74365	0.036574	0.567474
REPAIR_SYNTHESIS_FOR_GAP_FILLING_BY_DNA_POL_IN_TC_NER	0.761335	0	1.102294	1.298079	0.000486	1.339255	0.906748	0.011015	1.208045
SYNTHESIS_AND_INTERCONVERSION_OF_NUCLEOTIDE_DI_AND_TRIPHOSPHA	0.495164	0.000785	0.81846	0.731939	0.040875	1.201097	0.767719	0.032327	1.280663
SYNTHESIS_OF_DNA	0.575068	9.80E-05	0.589823	1.032637	0.00431	0.963818	0.733152	0.039056	0.718498
UNWINDING_OF_DNA	0.664002	7.00E-06	1.968073	0.884732	0.013615	1.719352	0.777411	0.028587	1.531343

Table S1. Pathways associated with LUAD survival validated in two independent datasets
logrank *P*-value, comparing tumors with the top half pathway aberrance score (Average Z) to the bottom.

	Beer			GSE8894			GSE3141		
	coef	pval	threshold	coef	pval	threshold	coef	pval	threshold
ADHERENS_JUNCTIONS_INTERACTIONS	0.580809	0.003937	0.515289	0.803043	0.033333	0.478781	0.78677	0.044593	0.99167
GAP_JUNCTION_DEGRADATION	0.568966	4.55E-03	0.182579	0.831931	0.027237	-0.001708	0.813155	0.037467	-0.967199
INTRINSIC_PATHWAY_FOR_APOPTOSIS	-0.472539	0.017116	0.035261	-0.744507	0.044561	0.208941	-0.836866	0.031967	0.165251
L1CAM_INTERACTIONS	0.706449	0.000528	0.157654	0.88618	0.018241	0.004561	0.792884	0.037562	0.188119
NOTCH_HLH_TRANSCRIPTION_PATHWAY	0.390127	4.95E-02	-0.141586	0.788812	0.032906	-0.211466	1.097072	0.005562	-0.069358
PHOSPHOLIPASE_C_MEDIATED_CASCADE	0.591627	0.0033	-0.491437	0.928898	0.013105	-0.575735	-0.917032	0.01827	-0.083575
SMOOTH_MUSCLE_CONTRACTION	0.655274	0.00125	0.437407	0.800452	0.033892	0.101368	0.937309	0.015528	0.711228

Table S2. Pathways associated with colon cancer survival validated in two independent datasets
logrank *P*-value, comparing tumors with the top half pathway aberrance score (Average Z) to the bottom.

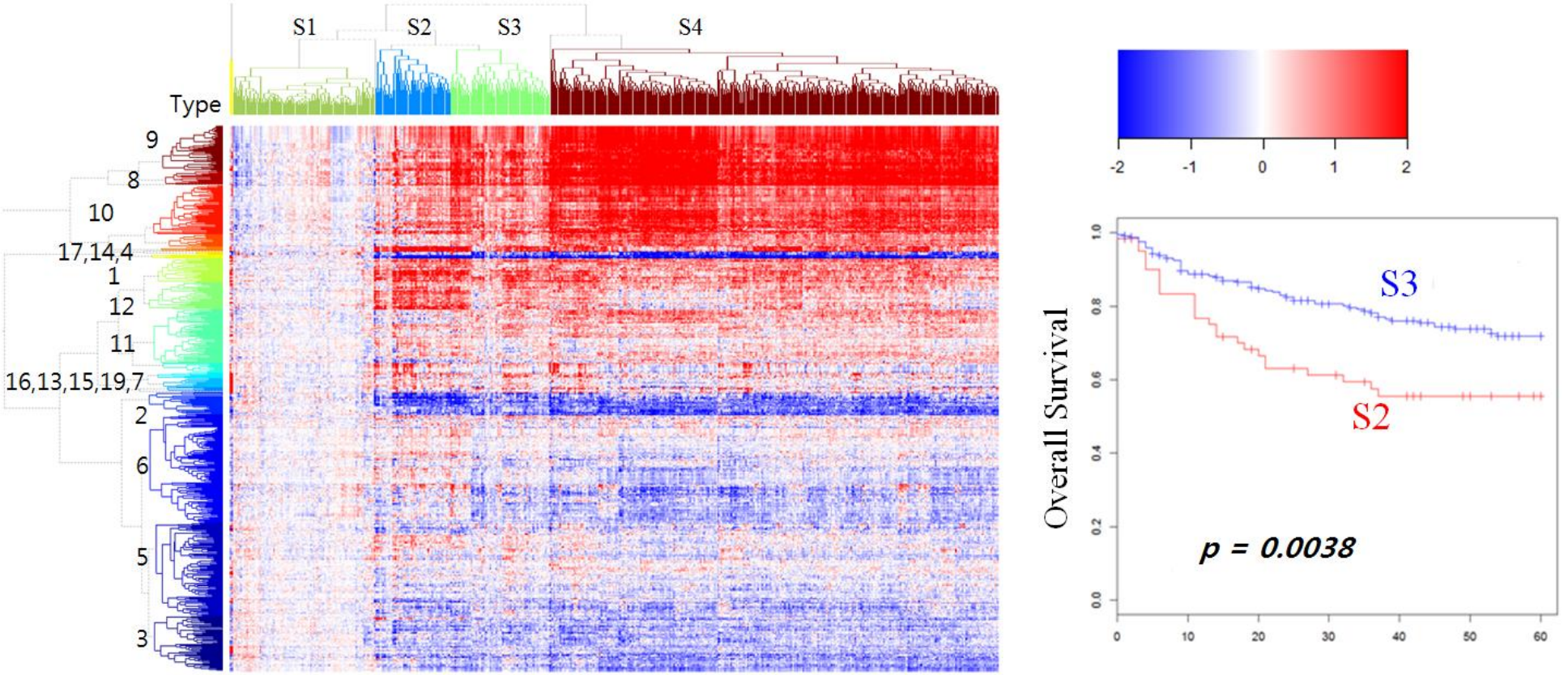

Fig. S1 Unbiased clustering using iPAS of colon cancer dataset. Pathways (n = 583) and samples (n = 443) are clustered according to iPAS (Average Z). Normal samples are clustered at left (S1). Tumors (S2~S4) deviate from normal, being both up- and down-regulated, (darker red and blue, respectively). Sample clusters represent well the overall survival of patients (P = 0.0038). There were no survival differences between the sample cluster pairs of (S2,S4) and (S3,S4).

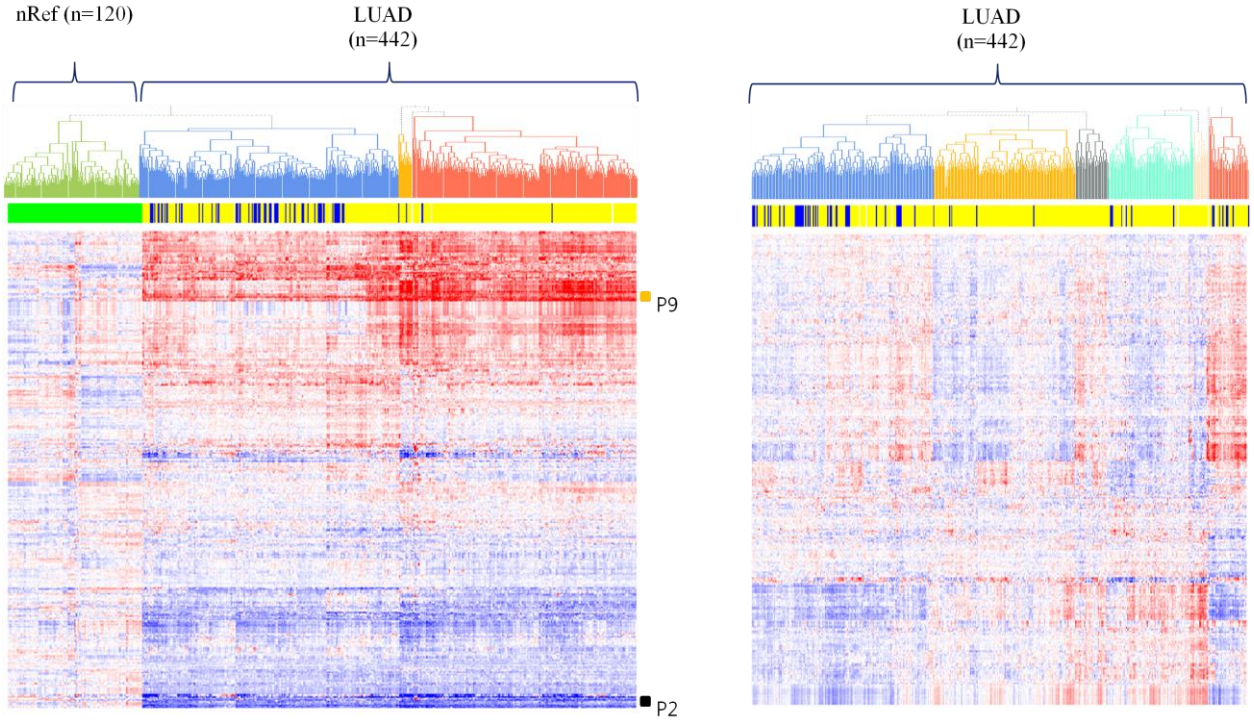

Fig. S2 nRef-based approach (left) and the conventional approach (right) provide different interpretations.
The same data was processed with two different approaches. The approach using nRef can identify globally up- or down-regulated pathways in cancer samples can also identify variant pathways across cancer samples. The conventional approach considers all cancer samples as a cohort, and then normalizes all of the samples together. Pathway score is represented in the conventional approach by averaging standardized gene expression values, where the mean and standard deviation of all cancer samples are used for standardization. Because an individual samples' pathway statistic is affected by the context of other cancer samples, pathways commonly up- or down-regulated in all cancer samples can be obscured.

Pathway name (REACTOME)	Average Z	GSEA	Fisher	Euclidean	Mahalanobis	Mean
REACTOME_AMINO_ACID_SYNTHESIS_AND_INTERCONVERSION_TRANSAMINATION	0.936	0.950	0.914	0.958	0.980	0.947
REACTOME_UNWINDING_OF_DNA	0.937	0.942	0.833	0.920	0.937	0.914
REACTOME_O_LINKED_GLYCOSYLATION_OF_MUCINS	0.925	0.939	0.833	0.955	0.910	0.912
REACTOME_SYNTHESIS_AND_INTERCONVERSION_OF_NUCLEOTIDE_DI_AND_TRIPHOSPHA	0.941	0.953	0.738	0.932	0.946	0.902
REACTOME_APC_CDC20_MEDIATED_DEGRADATION_OF_NEK2A	0.885	0.906	0.799	0.945	0.948	0.897
REACTOME_PURINE_RIBONUCLEOSIDE_MONOPHOSPHATE_BIOSYNTHESIS	0.905	0.915	0.820	0.921	0.912	0.895
REACTOME_PURINE_METABOLISM	0.915	0.918	0.729	0.945	0.936	0.889
REACTOME_DNA_STRAND_ELONGATION	0.889	0.920	0.783	0.930	0.916	0.888
REACTOME_DEGRADATION_OF_THE_EXTRACELLULAR_MATRIX	0.839	0.906	0.804	0.964	0.918	0.886
REACTOME_G1_S_SPECIFIC_TRANSCRIPTION	0.837	0.876	0.813	0.945	0.957	0.886
REACTOME_G0_AND_EARLY_G1	0.873	0.888	0.767	0.948	0.948	0.885
REACTOME_KINESINS	0.862	0.878	0.809	0.928	0.938	0.883
REACTOME_GLUCONEOGENESIS	0.890	0.910	0.783	0.903	0.902	0.877
REACTOME_ACTIVATION_OF_THE_PRE_REPLICATIVE_COMPLEX	0.892	0.908	0.737	0.909	0.918	0.873
REACTOME_E2F_MEDIATED_REGULATION_OF_DNA_REPLICATION	0.903	0.903	0.725	0.925	0.893	0.870
REACTOME_DEPOSITION_OF_NEW_CENPA_CONTAINING_NUCLEOSOMES_AT_THE_CENTROM	0.911	0.930	0.828	0.966	0.706	0.868
REACTOME_EXTENSION_OF_TELOMERES	0.840	0.889	0.762	0.913	0.926	0.866
REACTOME_CELL_CYCLE	0.894	0.922	0.766	0.955	0.780	0.863
REACTOME_INHIBITION_OF_THE_PROTEOLYTIC_ACTIVITY_OF_APC_C_REQUIRED_FOR_	0.852	0.881	0.745	0.888	0.951	0.863

Table S3. AUC of pathway-based classification of tumor sample via different pathway summary methods