ΕΘΝΙΚΟ ΙΔΡΥΜΑ ΕΡΕΥΝΩΝ
National Hellenic Research Foundation

e-NiOS
e-Noesis Inspired Operational Systems

Radiogenomics and Colon Cancer: Results of a Collaborative DKFZ-NHRF Study

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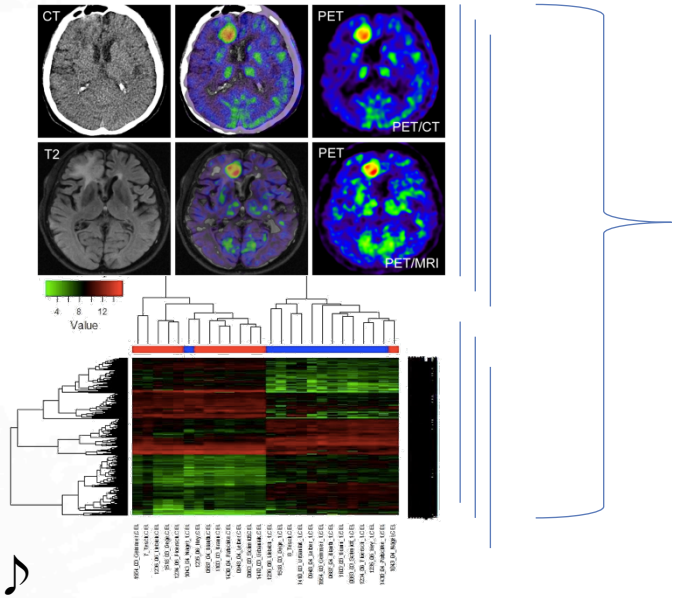
PJTECH CATALYST

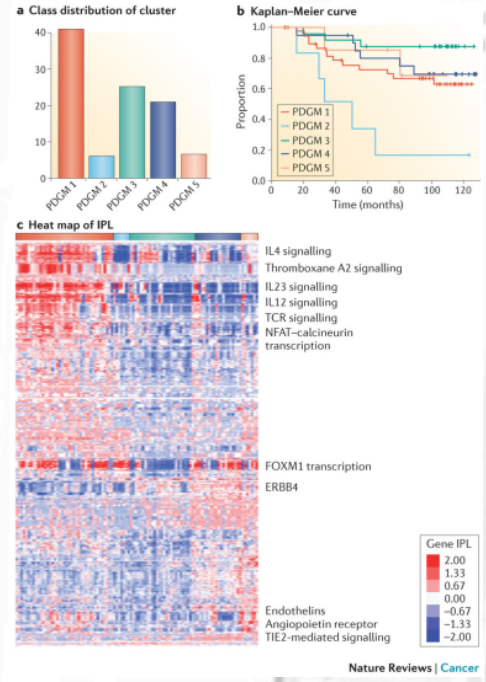
ACCC Scientific Symposium, Athens, GR, Dec, 8th 2017

iqbility
Driving Ideas ahead

Radiogenomics:A novel path for efficient disease characterization



Artificial Intelligence/ Big Data Computing



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- Digitized images (CT,MR, PET) more than pictures, they are quantitative data♪

♪

- Oncology :key application area, as patients undergo routinely either imaging and/or neat molecular characterization (tumor panels, sequencing of tumor samples)♪

- Integration of both layers, aids robust patient stratification, reveals causal phenotype–genotype associations♪

Composite signature approach:♪

♪

- Interprets patients' high–throughput omic data, through advanced AI techniques, so as to derive highly descriptive, compact signatures♪

♪

- Optimization of the initial molecular signatures, through epidemiological evaluation♪

- Signature–oriented, association with imaging/ clinical features for robust phenotypic analysis of patient cohorts, for better diagnostic / therapeutic stratification♪

CRC Dataset profile

- **30 patients** diagnosed with CRC provided by the German Cancer Research Center, Heidelberg
- 2 different Affymetrix microarray platforms: **HG-U133A** (**13** patients-**26** matched samples) & **HG-U133plus2** (**17** patients-**34** matched samples)-60 total samples.
- Examined samples acquired from frozen tissue sections of surgically removed primary colon tumor from each patient and adjacent normal mucosa
- 6 of the patients had synchronous metastases.
- Molecular data complemented by kinetic measurements of glucose uptake rate by cancer cells, as extrapolated by PET measurements.

Statistical Selection

- Non-metastatic cancer samples vs. control samples (**1853 DE genes**)
- "metastatic" vs. adjacent controls (**1166 DE genes**)
- "total" CRCs versus controls (**1760 DE**)

↓

- Common DE genes among all 3 comparisons: **911 genes**

↓

- Exploitation of 3 distinct Ontological vocabularies (Gene Ontology,REACTOME, MGI)

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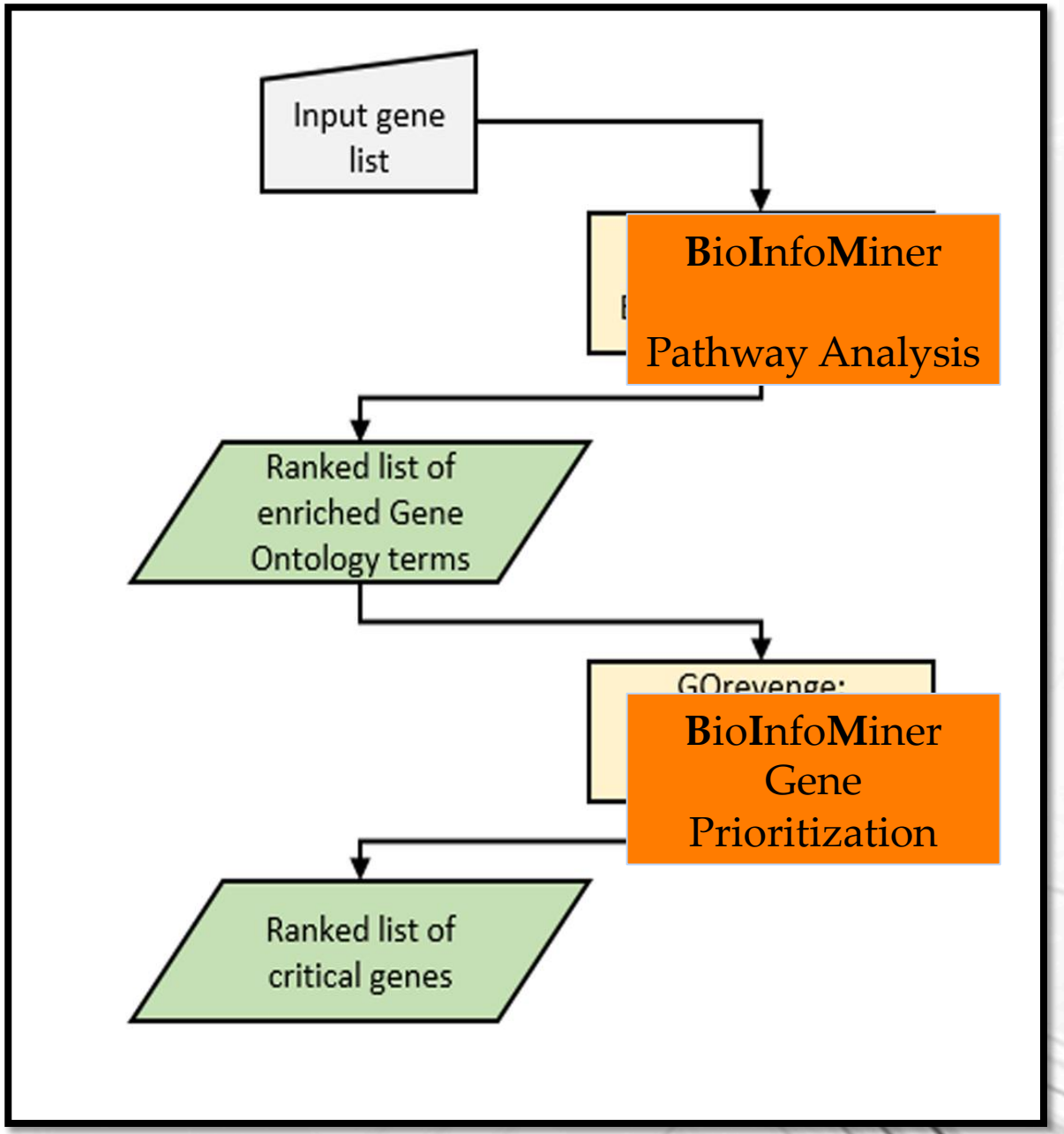
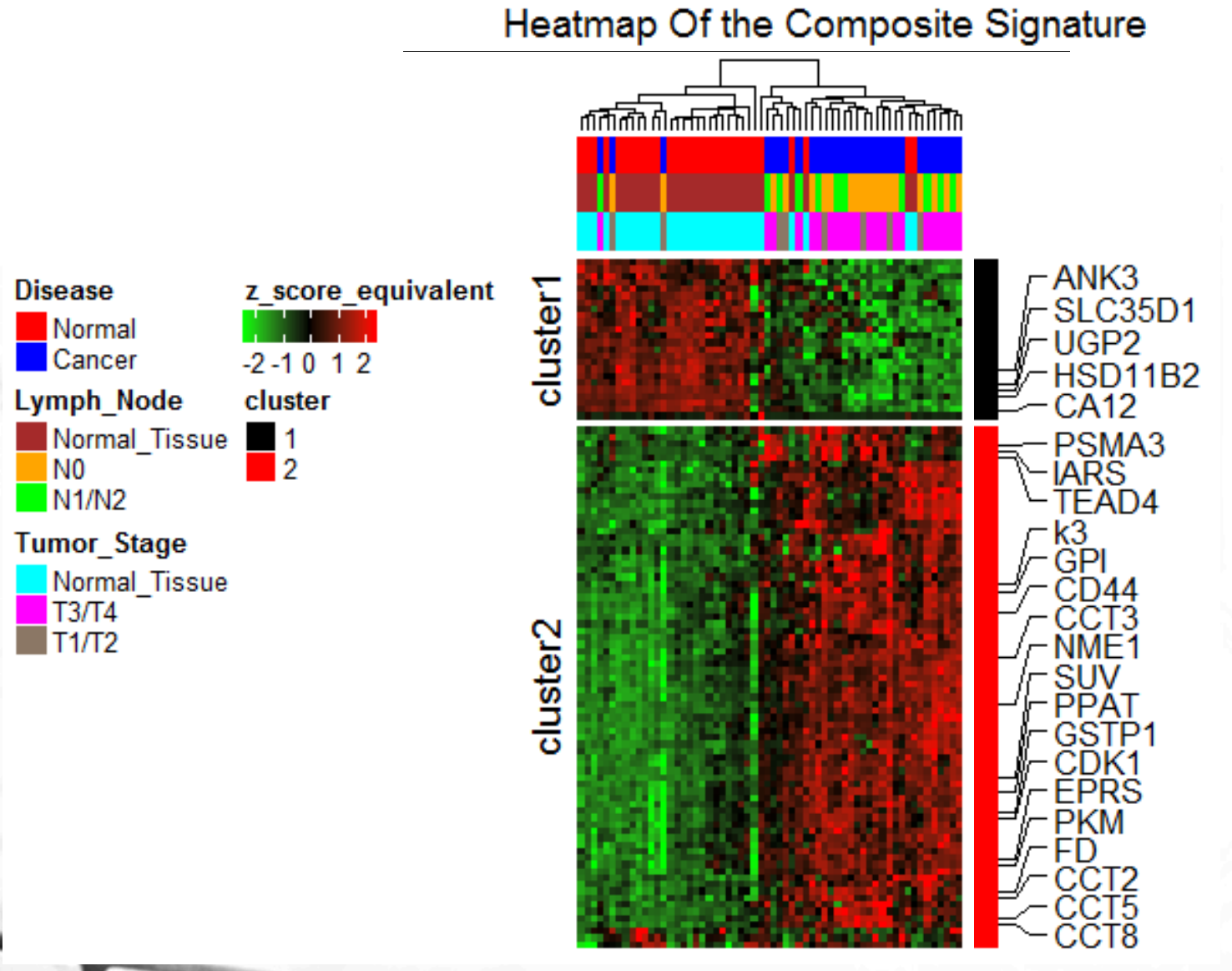
- Final list of hub genes from all 3 topological nets: **94 genes**



Integration with PET kinetic data
Composite signature of 102 features



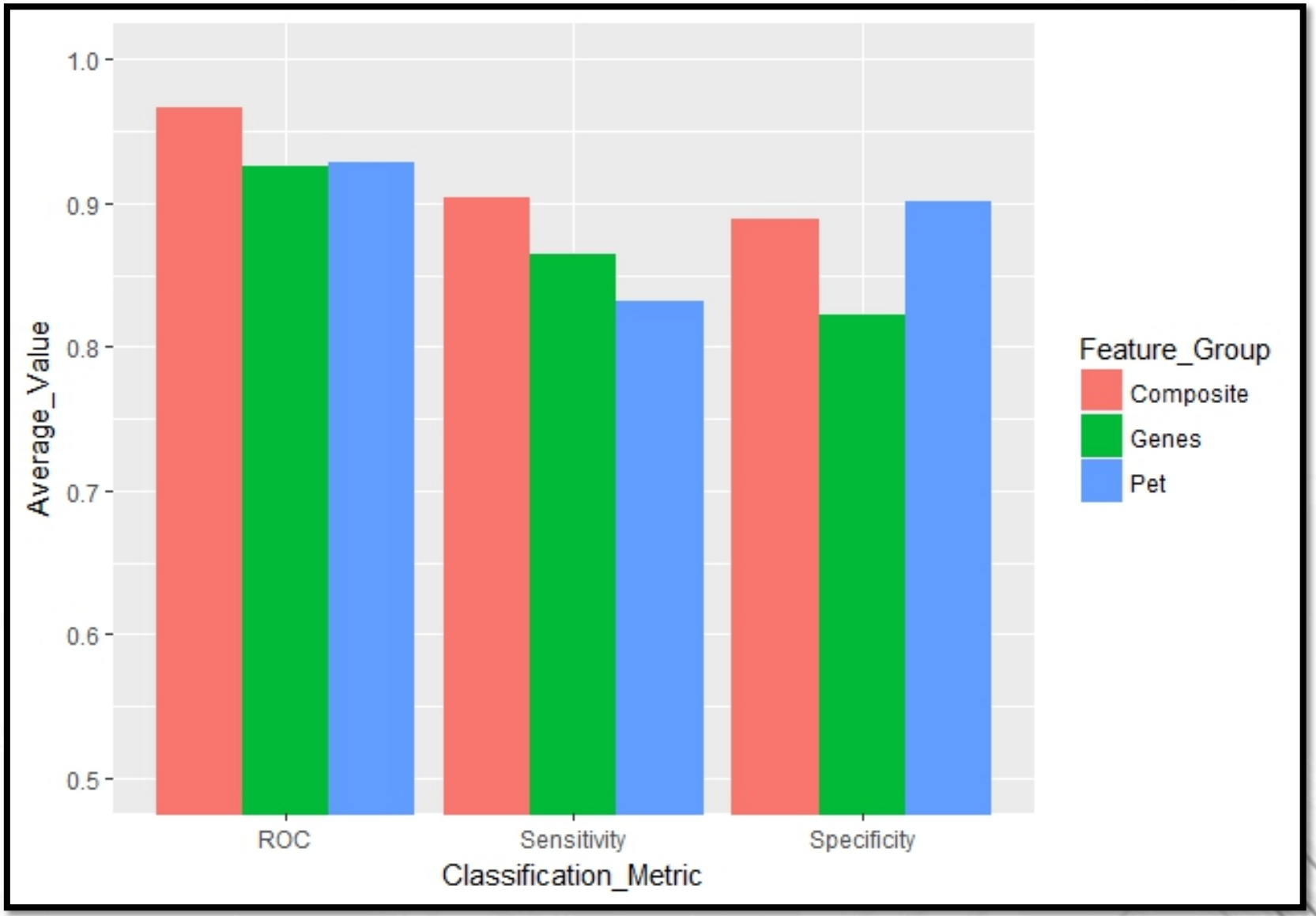
Genes showing negative correlation with PET variables:

- ✓ UDP-glucuronate biosynthetic process
- ✓ carbohydrate derivative biosynthetic process

Genes showing positive correlation with PET variables:

- ✓ positive regulation of telomere maintenance via telomerase
- ✓ positive regulation of telomere maintenance via recombination
- ✓ cell-cell recognition

Evaluation of the relative performance of the three initial signatures (102-Composite, 94-Gene, 8-PET-kinetic)



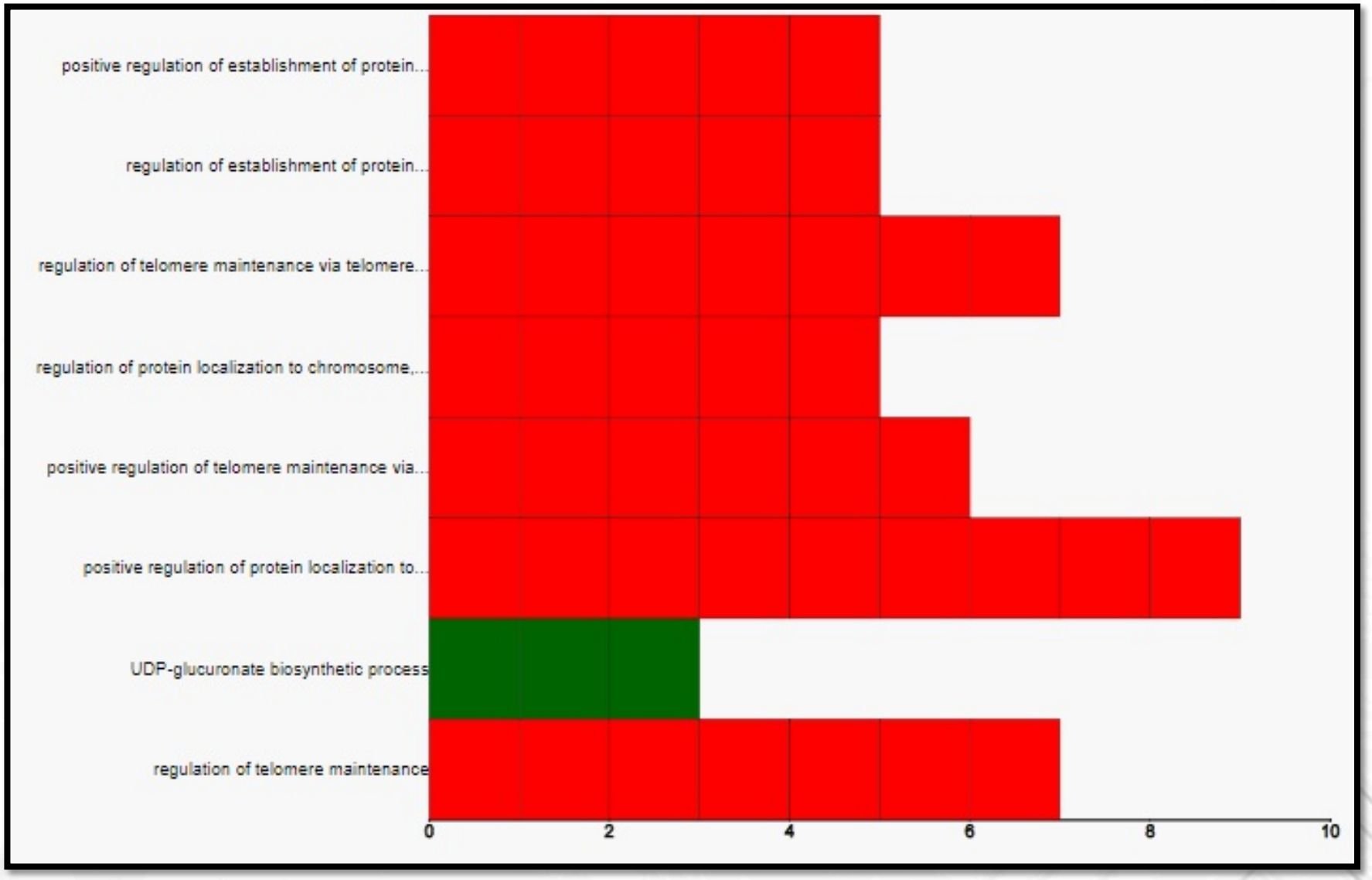
Association of gene expression and clinical data

GPI: Pluripotent functionality, glycolysis,, tumor-motility, angiogenesis

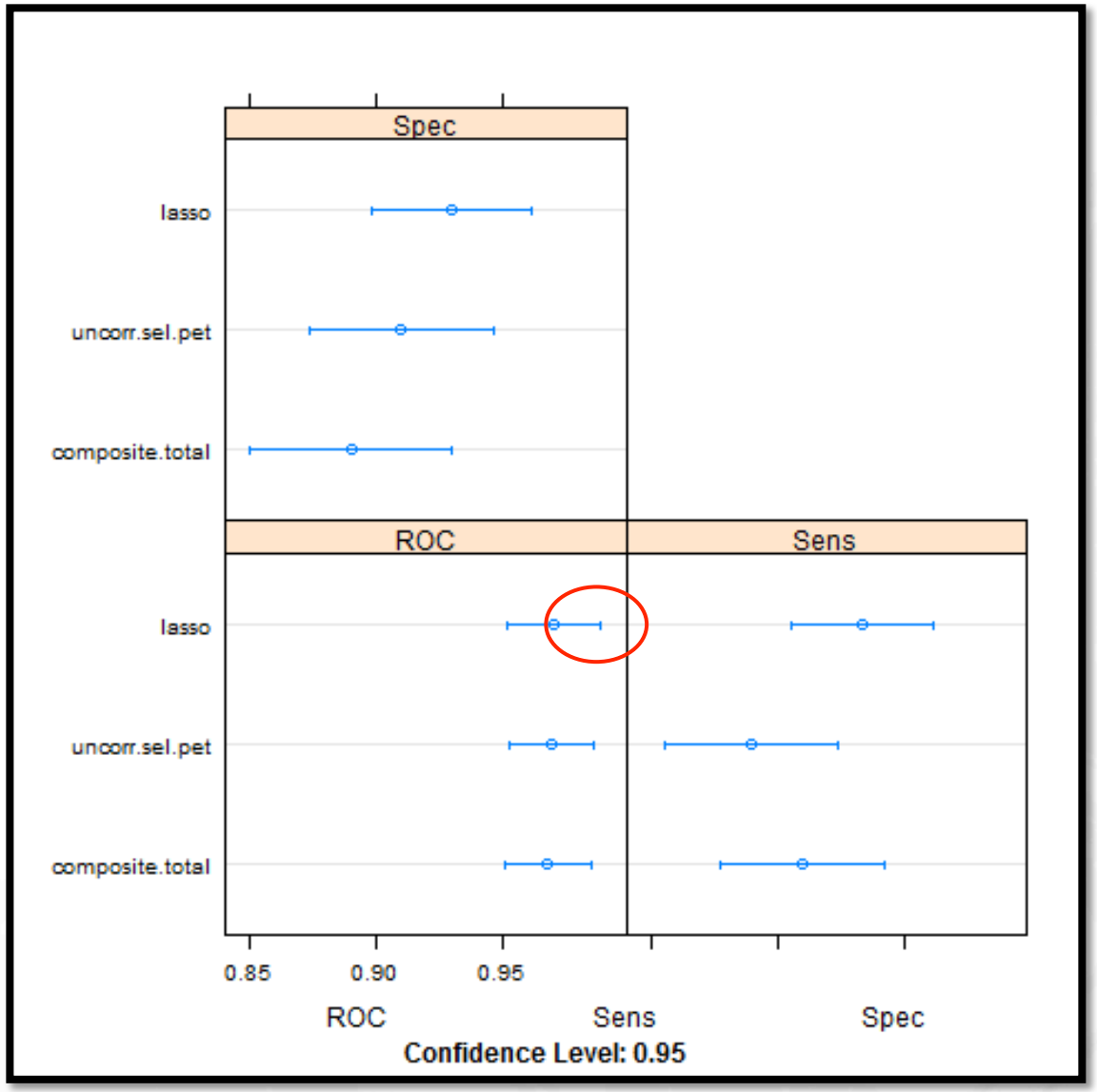
CD44: Antigen presentation, immunomodulation, Stem cell marker

UGP2: Important intermediary in carbohydrate metabolism, involved in gluconeogenesis, lactogenesis

Functional implication of 4 key PET parameters (FD, SUV, k3, INF) -- highly correlated with 46 out of the 94 genes



Optimization of the CRC Composite Signature



- Dimensionality reduction of the initial composite signature
- Regularization of the signature in order to select features with distinct role
- Important for application of targeted therapeutic approaches

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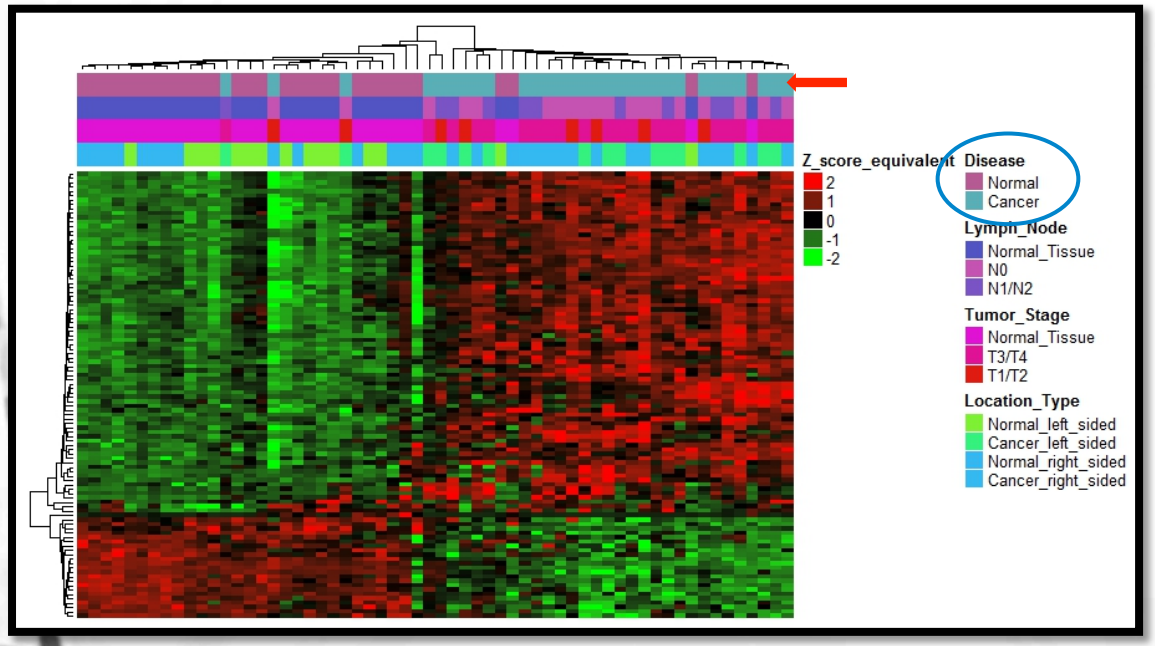
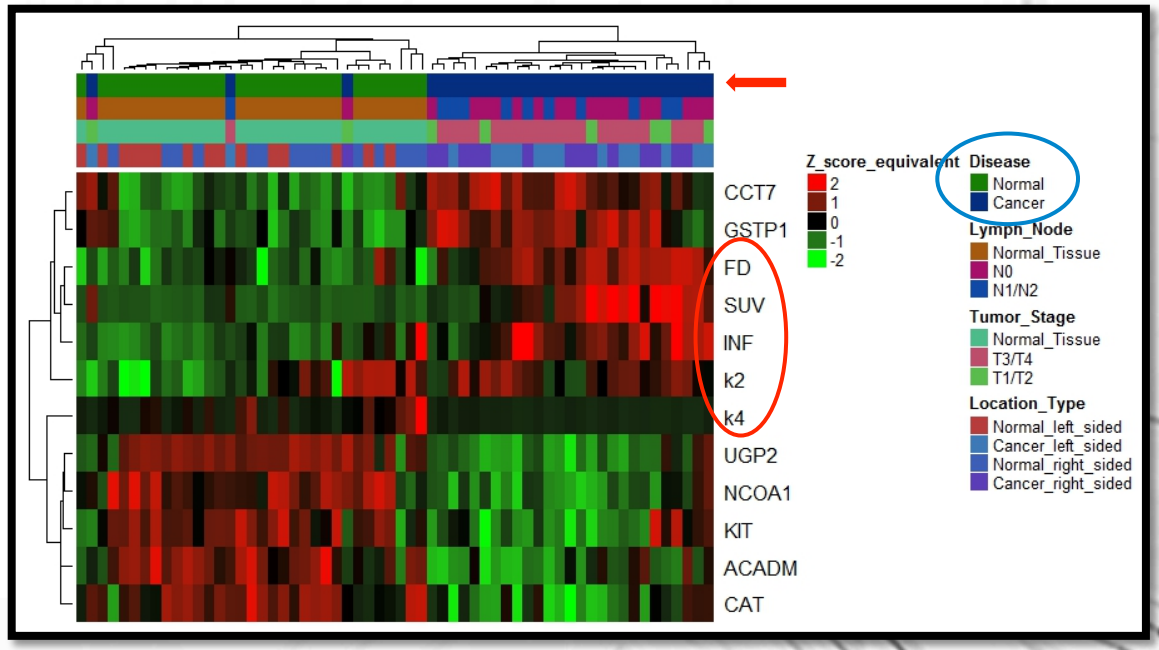
Comparative evaluation of initial and compact composite signatures

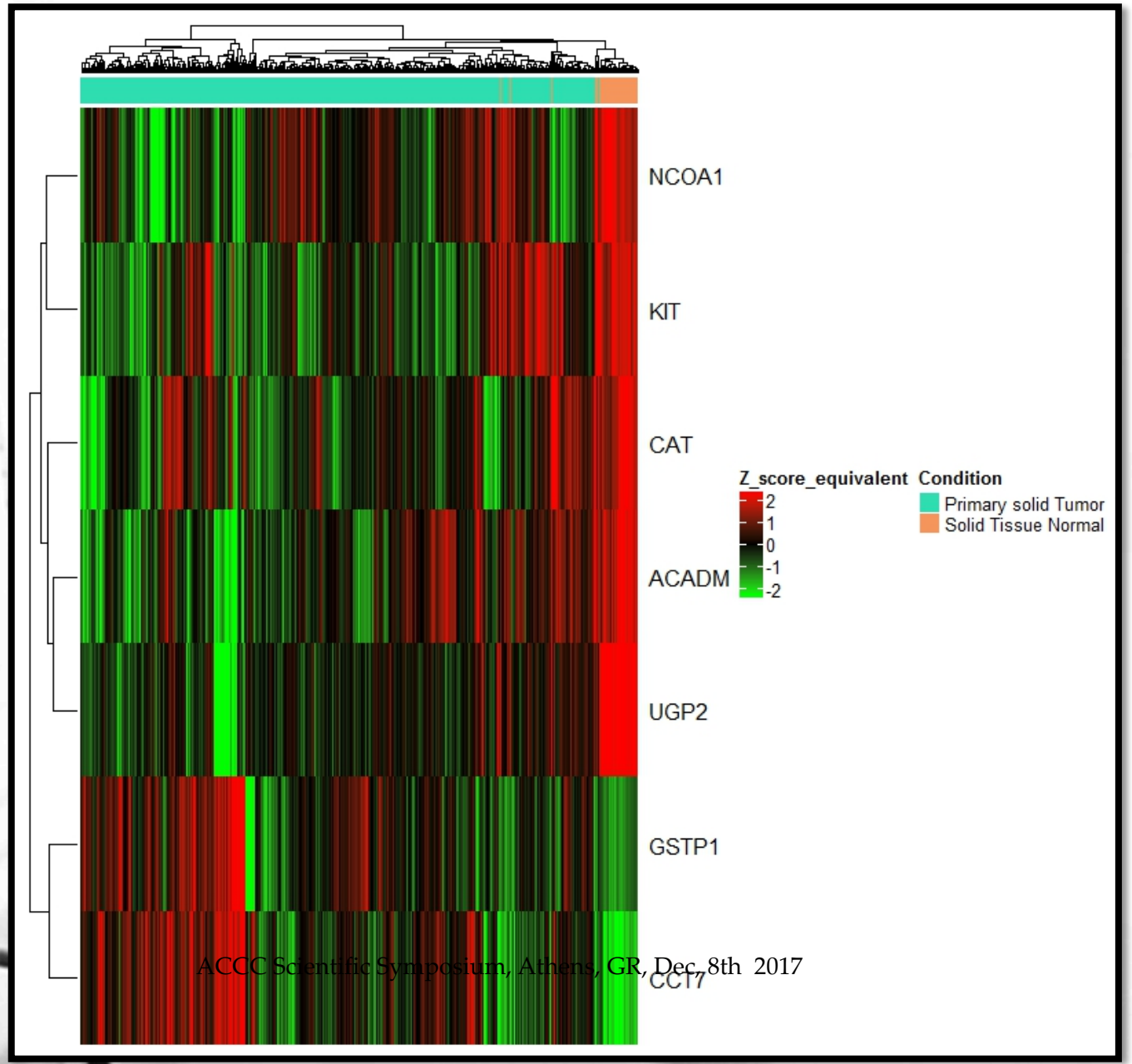
Composite signature of 102 features



Small final compact signature of 12 features

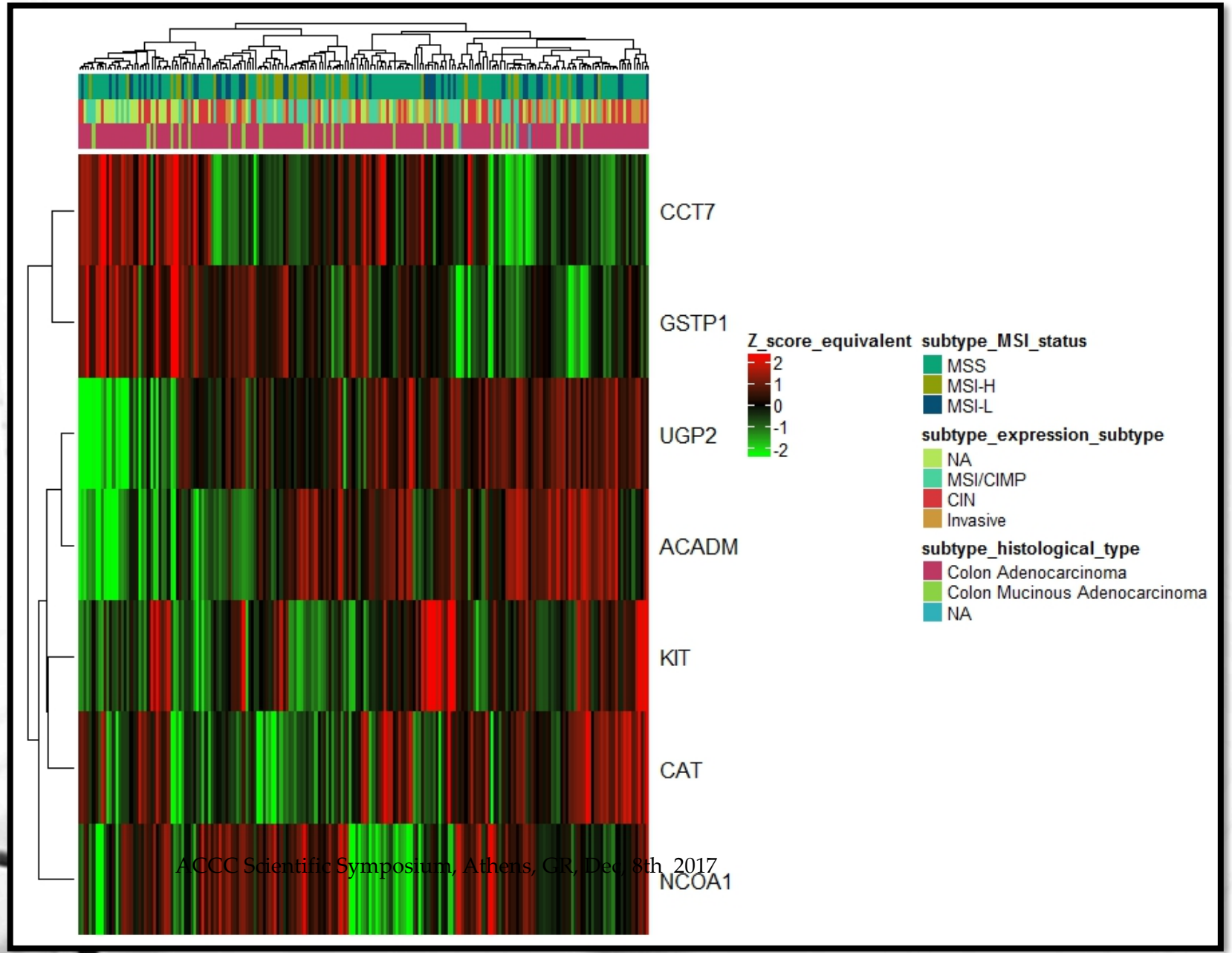


TCGA COAD RNA-Seq dataset-7 genes from lasso selection



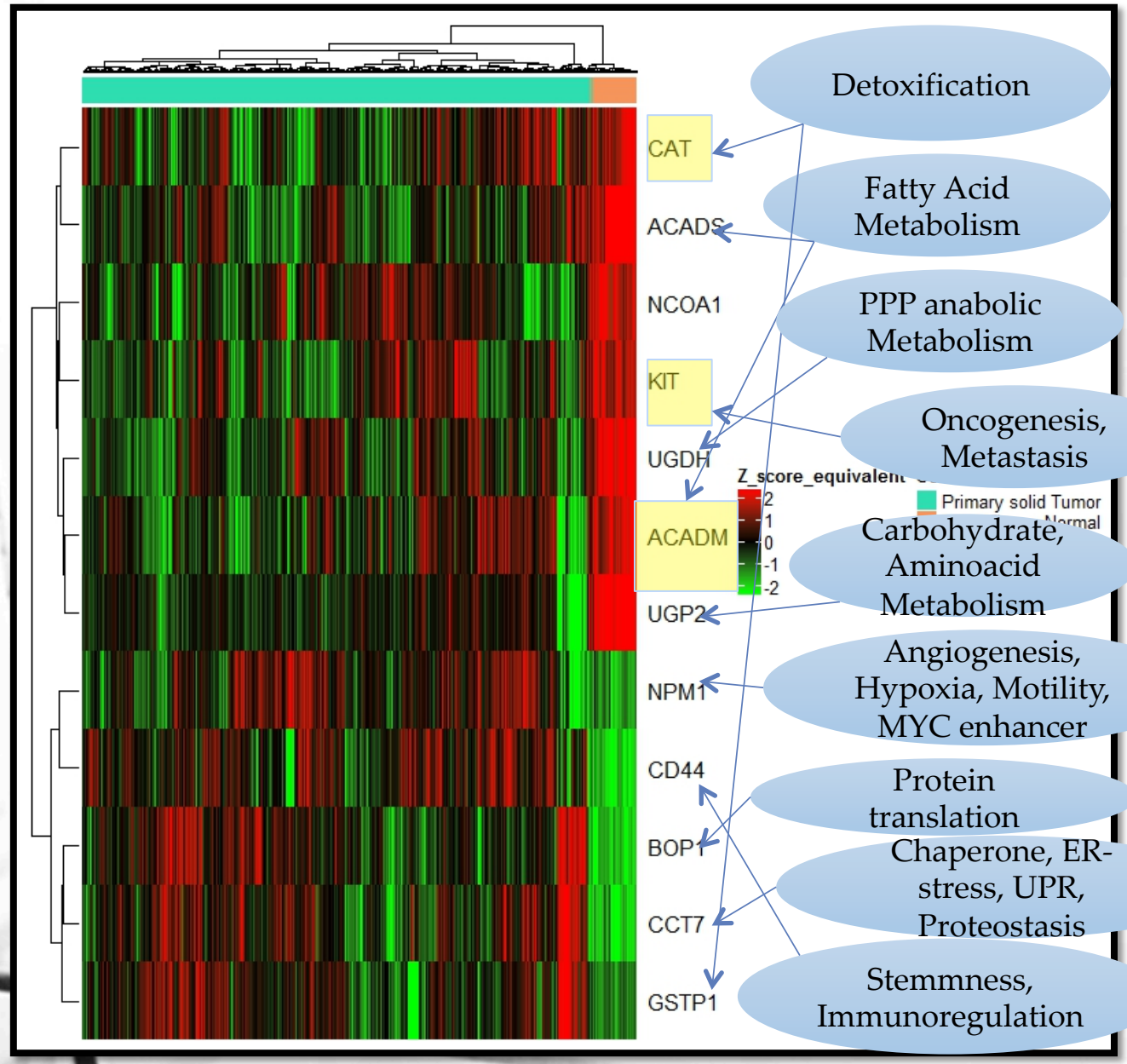
Hierarchical clustering with 7 genes from the 12 selected microarray lasso features (distance: pearson, linkage: average)-scaled HTSeq-counts (vst-transformed)-506 samples: 465 primary solid Tumors and 41 Solid Tissue Normal samples

TCGA COAD RNA-Seq dataset-7 genes-COAD subtypes



Hierarchical clustering with 7 genes from the 12 selected microarray lasso features (distance: pearson, linkage: average)-scaled HTSeq-counts (vst-transformed)-198 samples: only cancer samples with available subtype information

Epidemiological Evaluation of the compact signature in high-quality CRC RNA-Seq samples of TCGA Repository-



Hierarchical clustering with 12 genes (distance: euclidean, linkage: ward)-scaled HTSeq-counts (vst-transformed)-506 samples: 465 primary solid Tumors and 41 Solid Tissue Normal samples

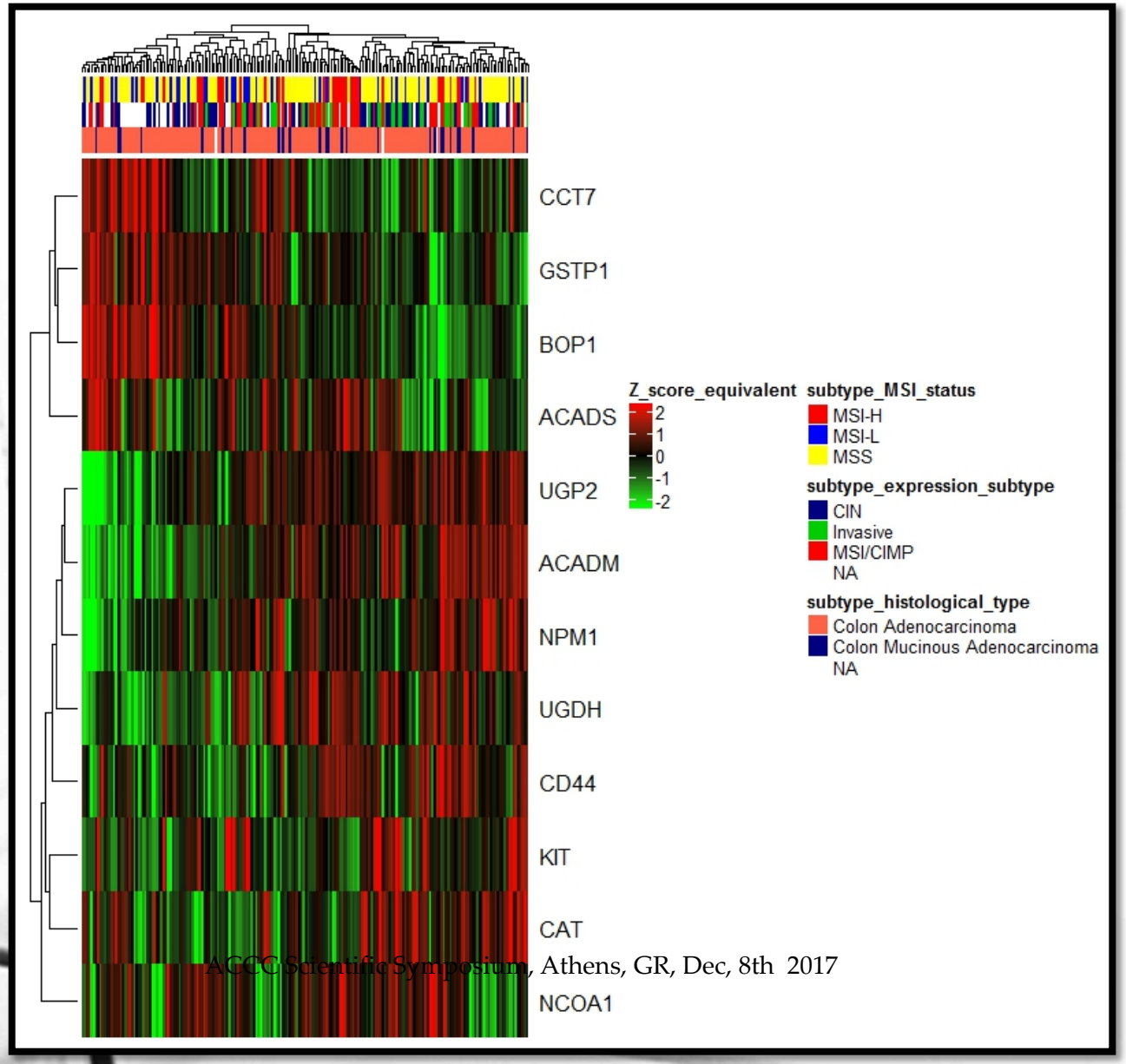
Genes totally uncorrelated with PET variables

CAT:key antioxidant heme enzyme, active against toxic hydrogen peroxide

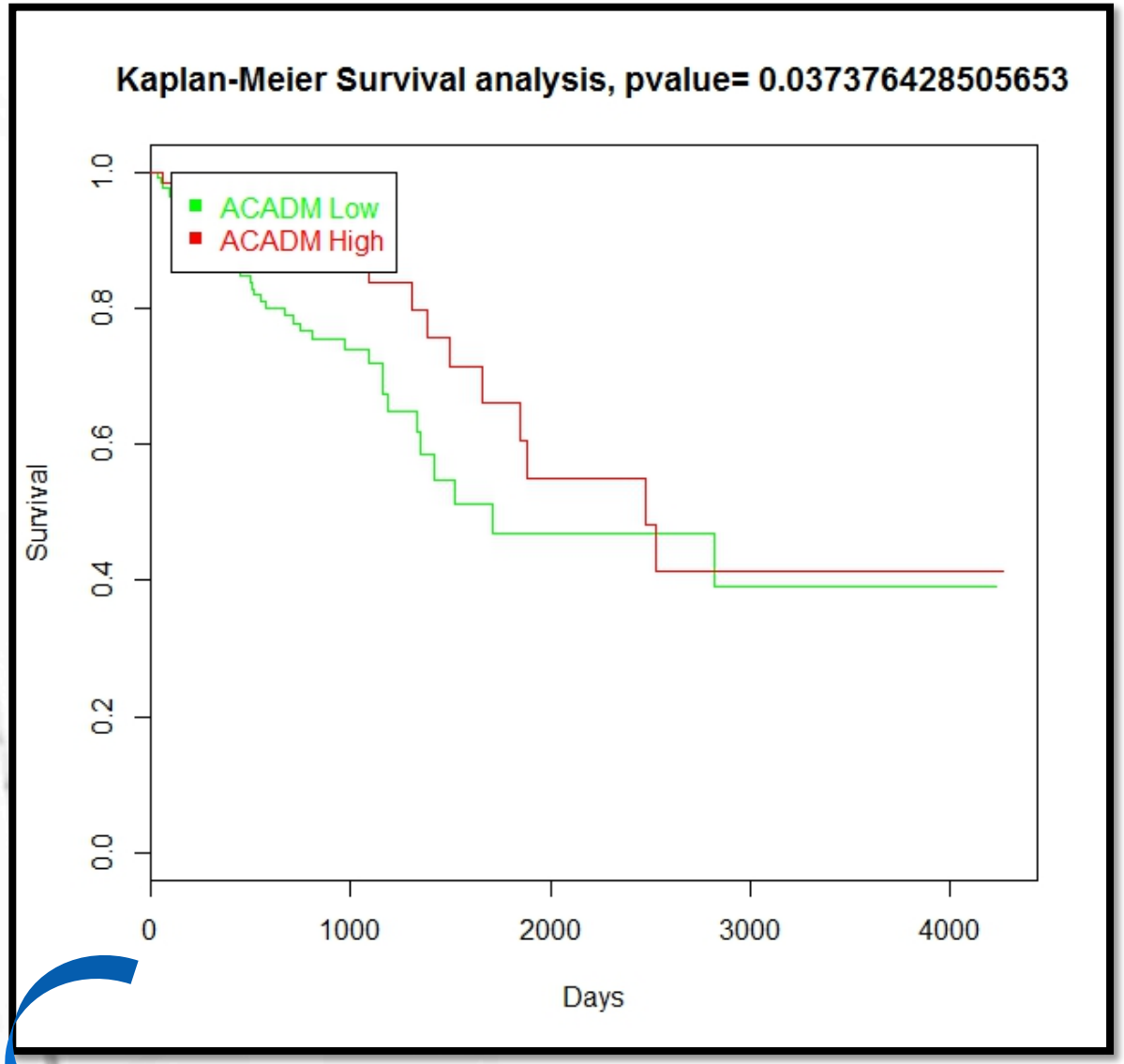
KIT:c-KIT proto-oncogene,tyrosine kinase cell-surface receptor, active in gastrointestinal tumors, metastatic marker

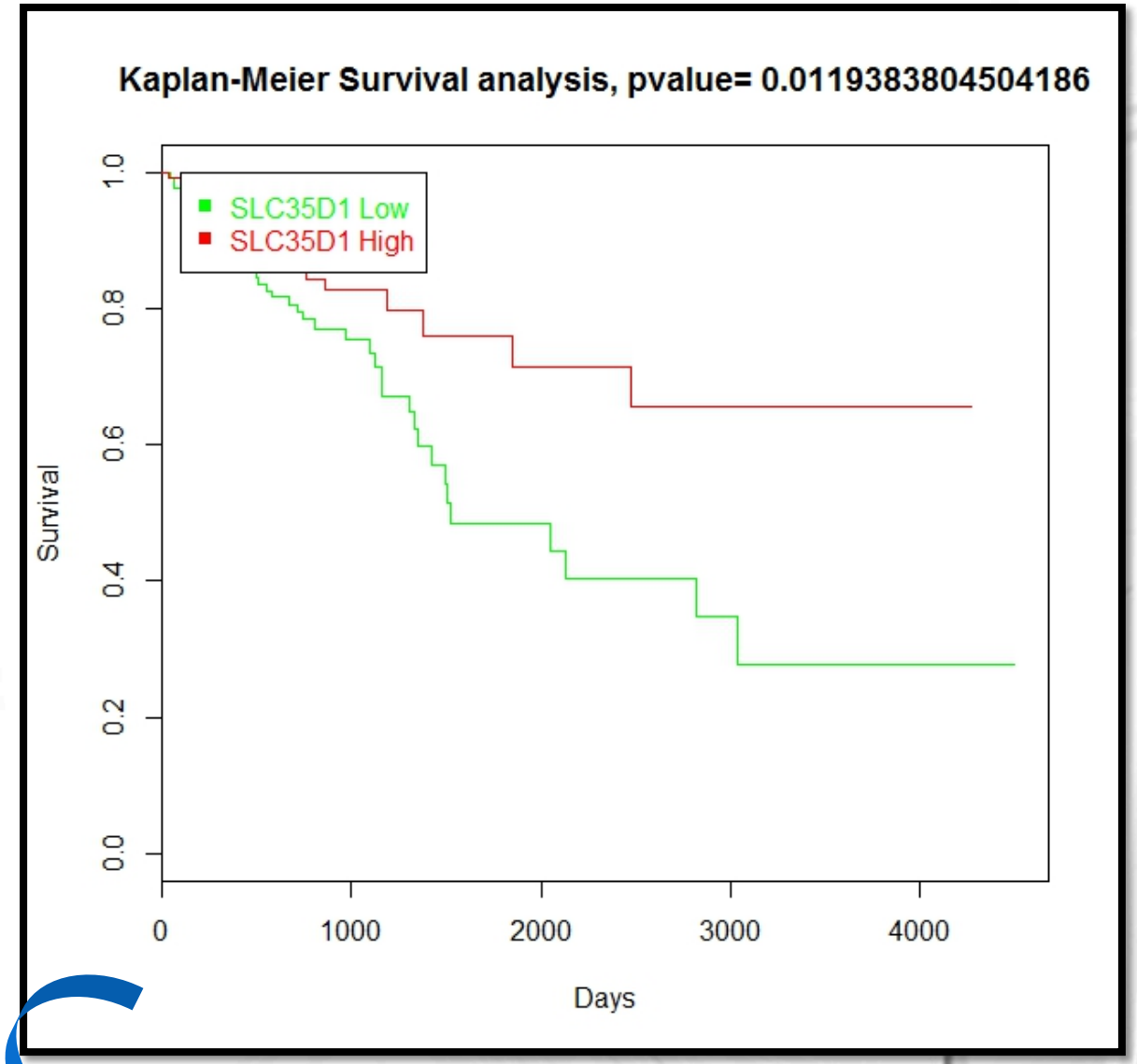
ACADM:acyl-CoA dehydrogenase medium chain, initial step of fatty acid beta-oxidation

TCGA COAD RNA-Seq dataset-12 genes-COAD subtypes



Hierarchical clustering with 12 genes (distance: pearson, linkage: average)-scaled HTSeq-counts (vst-transformed)-198 samples: only cancer samples with available subtype information





Included also in the 12 lasso selected features-main orchestrator of the fatty-acid metabolism pathway

Negative correlation with SUV & FD clinical variables-participates in UDP-glucuronate metabolic process

Summary

- A powerful generic methodology for integration, interpretation and stratification of complex clinical data in a real CRC dataset
- Derivation of an initial highly informative set of 94 differentiated genes to be associated with the respective 8 kinetic PET variables fpr each patient.
- Inference of a compact CRC composite signature associated with distinct modes of tumor physiology (carbohydrate/aminoacid/ PPP anabolic/fatty acid metabolism, stemness, immunomodulation, ER,telomere biology etc)
- This CRC signature was further validated by an independent collection of high quality RNA-Seq samples from The Cancer Genome Atlas (COAD-521 samples), detailing those molecular pathways, represented efficiently by the given PET kinetic parameters
- More importantly provides concrete target genes, with important discriminatory potential that could be targeted by novel contrast agents

Acknowledgements

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