

# CONSENSUS MOLECULAR SUBTYPES OF MORPHOLOGICAL REGIONS ON COLORECTAL TUMORS

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## INTRODUCTION

- Intra-tumor heterogeneity and the tumor sampling strategies for profiling greatly influence the consensus molecular subtyping [1,2].
- Molecular subtypes correlate with tumor morphology [3].
- Morphological features can predict the CMSs [4,5]

## AIM

### Use morphological regions to anchor the profiling and study the CMS mixture

- Study intra-tumor heterogeneity from CMS perspective
- Improve stability of the gene signatures
- Trade-off between whole-tumor and TME profiling

## RESULTS

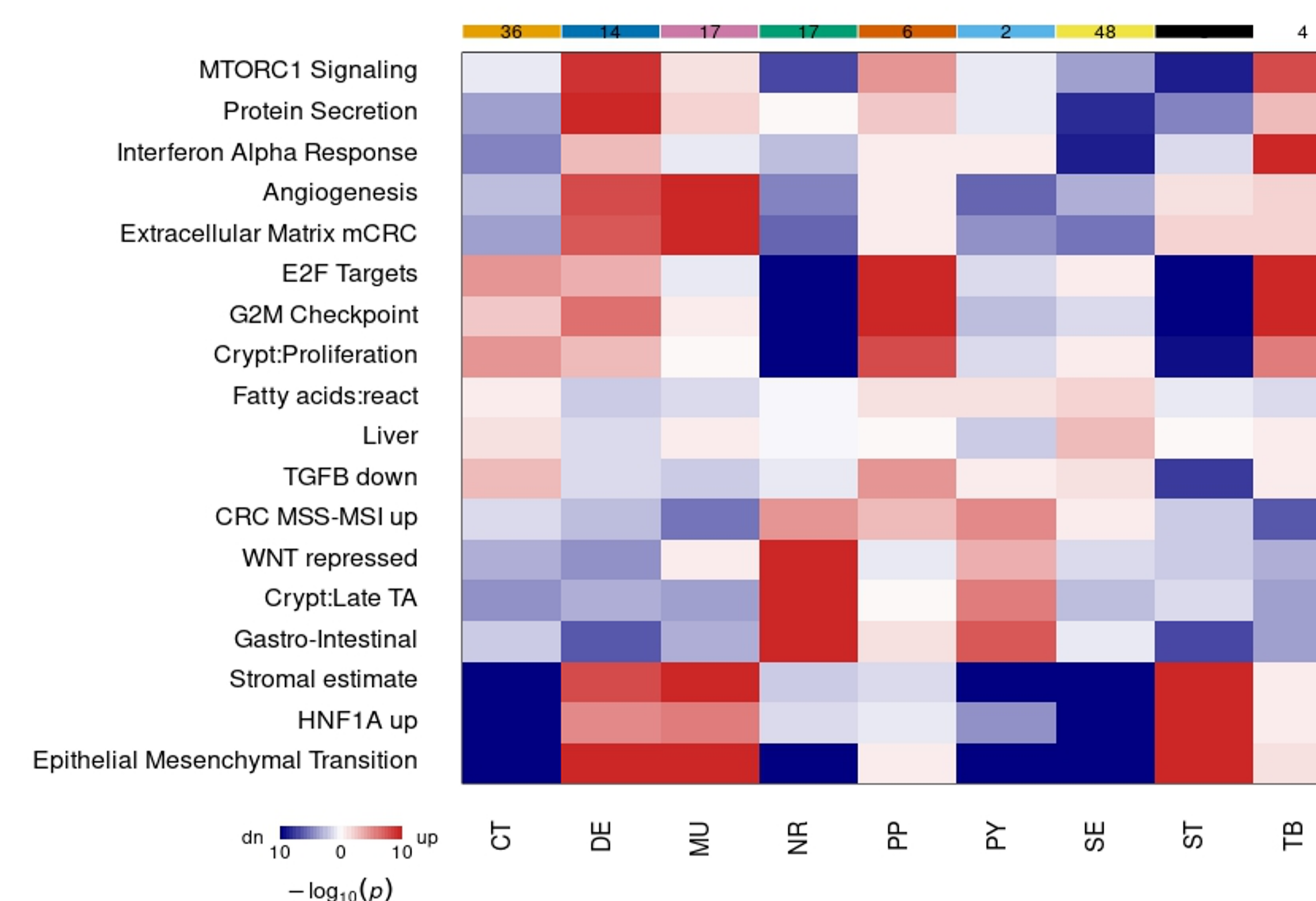
- 100 different cases led to 152 regional RNA profiles + 100 whole-tumor
- No subtype was assigned to 22% (whole-tumor) and 23% (regional) profiles, respectively

Complex tubular	CT	34	Desmoplastic	DE	14
Mucinous	MU	17	Normal	NR	17
Papillary	PP	6	Polyp	PY	2
Serrated	SE	48	Stroma	ST	8
Solid trabecular	TB	4			

### Whole-tumor CMS classification vs regional classification:

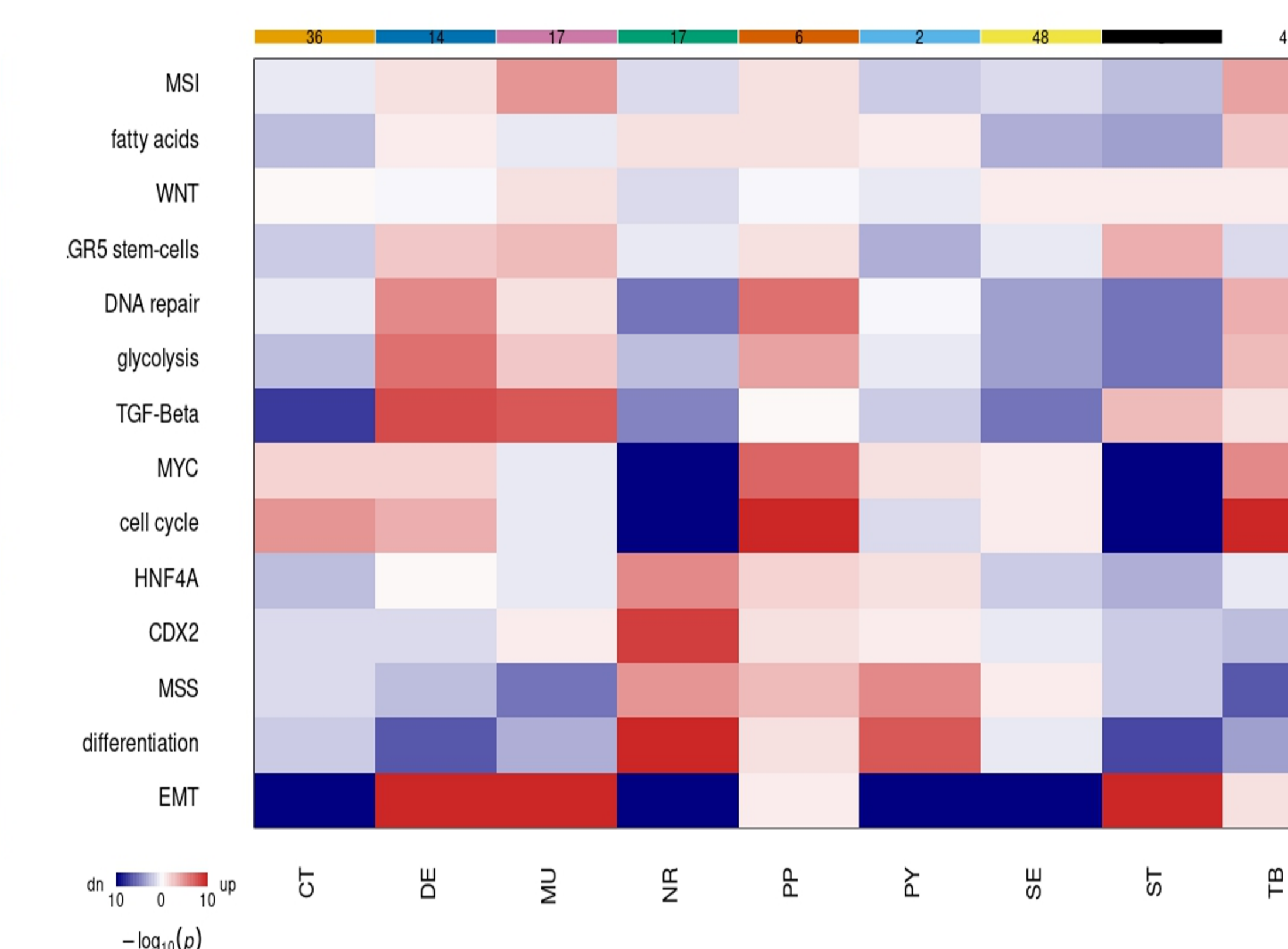
- CMS1,2,3 classification had good concordance between whole-tumor and at least one regional profile
- CMS4 less stable: for whole tumor CMS4, 44% of the regions were CMS4, and 21% CMS2

- Complex tubular (CT): mostly labeled as CMS1 (41%) and CMS2 (32%);
- Desmoplastic (DE): CMS4 (54%) and CMS1 (31%)
- The subtype of DE, when in combination with any other region types, determined the whole tumor subtype
- Serrated (SE): mostly labeled as CMS2 (42%) and CMS3 (32%);
- All tumor-adjacent stroma (ST) was labeled as CMS4.
- Mucinous (MU): CMS4 (60%).



Region	Enrichment vs rest
CT	MYC-targets, DNA repair, MTORC1, unfolded protein response
SE	DNA replication, regulation of apoptosis, MYC targets, Wnt/B-catenin
DE	EMT, TGFb, unfolded protein response, apoptosis
MU	EMT, TGFb, inflammatory response, KRAS signaling

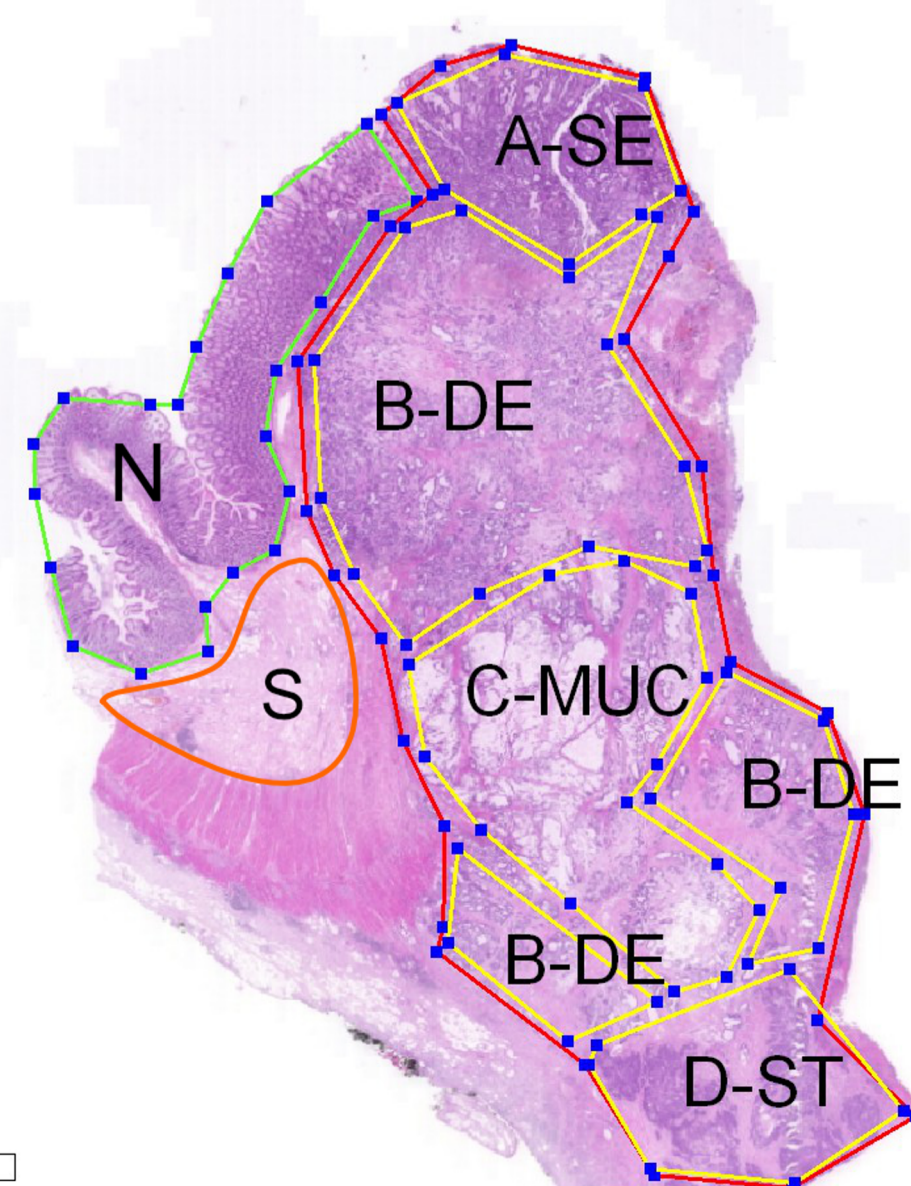
GSEA analysis – hallmark signatures



## METHOD

### Morphology-guided transcriptomics

- Use whole tumor profile for baseline
- CMScaller for classifying resulting profiles
- GSEA analysis



## CONCLUSIONS

- morphological regions may have a different molecular subtype than the whole tumor
- gene expression classifiers are sensitive to tumor sampling protocol
- need for clear specification of region(s) used for RNA profiling
- multi-region sampling may lead to CMS refinement
- CMS4 EMT characteristics are most probably due to the desmoplastic reaction.

## REFERENCES

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## CONTACT INFORMATION

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