TCGA computational histopathology pipeline reveals subtypes and their molecular signature

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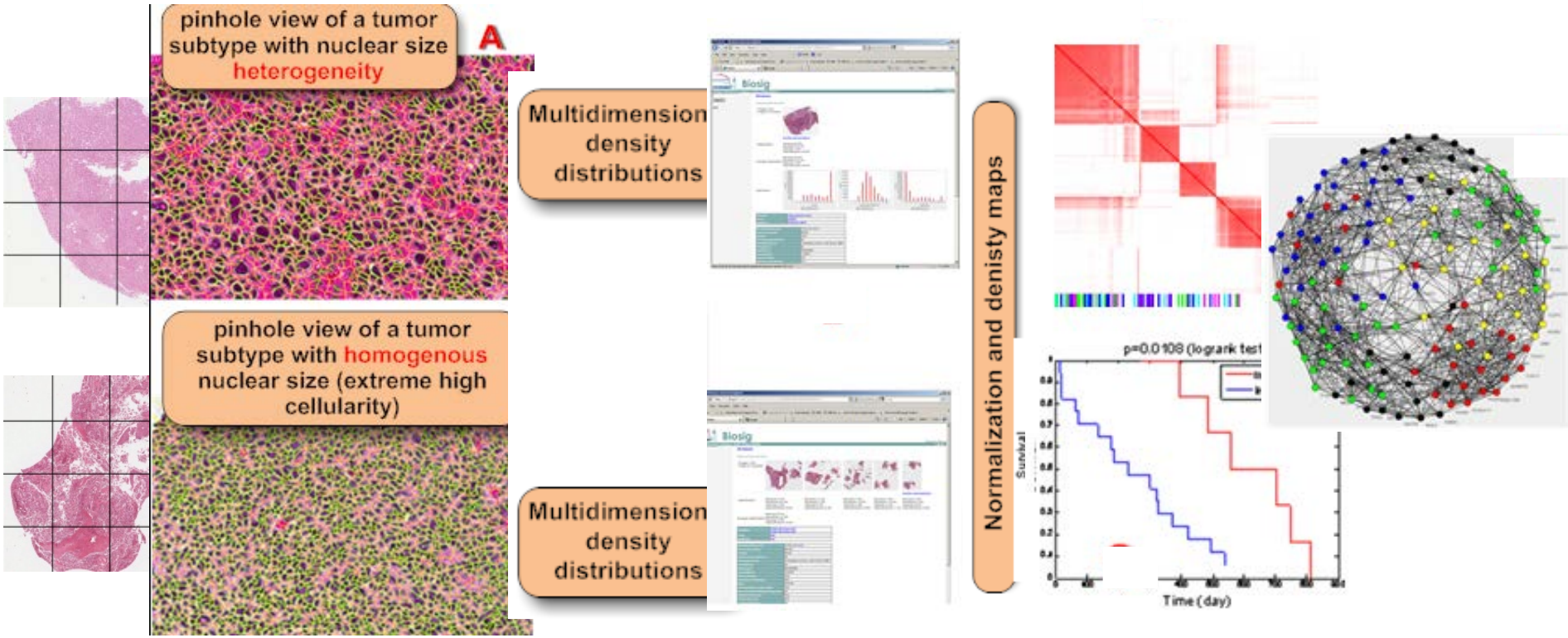
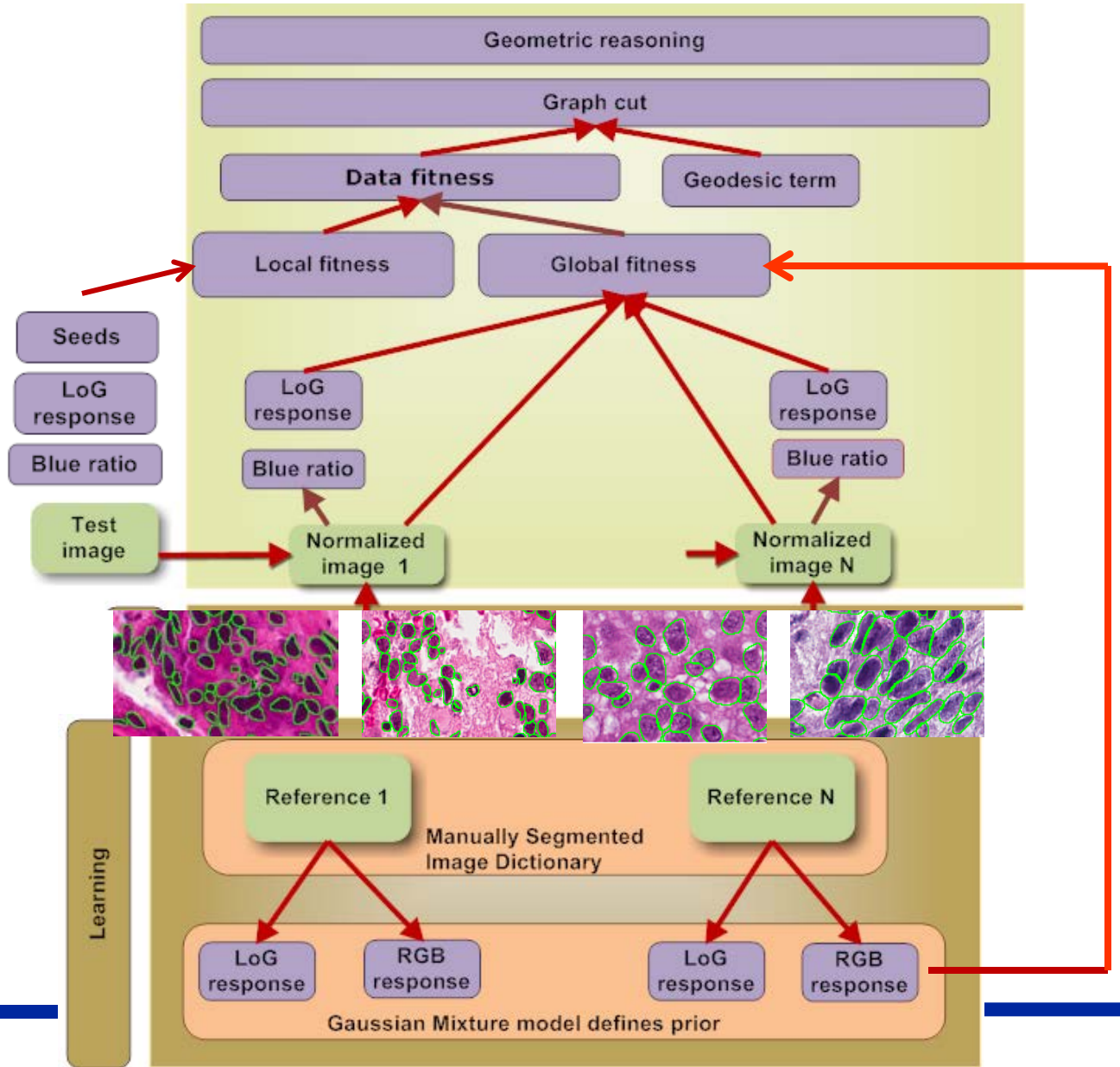
Computational histopathology pipeline captures molecular basis for each morphometric subtype



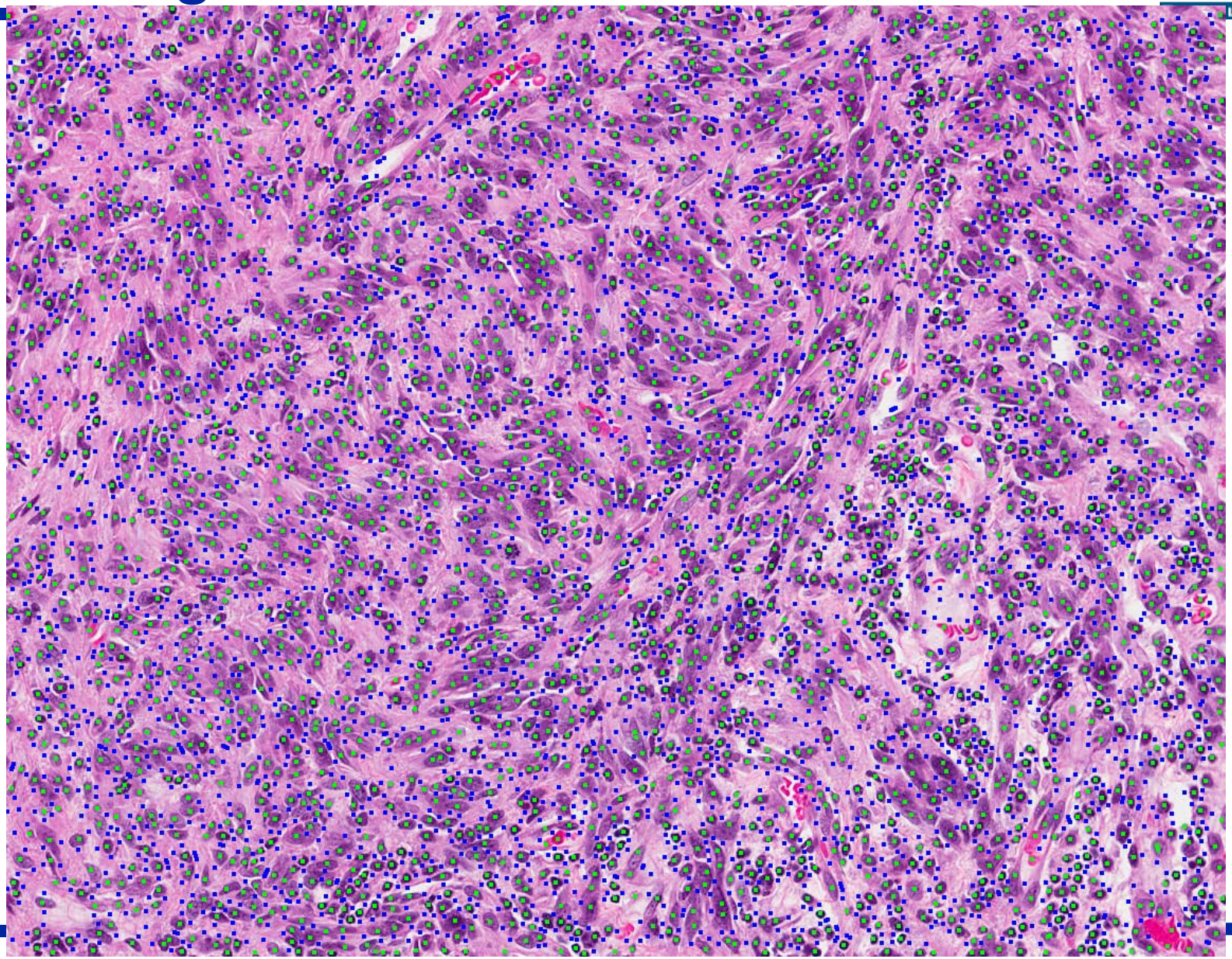
Use case and target for analysis

- Glioblastoma multiforme (GBM)
  - Curated by removing tissue sections with artifacts (e.g., fold in tissue, pen mark, scanning anamoly)
  - Sample size
    - 380 tissue sections selected out of 447
      - 146 patients selected out of 152
- Challenges?
  - Technical and biological variations, very large datasets
- Approach
  - Development of robust and efficient image analysis algorithms
  - Computing morphometric features and meta-features
  - Subtyping based on selected features or reduced dimensionality (e.g., PCA, MDS)
  - Molecular association with morphometric subtypes

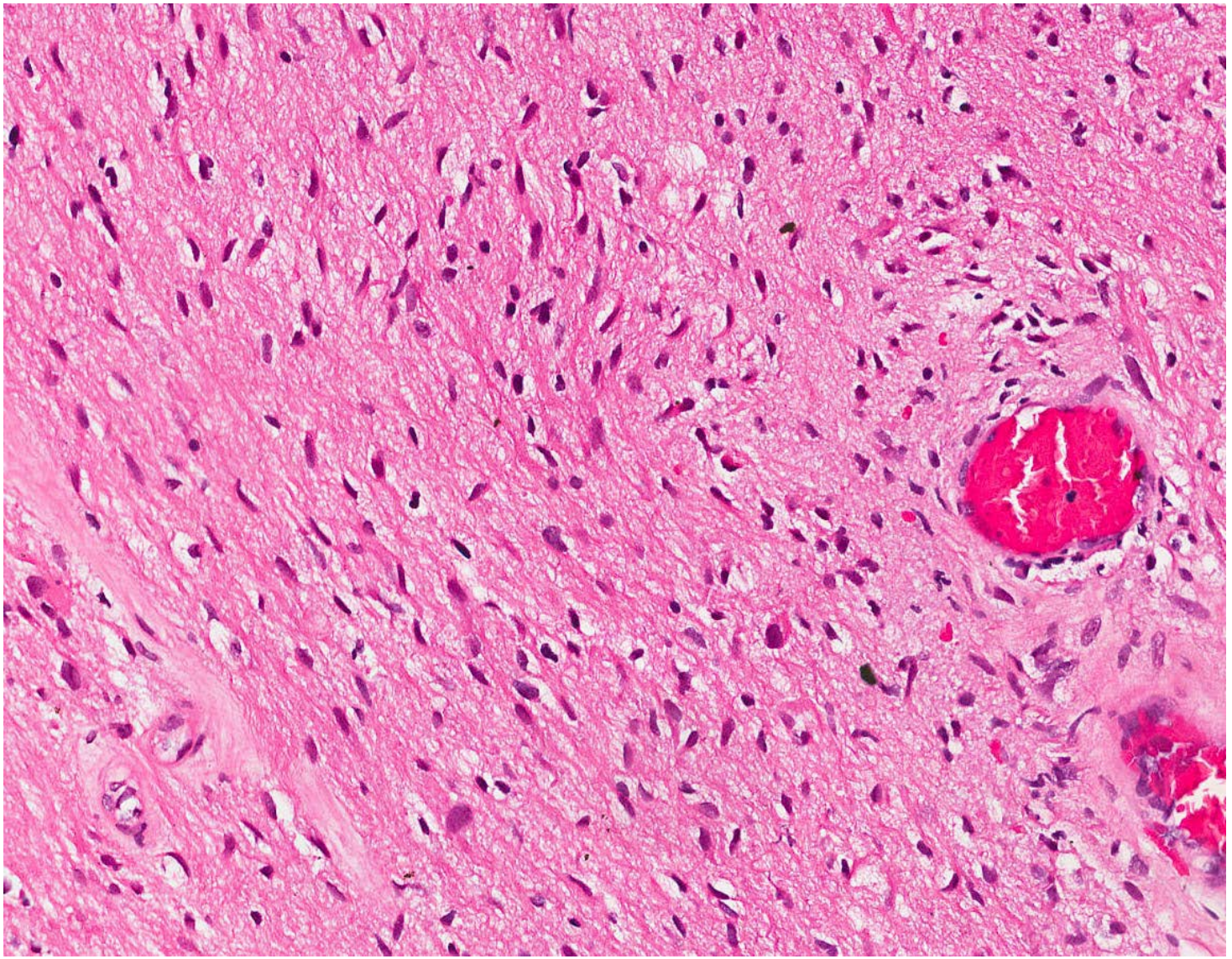
New algorithm enhances nuclear segmentation in the presence of technical variations



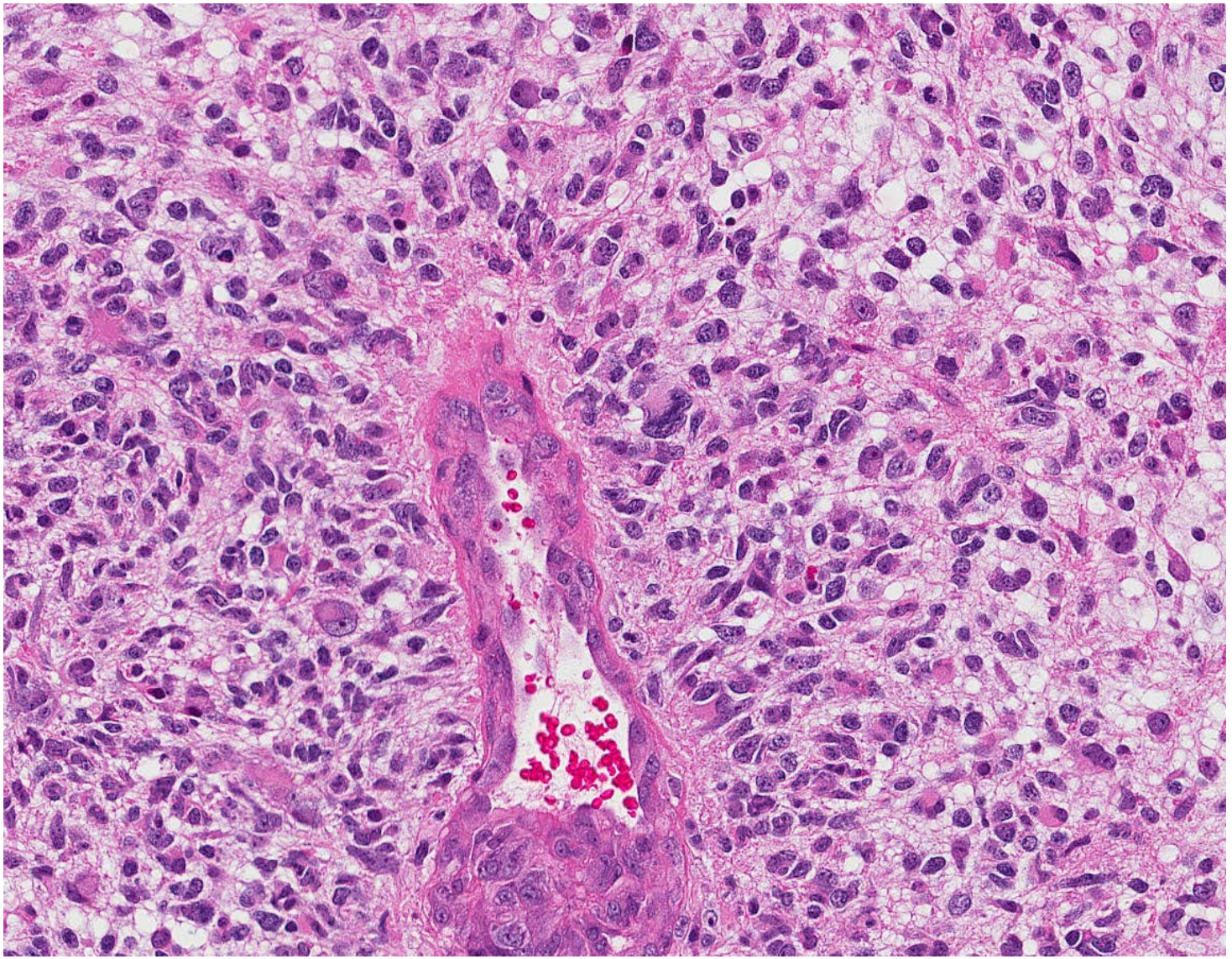
Seed detection provides shape signature and local statistics



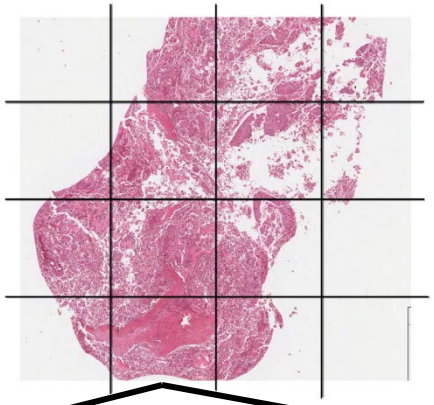
Cell-by-cell segmentation result



Cell-by-cell segmentation result

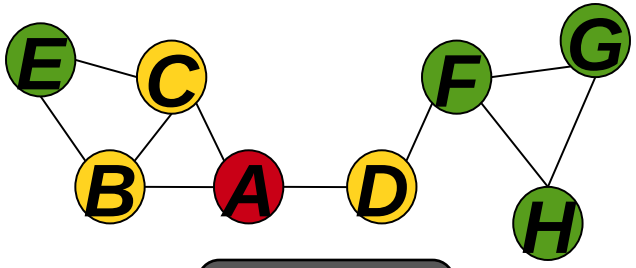


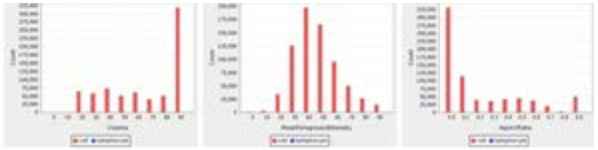
Representation



Structural features

Cell-by-cell measurement





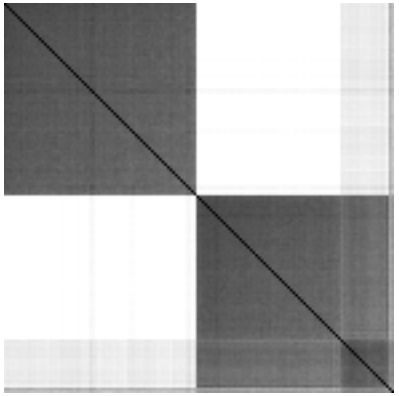
A vector

A multidimensional distribution

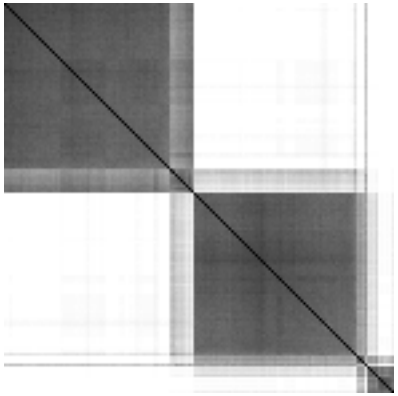
Normalization across all tissue sections

What are subtypes based on cellularity and nuclear size at the patient level

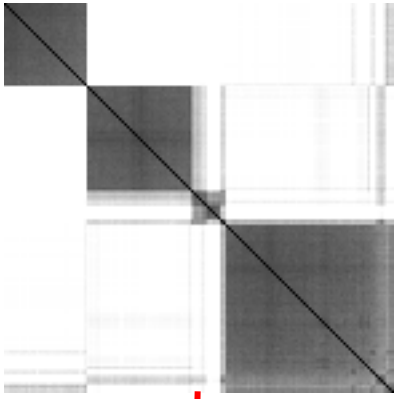
2 clusters



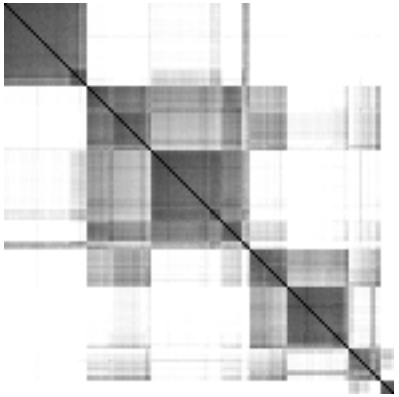
3 clusters



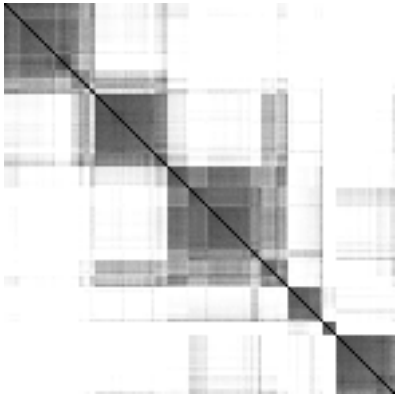
4 clusters

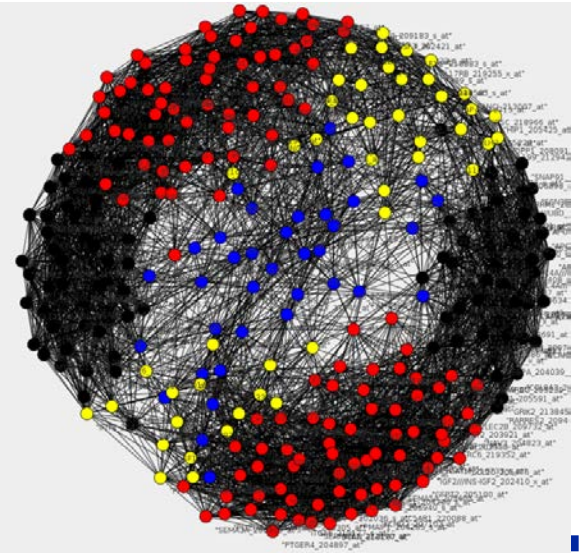


5 clusters

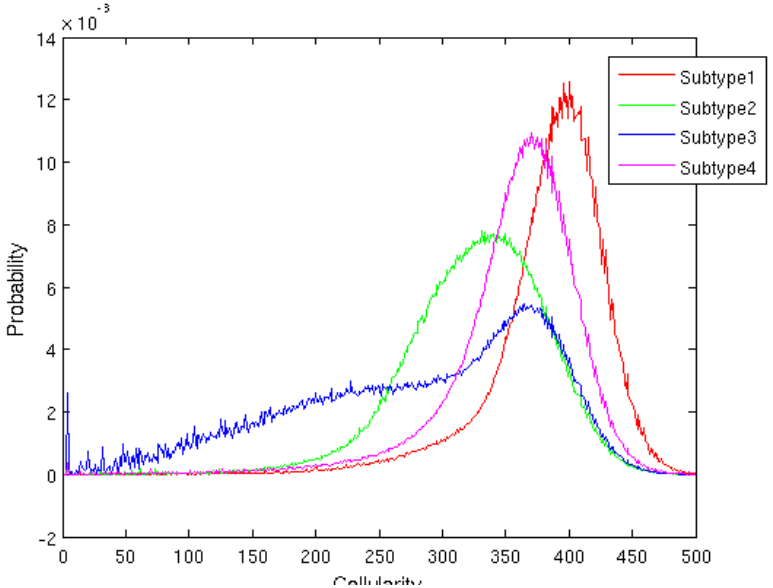


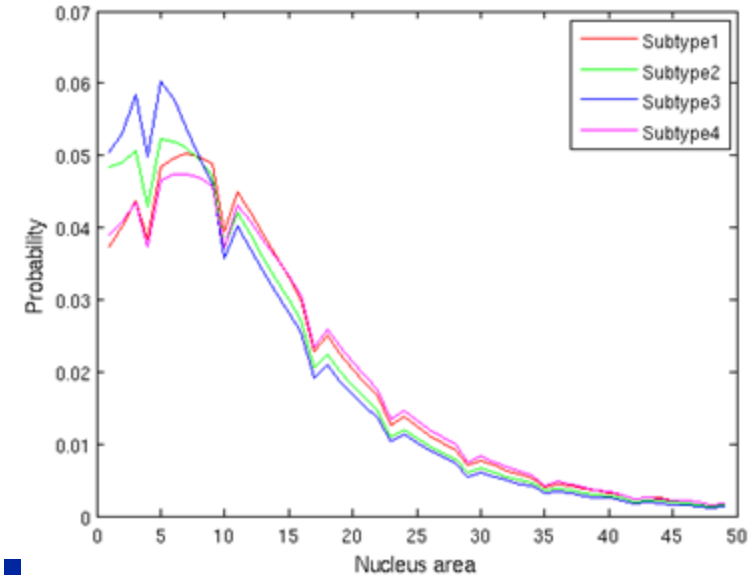
6 clusters

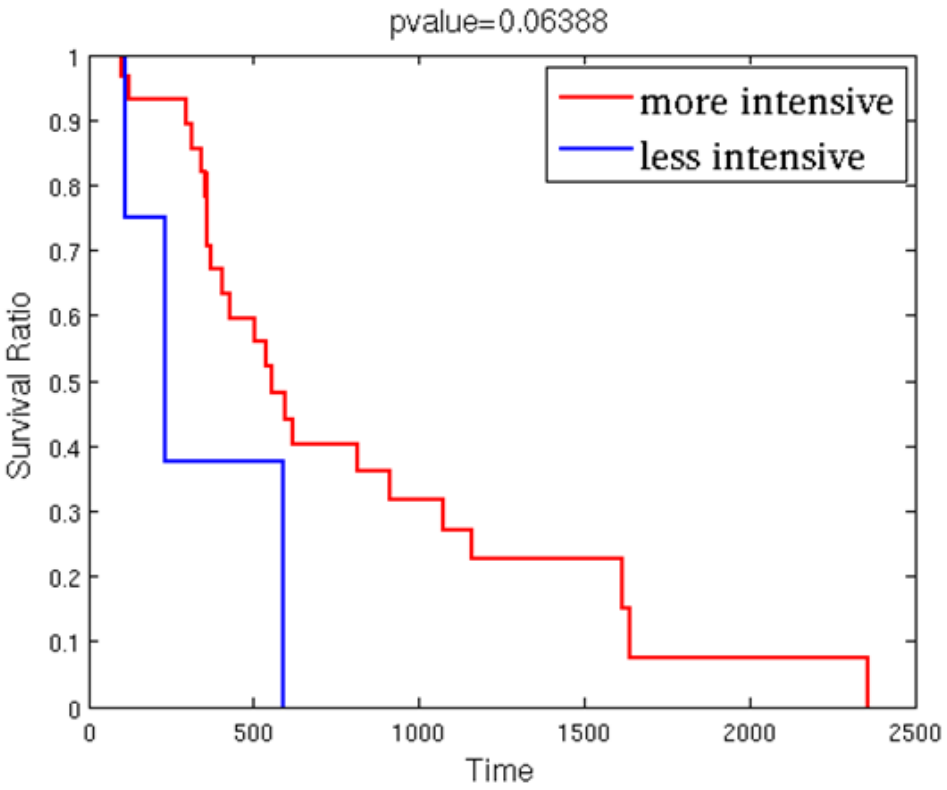




What is the distribution of each subtype and how well each subtype predicts survival as a function of treatment?







Subtype 2

What are the molecular basis of each subtype?

- Gene selection
  - Univariate or multivariate methods
  - Pathway or subnetwork enrichment analysis

Subtype1

Name	Overlapping Entities	p-value
Focal Adhesion Regulation	CAV1,MET,ERBB4,KIT,PDGFRA,RASA4	0.000208
Actin Cytoskeleton Regulation	MET,ERBB4,KIT,PDGFRA,SGCE,RASA4,PDLIM3	0.000555
Gap Junction Regulation	MET,ERBB4,KIT,NPY2R,PDGFRA,RASA4	0.008248
Adherens Junction Regulation	DAAM2,MET,ERBB4,KIT,PDGFRA,CDH6	0.011068
KIT -> STAT signaling	KIT	0.017364
HGFR -> STAT signaling	MET	0.023089
PDGFR -> STAT signaling	PDGFRA	0.025939
HGFR -> FOXO3A signaling	MET	0.054015

Subtype3

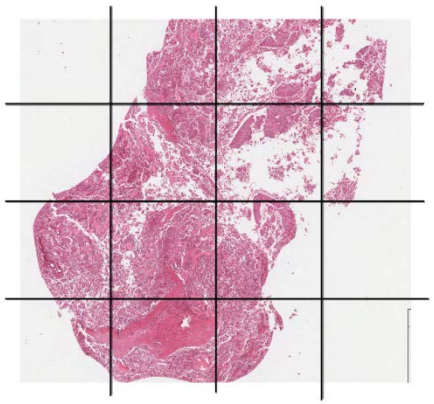
Name	Overlapping Entities	p-value
CCR1 -> STAT signaling	CCL4,CCL3	0.003127
CCR5 -> TP53 signaling	CCL4,CCL3	0.004022
Gap Junction Regulation	GNAO1,CCL4,HRH1,KIT,CCL3,CALCRL,ADCY2,FGF12,RASA4	0.008737
KIT -> STAT signaling	KIT	0.033533

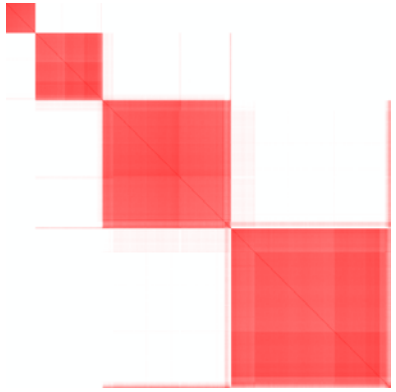
Subtype4

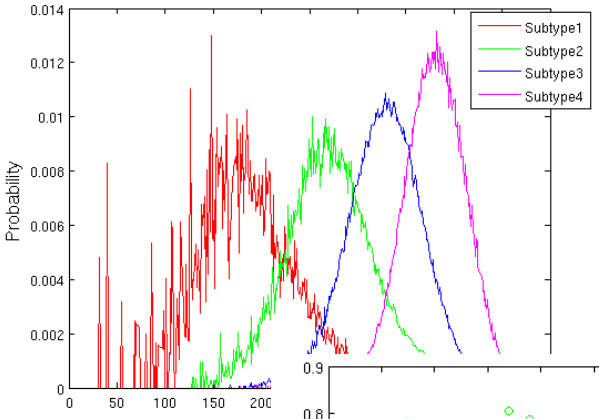
Name	Overlapping Entities	p-value
IL11R -> STAT3 signaling	IL11RA	0.018322
ThromboxaneR -> CREB signaling	RASGRP1,GNG4	0.026307
EphrinR -> actin signaling	EFNB3,SGCE,EPB41L2	0.02702

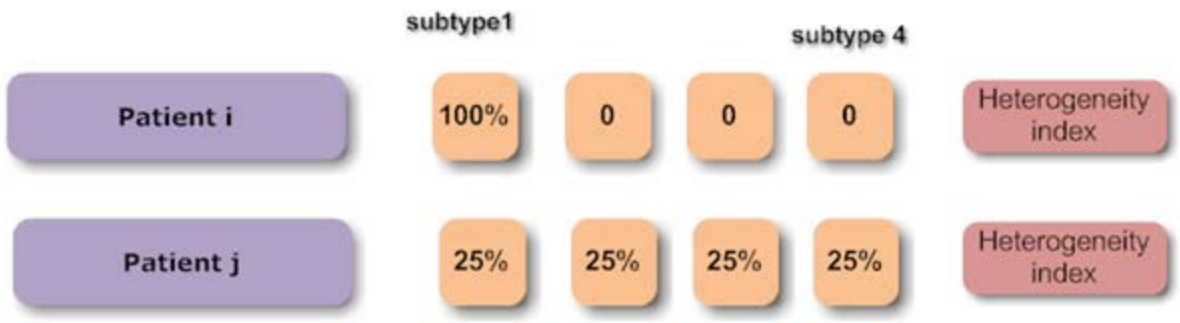
Can tumor composition be characterized?

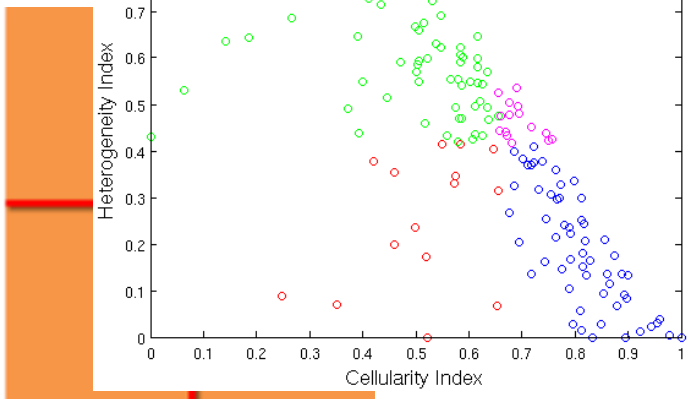
- Since tumor is heterogeneous, can we query for subtypes at the block levels and learn about tumor composition?



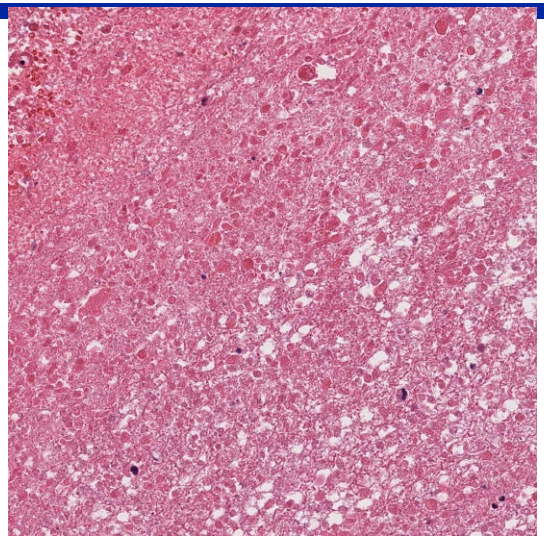




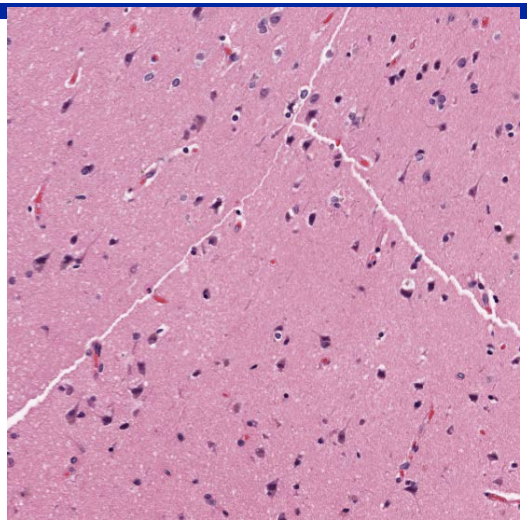




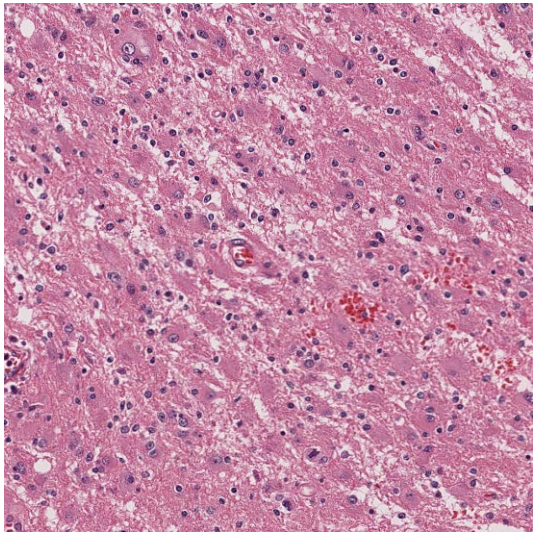
What are the tumor histology subtypes?



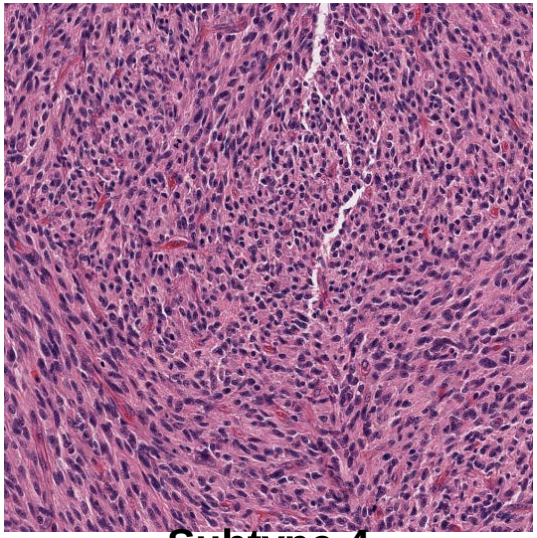
Subtype 1



Subtype 2



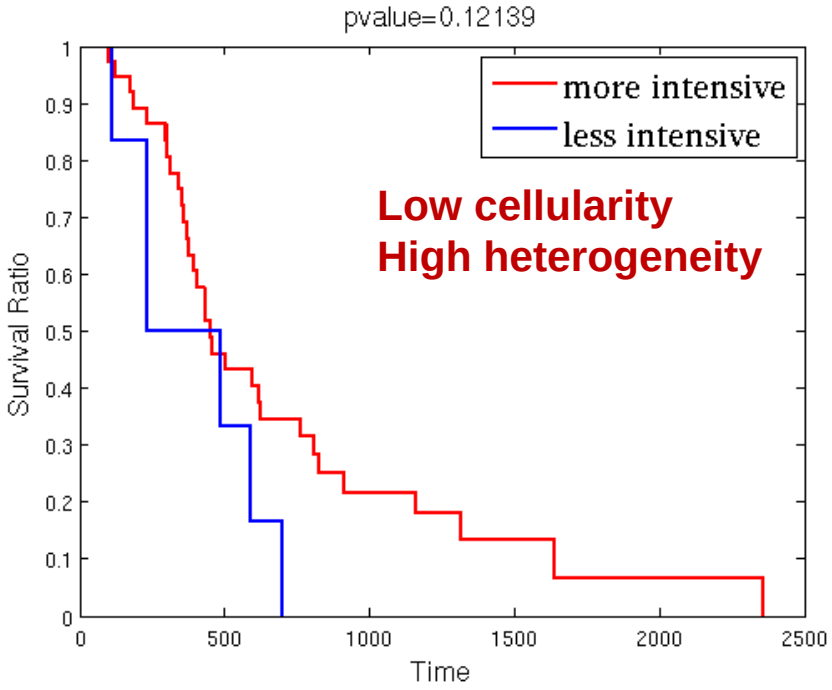
Subtype 3

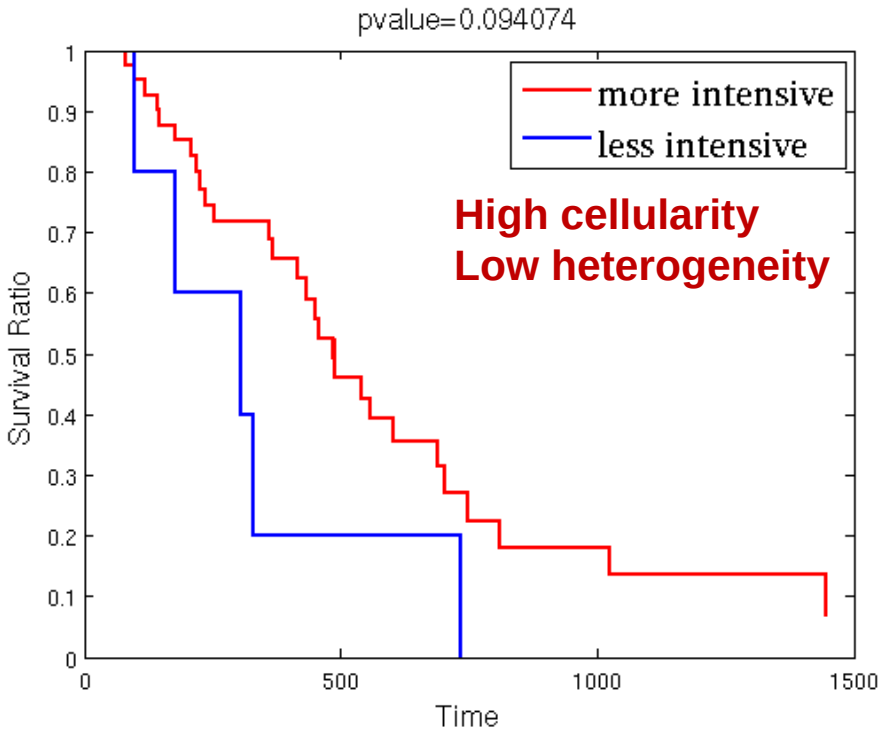


Subtype 4

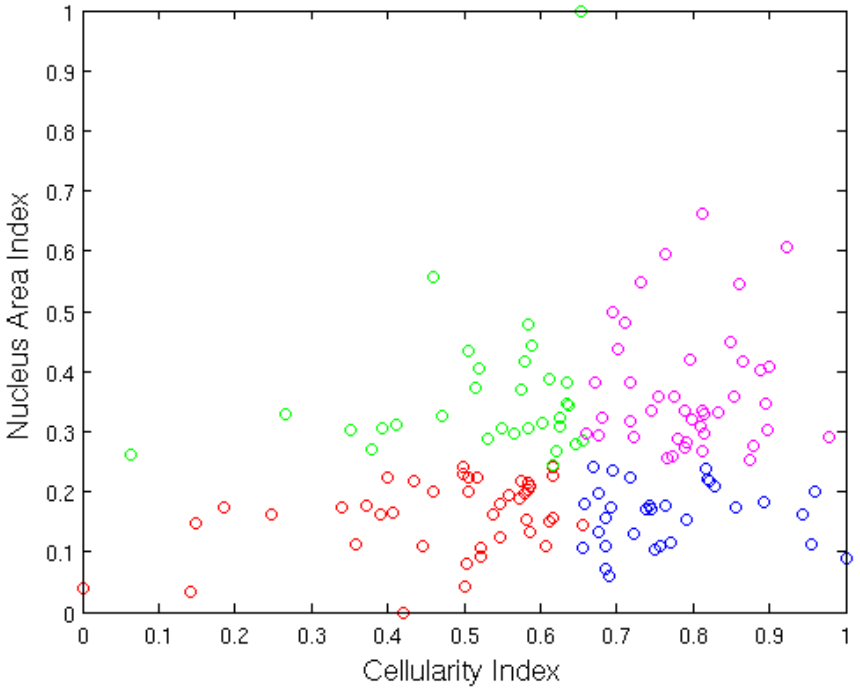
Does heterogeneity play a role in survival as a result of a more intense therapy ?

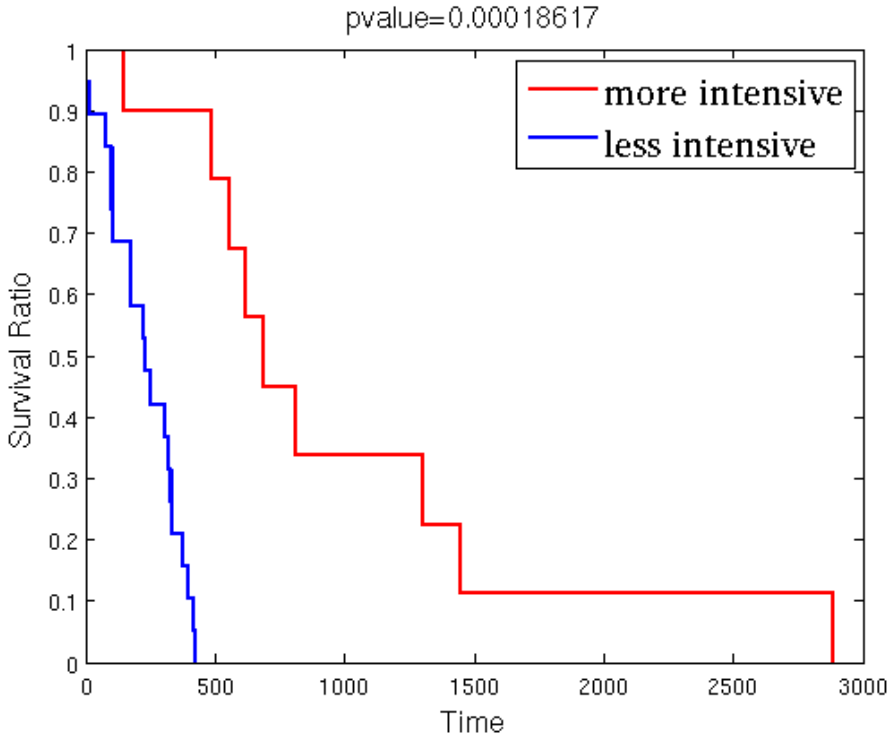
Loosely defined semantics of high and low!





Another view: Are cellularity and nuclear size correlated? And outcome?





High cellularity and low nuclear size are better predictive of a more aggressive therapy

Conclusion

- There are many ways to slice through the data and metadata
  - Cellularity, nuclear size
  - Heterogeneity
- Different indices lead to alternative subtypings
  - Alternative biological interpretation is possible
- Genomic association has the potential to reveal new insight
- Web site: tcga.lbl.gov
  - "Google map" like viewing of tissue sections with segmentation results overlaid