Integrative Analysis of the IvyGAP data

UPenn

Christos Davatzikos
Spyridon Bakas

Stony Brook

Joel Saltz

MGH

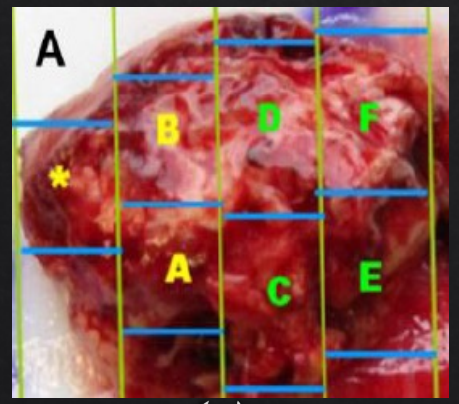
Bruce Rosen
Jayashree Kalpathy-Cramer

UT MD Anderson

John Weinstein
Bradley Broom
Arvind Rao

The Ivy Glioblastoma Atlas Project (GAP) data

- 39 GBM patients
  - Longitudinal Data Collection (Multiple Timepoints, average=10)
  - Clinical information (demographics, medications, surgery, Cx, Rx)
  - Tumor partitioning in multiple sections ***(a)***
  - Imaging - Radiology ***(b)***, Histology ***(c)***
  - Annotations of anatomically distinct regions in histology images ***(d)***
    - e.g., Leading Edge, Infiltrating Tumor, Necrosis, Pseudopalisading cells
  - Molecular Expression in each of these regions ***(e)***
  - In Situ Hybridization (ISH) ***(f)***
  - RNA-Seq following H&E staining
  - Availability of molecular subtypes



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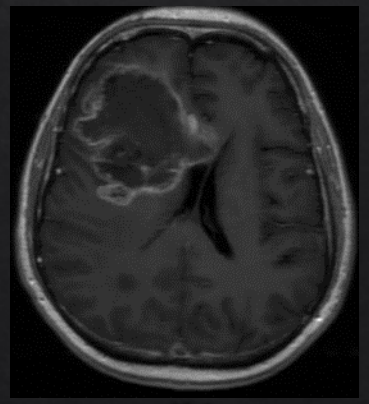
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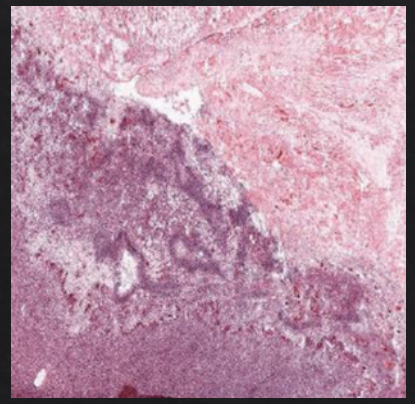
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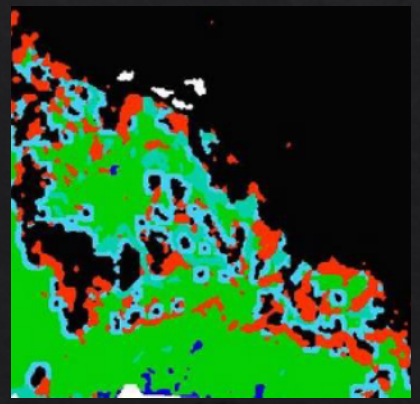
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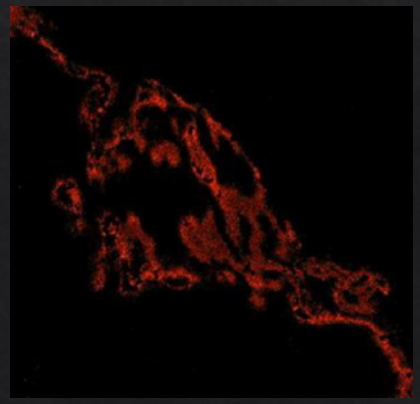
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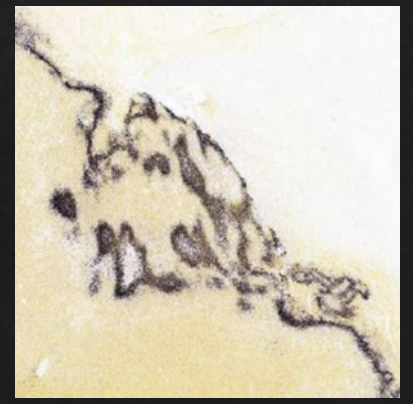
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Overview of the Integrative Analysis

- Aim 1: Assessment of histologic imaging [**Stony Brook**]
  - Carry out spatial analyses to characterize the interplay between distinct histology regions (necrosis, enhancing region, infiltrating regions etc) and tumor protein and gene expression.
- Aim 2: Assessment of radiologic imaging [**UPenn, MGH**]
  - Obtain radiographic (MRI) signatures of clinically relevant molecular characteristics from the various tumor regions (i.e. edema, enhancing and non-enhancing tumor), whilst leveraging multi-parametric pattern analysis and machine learning methods.
- Aim 3: Public portal of Next-Generation Clustered Heat Maps [**UT MD Anderson**]
  - Develop a compendium and public portal of next-generation clustered heat maps (NG-CHMs) for visualization of patterns in imaging data (radiomic and histomic) on tumors and to assess the relationship of those patterns to genomic and clinical data.
- Aim 4: Data-driven visualization of features and associations [**SBrook, UPenn, MGH, UT_MD**]
  - Develop prototype spatial visual analytics infrastructure capable of depicting relationship between multi-scale characterizations of tumor niches.

A1. Assessment of histologic imaging

Goal

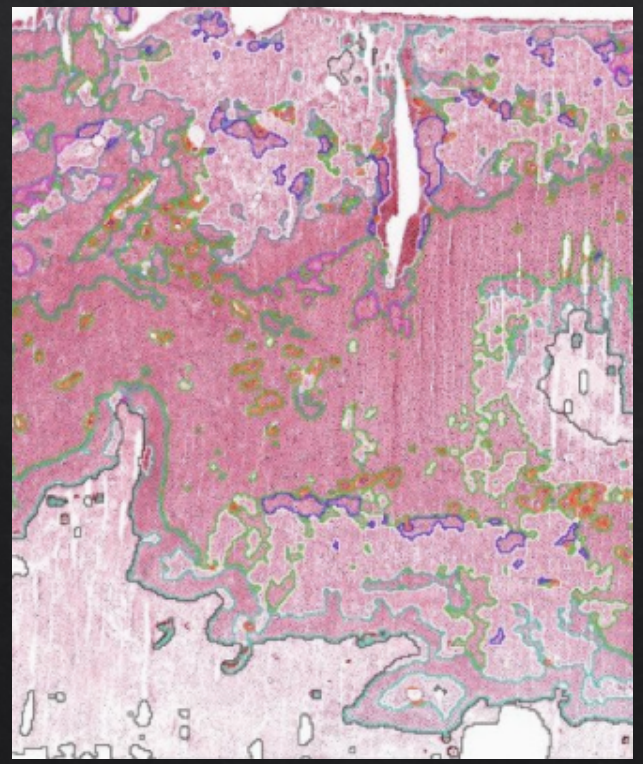
- Carry out spatial analyses to characterize the interplay between distinct histological regions (cellular tumor (CT), leading edge (LE), infiltrating tumor (IT), necrotic area of cellular tumor (CTne) .. in situ hybridization (ISH) and gene expression.
- ***Collaboration with Nadia Tsankova, Neuro Pathologist Mt Sinai***

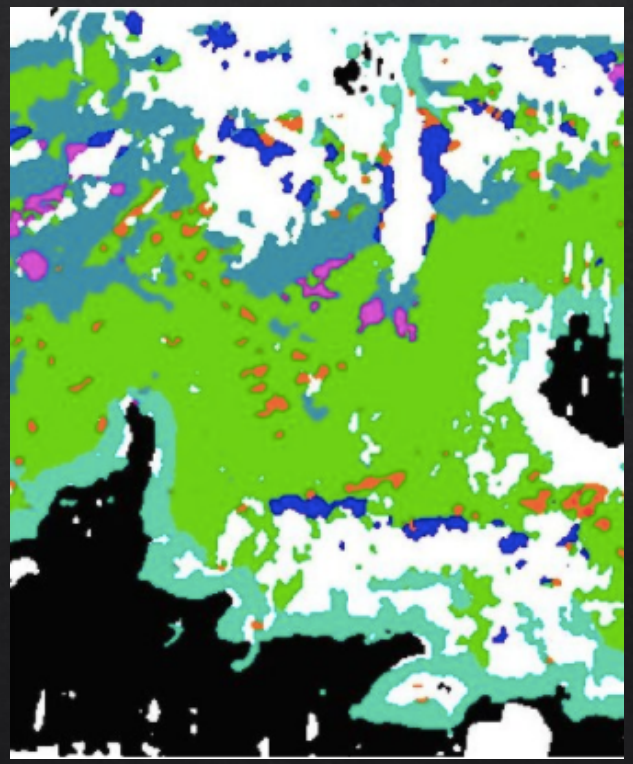
Fall 2017 Foundational work:

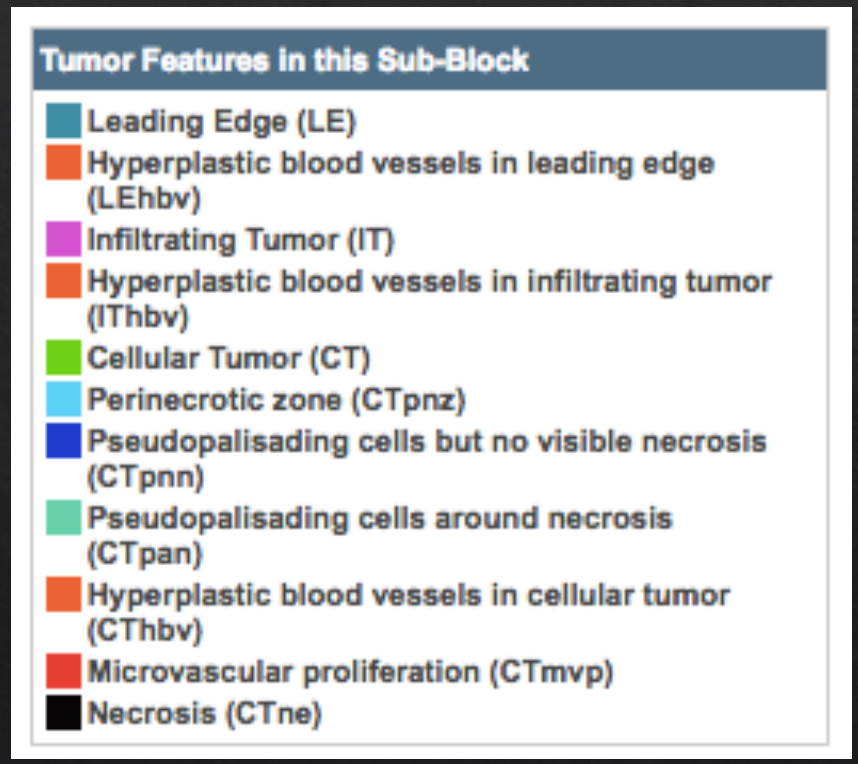
- Extension of QuIP framework to register images and quantify regional, nuclear, cytoplasmic marker density
- Download approximately 50K Pathology images
- In process of carrying out image format conversions

A1. Assessment of histologic imaging

IvyGAP Tumor Region Segmentation

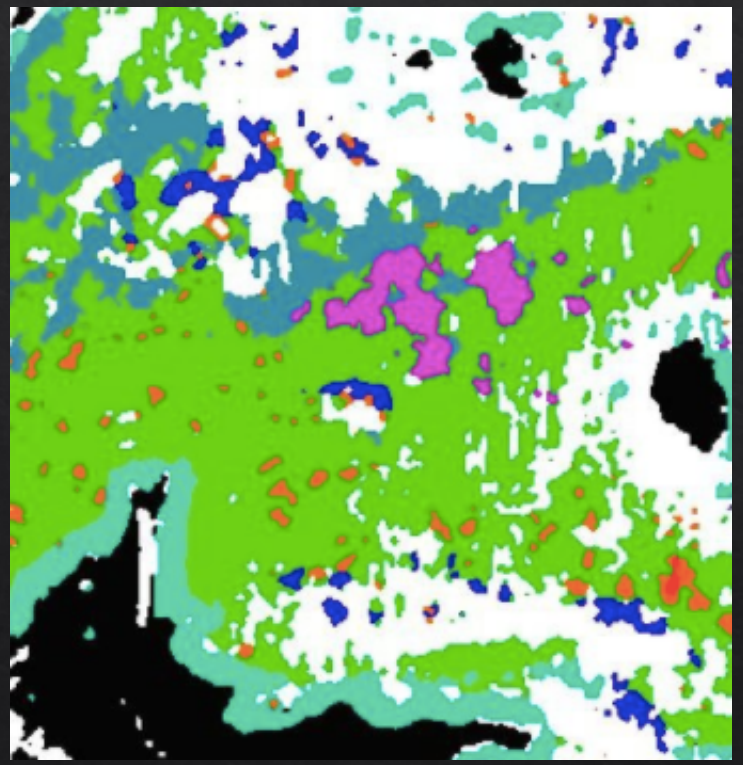


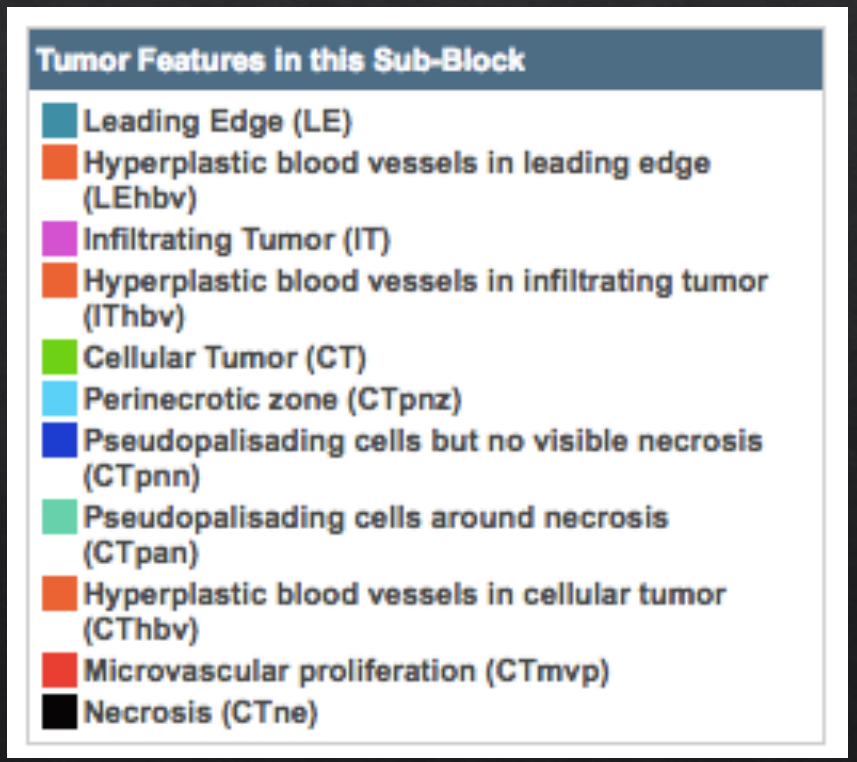




A1. Assessment of histologic imaging

Example ISH Marker Study





A1. Assessment of histologic imaging

Current strategic plan:

in collaboration with Neuro-pathologist Nadia Tsankova

I. Characterize metabolic adaptations in areas of infiltrating tumor – IT and LE versus other areas
   - How are the metabolic adaptations in migratory areas similar and different from other areas?
   - Is there a difference between classical (CL) / mesenchymal (MES) / proneural (PN) GBM subtypes in the above metabolic characteristics?

II. Relationship between GBM Stem Cells and Migration
   - Which stem cell markers are seen in LE and IT areas?

III. Relationship between GBM Stem Cells and GBM subtypes (CL, PN, MES)
   - Differences in stem cell marker expression in classical, mesenchymal, proneural

Computational Approach

- Cell segmentation and classification to obtain a detailed classification of niches within histologically defined regions – focus on infiltrating vs cellular tumor regions
- Employ registered ISH markers to improve resolution of niches
- Address scientific aims I, II and III though linked segmentation of tumor niches and characterization of gene expression in different tumor niche regions

A1. Assessment of histologic imaging

New Software / Public Data Release

- Integration of False Color Overlay and Image Registration into QuIP software suite
- Tumor niche characterization, nuclear segmentation, classification data will be publicly released
- Subject to IvyGAP approval, intend to host IvyGAP analyses on TCIA

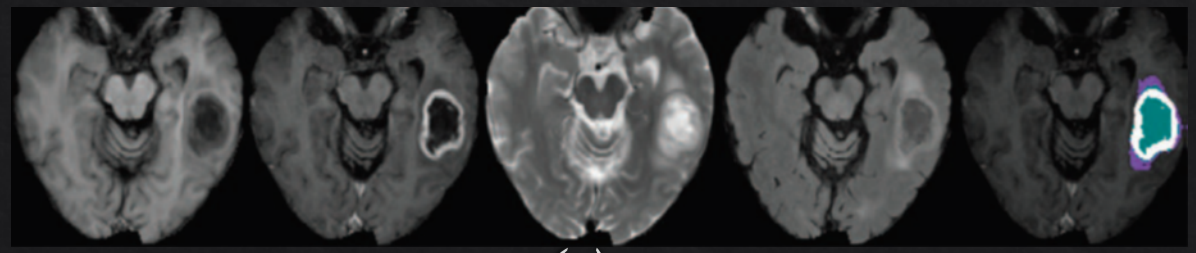
A2. Assessment of radiologic imaging

Goal

- Obtain radiographic (MRI) signatures of clinically relevant molecular characteristics from the various tumor regions (i.e. edema, enhancing and non-enhancing tumor), whilst leveraging multi-parametric pattern analysis and machine learning methods.

Previous work:

- Multimodal segmentation of GBM sub-regions (edema, enhancing, non-enhancing tumor) ***(a)***
  Kwon, et al., TMI 2014 - Bakas et al., LNCS 2016 - Zeng et al., LNCS 2017 - Kamnitsas et al., LNCS 2017
- Extraction of quantitative imaging features (radiomics + spatial patterns of cancer distribution, biophysical growth model parameters)
  - Release of segmentations and features for the TCIA glioma collections (Bakas et al., Nature Scientific Data, 2017)
- Identification of imaging signatures of molecular characteristics ***(b)***
  - EGFRvIII imaging biomarker (Bakas et al., Clinical Cancer Research, 2017)



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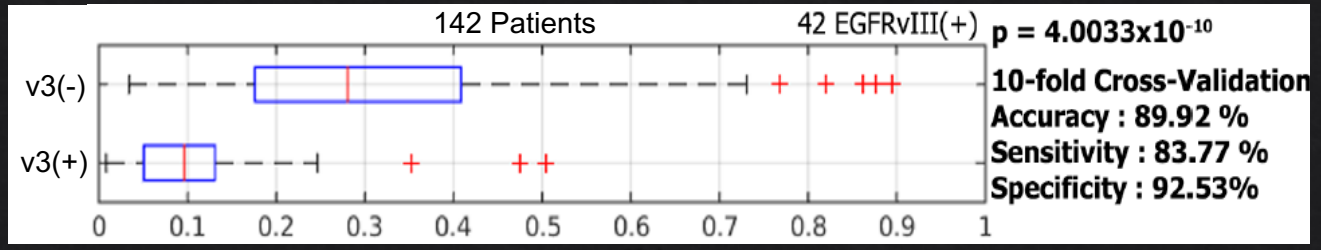

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A2. Assessment of radiologic imaging

Goal

- Obtain radiographic (MRI) signatures of clinically relevant molecular characteristics from the various tumor regions (i.e. edema, enhancing and non-enhancing tumor), whilst leveraging multi-parametric pattern analysis and machine learning methods.

Current strategic plan:

- Segmentation of GBM sub-regions (edema, enhancing, non-enhancing tumor)
- Extraction of quantitative imaging phenomic (QIP) features (beyond radiomics)
- Identify collinearity and potential redundancy of extracted QIP features across labs [**UPenn/MGH**]
- Identify correlations between QIP features and the collective molecular information for each of the various tumor partitions, across the resected tumor, as provided through IvyGAP.

- Extended intentions: Conduct the same analysis as above after extending the segmentation labels to match the histologically distinct regions provided by IvyGAP.

A2. Assessment of radiologic imaging

Goal

- Obtain radiographic (MRI) signatures of clinically relevant molecular characteristics from the various tumor regions (i.e. edema, enhancing and non-enhancing tumor), whilst leveraging multi-parametric pattern analysis and machine learning methods.

Public Release:

- Identified correlations and trained models allowing users to calculate *in vivo* molecular signatures (e.g., IDH, EGFR), will be released through:
  - the Cancer Imaging Phenomics Toolkit (CaPTk) [**UPenn** - parent U24 grant]
  - Docker containers [**MGH**]
- Segmentation labels and QIP features will be released through:
  - CBICA's online Image Processing Portal (ipp.cbica.upenn.edu) [**UPenn**]
  - C-BIBOP [**MGH**]
  - **NIH's TCIA** as Analysis Results

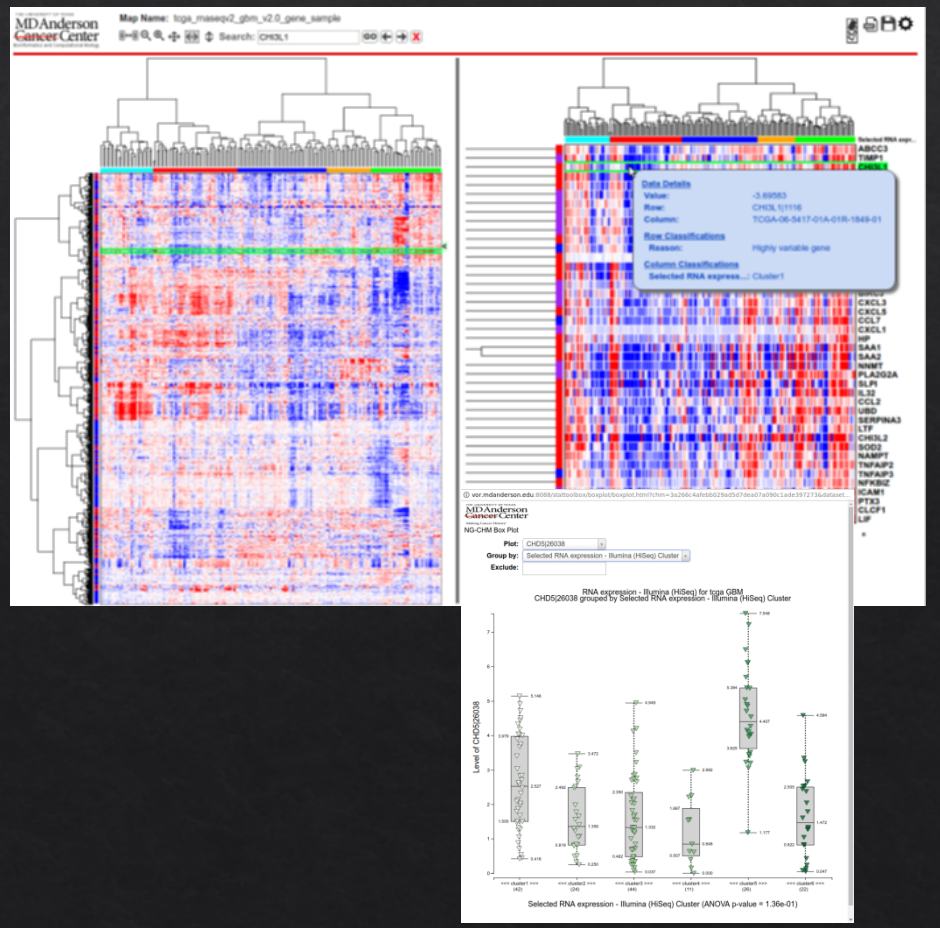
A3. Portal of Next-Generation Clustered Heat Maps

Background:

- NG-CHMs enable interactive exploration of very large heat maps
- Extreme zooming and panning, link-outs, high-res graphics
- Color scheme changes on the fly, storage of metadata
- A toolbox of integrated statistical tools

- A compendium of NG-CHMs for TCGA data:
  http://tcga.ngchm.net/ (statistical toolbox to be added soon)

- Next-Generation Clustered Heatmaps in Galaxy
  > BM Broom et al, Cancer Research, 2017
  http://cancerres.aacrjournals.org/content/77/21/e23



A3. Portal of Next-Generation Clustered Heat Maps

Goal and Strategic Plan:

Develop a compendium and public portal of next-generation clustered heat maps (NG-CHMs) for visualization of patterns in imaging data (radiomic and histomic) on tumors and to assess the relationship of those patterns to genomic and clinical data.

A4. Visualization of features & associations

Goal

- Develop prototype spatial visual analytics infrastructure capable of depicting relationship between multi-scale characterizations of tumor niches.
- Public data management portal allowing selection of patient sub-groups based on various parameters, including clinical, radiographic, and histologic. [**Stony Brook/MGH**]

Fall 2017 Foundational work: Development of QuIP image overlay capabilities [**Stony Brook**]

Integrative Analyses / Synergies:

- Associate findings of A1 (histologically identified tumor niches) and A2 (radiographic signatures) [**S.Brook/UPenn/MGH**]
- Leverage NG-CHM to explore associations between histological and genomic tumor niche characterization [**S.Brook/UT_MD**]

Public Release:

- Complex computational algorithms (e.g., segmentation, feature extraction, machine learning models) through:
  - the online Image Processing Portal (ipp.cbica.upenn.edu) [**UPenn**]
  - Docker containers [**MGH**]

New QuIP caMicroscope Capability: False color overlaid Images