

Molecular Phenotyping of Cancer

Molecular Phenotyping of Cancer

Betty Jones

Early clinic return prompted by medical oncology.

36 year-old African American woman.

Status post lumpectomy followed by mastectomy for invasive breast cancer (after MRI) by previous service chief.

ER negative, PR negative & HER2 negative

Negative axillary node dissection

Multifocal disease: initial primary ~ 1cm, second primary 1.5 cm

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Treated with TAC.
(docetaxel/doxorubicin/cyclophosphamide x 6 cycles)
Aggressive locoregional control with chest wall radiation.

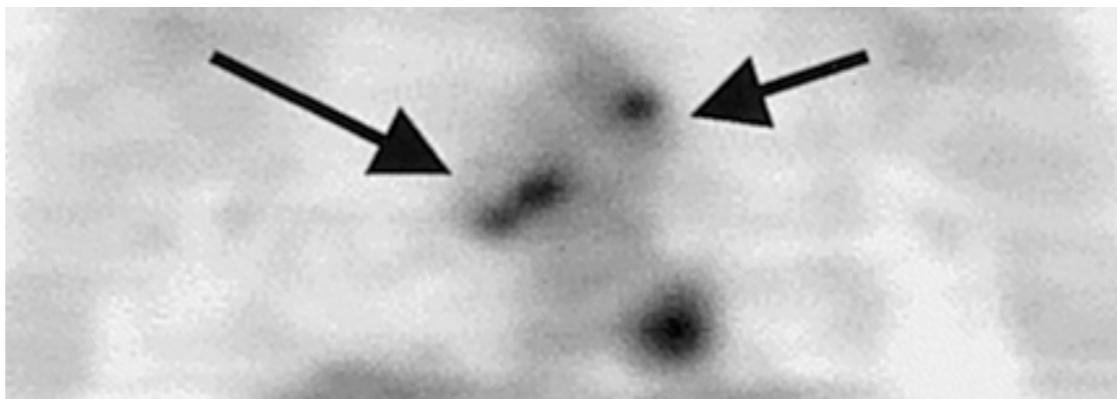
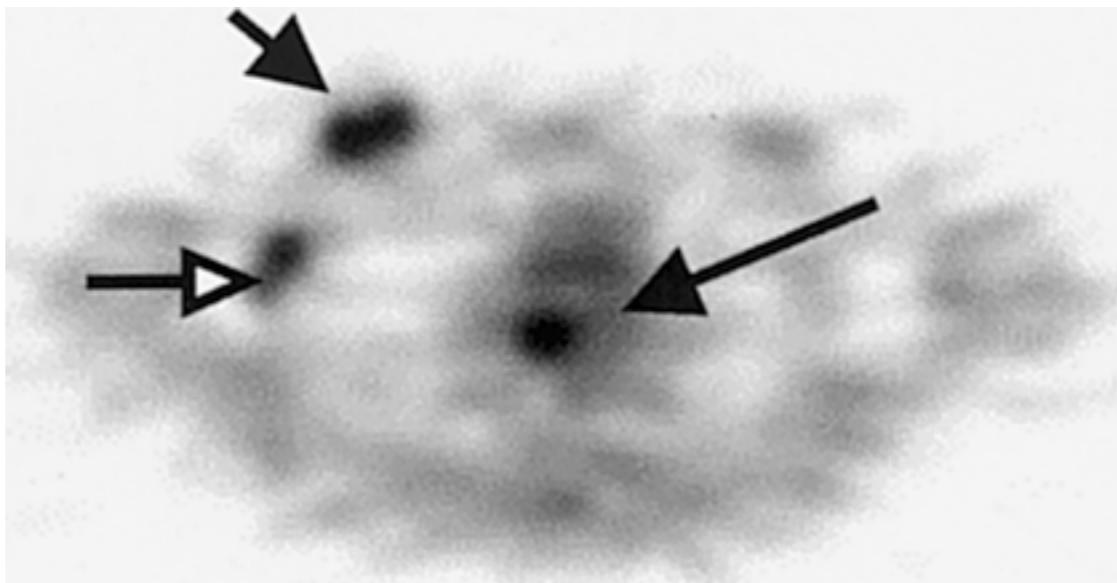
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Presents to clinic with 2 cm soft tissue nodule on the lateral aspect of her mastectomy scar.
Tattooed mass margins in clinic.
Sent for expedited sonographically-guided core biopsy.
Expedited PET imaging.

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Betty Jones



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Transferred her management to Duke Medical Oncology.

Treated with single agent carboplatin.

Progressed on chemotherapy, elected not to undergo further therapy.

Transferred to palliative medical service and expired.

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What were her options?

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Betty Jones

What were her options?

Standard Stuff (Old Fashioned Targets)

Anthracyclines

Taxanes

Anti-Metabolites

Platinum Agents

Targeted Agents

Cetuximab + Platinum (BALI-1)

Bevacizumab (GeparQuinto)

PARP Inhibitors

SRC Inhibitors

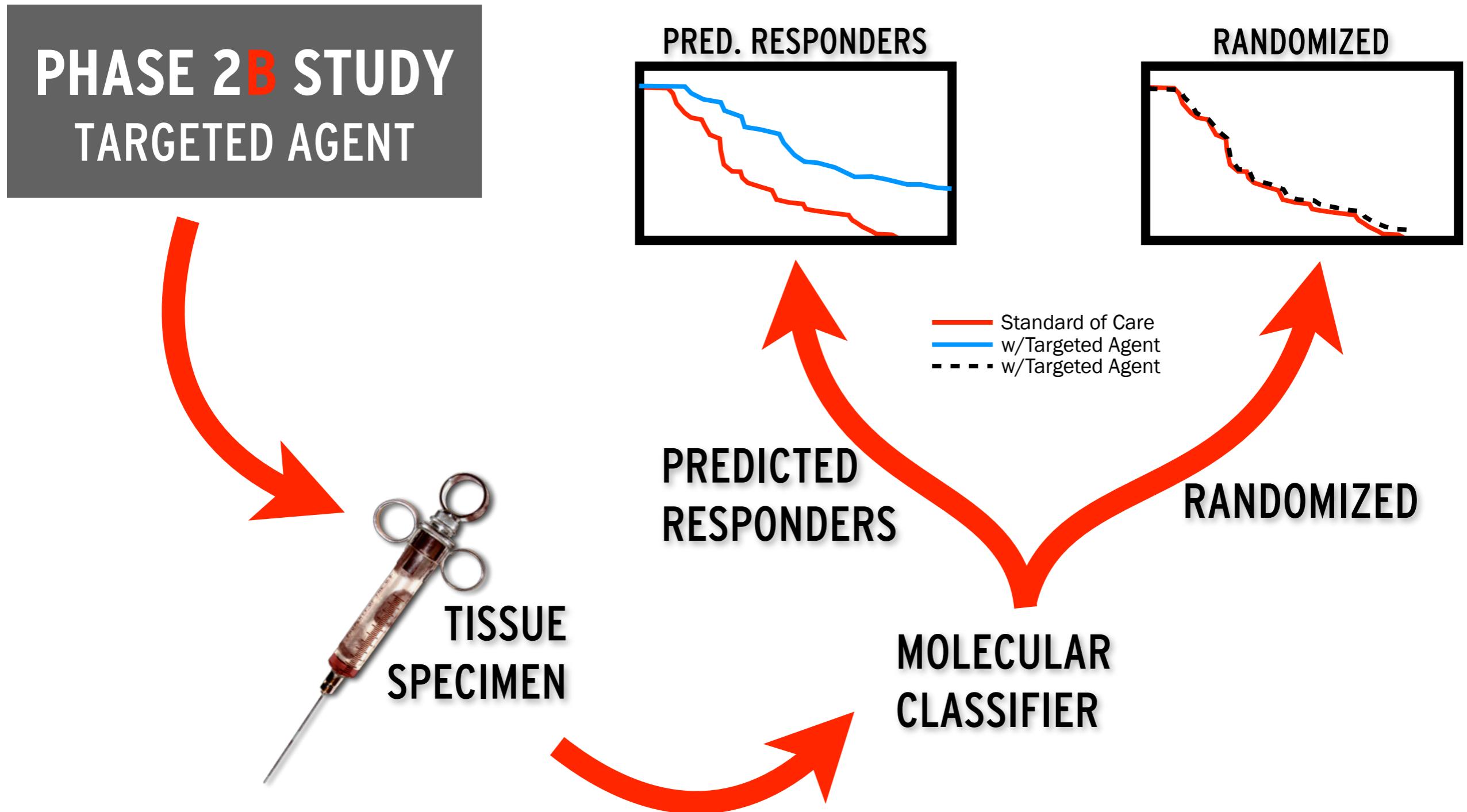
HDAC Inhibitors (ER-alpha)

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“

...to make this a valuable approach would require a better strategy for identifying the subset of patients within TNBC who would most likely respond, and... further use of anti-EGFR strategies in breast cancer will depend on an effective selection strategy that currently does not exist”

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“ Clinical equipoise occurs “if there is genuine uncertainty within the expert medical community... about the preferred treatment. ”

— Freedman, B., NEJM, 1987

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Focus the Question

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Focus the Question, then...

“infer accurate molecular predictors of a tumor’s therapeutic vulnerabilities and clinical behavior by training... on panels of tumor samples with molecular characterization and phenotypic data, while maximally leveraging additional information from complementary experiments and biological databases.”

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Focus the Question, then...

“we will take the stance that a molecular phenotype should be a phenotypic model. Molecular classification of cancer is dominated by descriptions rather than predictive models of phenotype.”

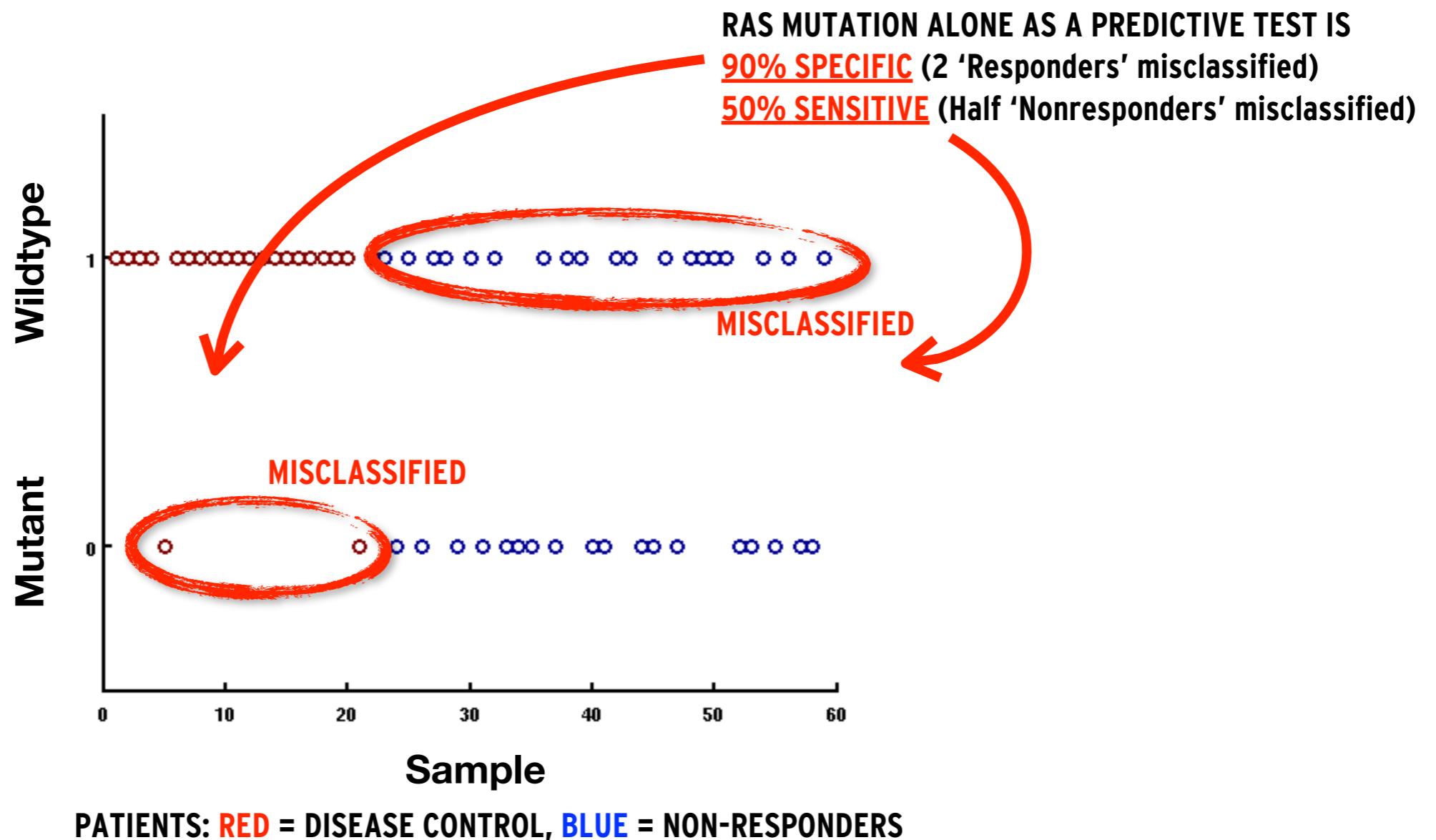
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Focus the Question, then...

“At the same time, a model need not be perfect. If it improves upon the *status quo* for clinical decision making, a predictive characterization represents an advance on the state-of-the-art. Strategically as we prioritize aspects of this project during its evolution, we want to identify clinical situations in which the state-of-the-art is ripe for improvement.”

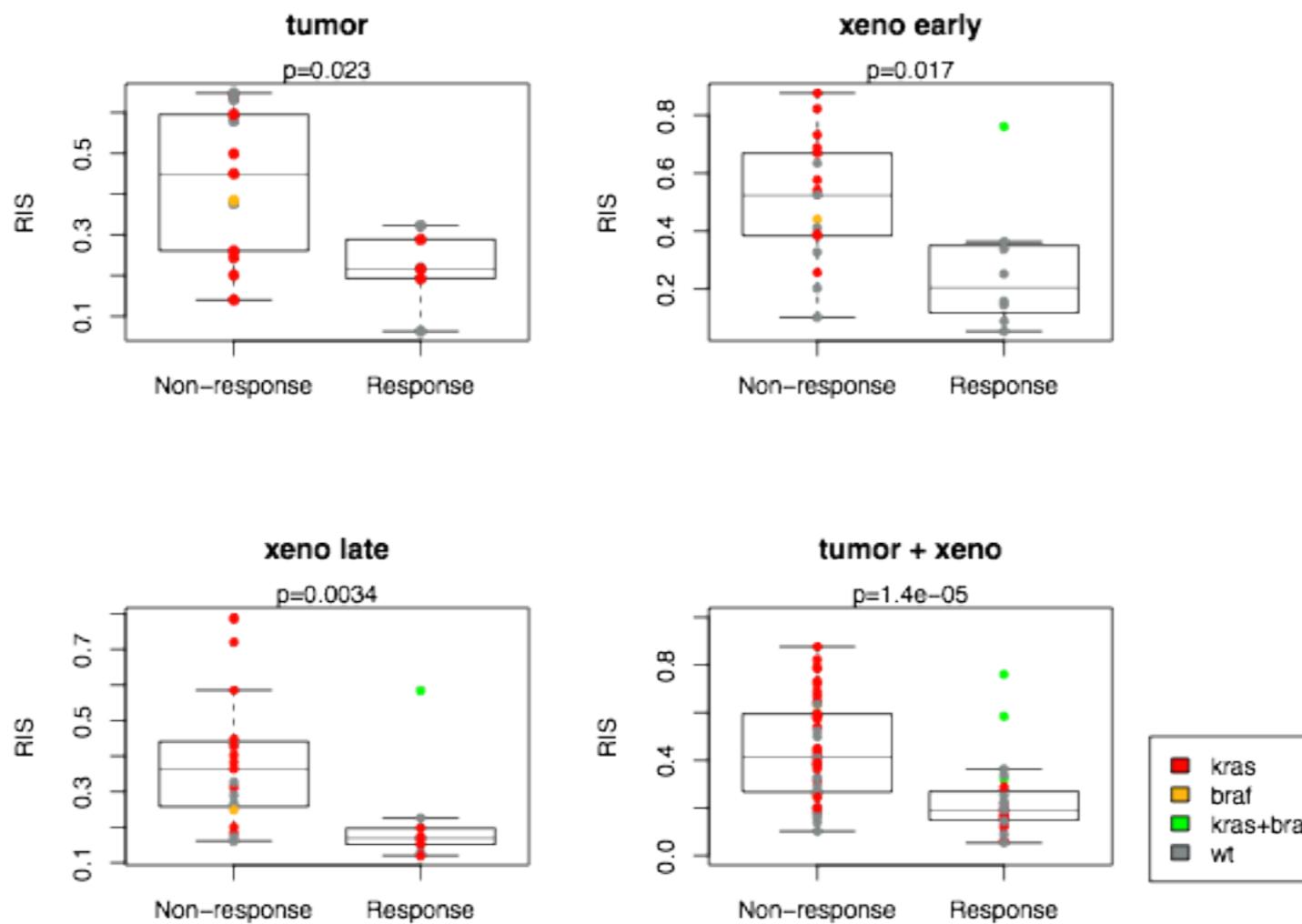
CETUXIMAB: METASTATIC COLORECTAL CANCER

BMS DATASET: 59 PATIENTS TREATED WITH CETUXIMAB WITH RAS STATUS



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Validation of RIS in 1° Tumors & Xenografts
Response to Cetuximab



— J. Guinney, RAS Project

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Koo Foundation SYSCC
Modeling HER2 Axis &
Elucidating Trastuzumab
Resistance
Deployable Models @ POC

H3
“Hardening” Cell Line Workflows

CCLE & Sanger
Modeling Therapeutic Sensitivity

TCGA
Cross-Malignancy Analyses

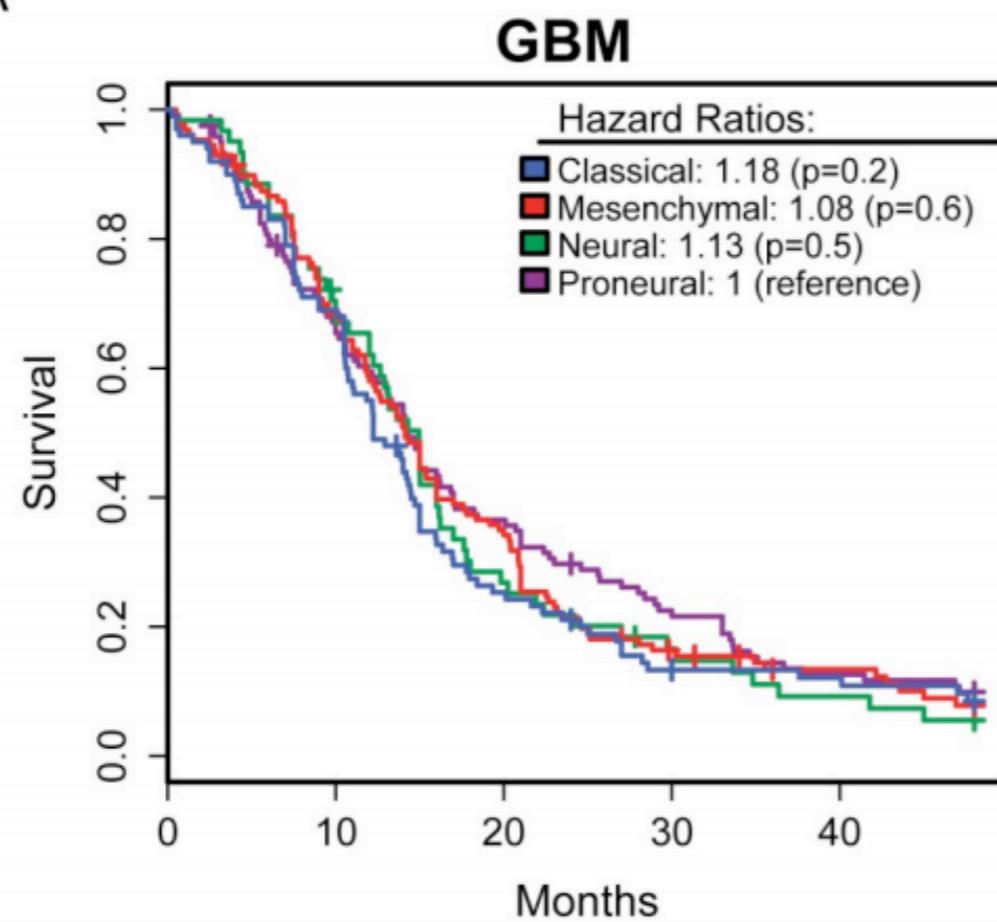
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Focus the Question

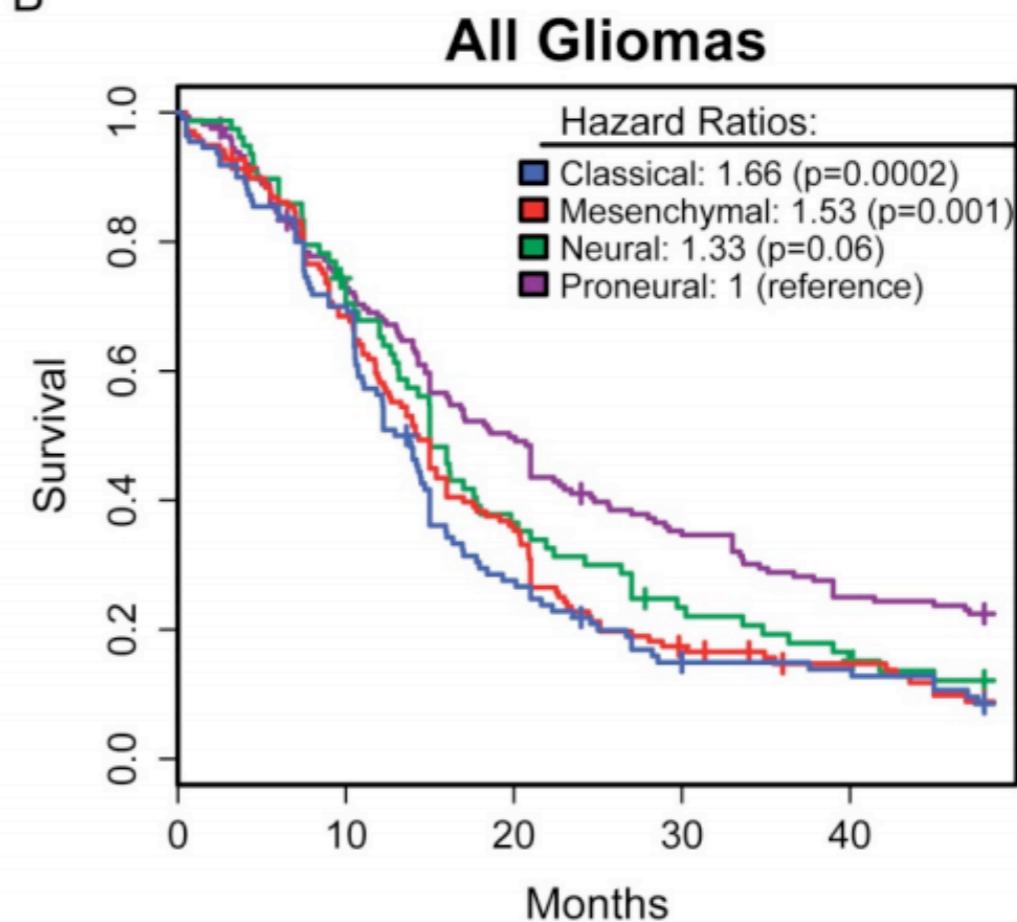
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Verhaak et al., Figure S7

A



B



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Synapse | BETA | CONTRIBUTE to the CURE | Erich Huang | Everything | Search | Download | Edit | Share | Add | Tools |

Home > Survival-Driven Class Di...

Survival-Driven Class Discovery in Glioblastoma (syn275012)

Added by: Erich Huang on: Tue Apr 17 13:03:33 GMT-700 2012
Last updated by: Erich Huang on: Wed Apr 18 14:53:01 GMT-700 2012

Description

While molecular subtyping of glioblastoma is expected to facilitate therapeutic strategies tailored to the unique biological characteristics of a patient's tumor, reported subtypes in GBM appear less stable than those noted in breast cancer. To address this question, we are taking an explicitly model-based approach by first identifying transcripts strongly associated with survival in the TCGA cohort, and using high dimensional Gaussian mixture modeling for class discovery that can be prospectively validated.

Initial analysis suggests that transcriptional data defines three subtypes in the TCGA (Affymetrix), one of which (Class 2) demonstrates significantly different survival characteristics. Class 2 is enriched for patients (9/10) IDH1 mutations that have previously been shown to be associated with improved survival. Next phase of this study will be to understand the biology related to these classes and associate/correlate these classes with measurable phenotypes such as radiographic characteristics.

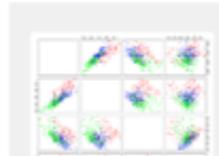
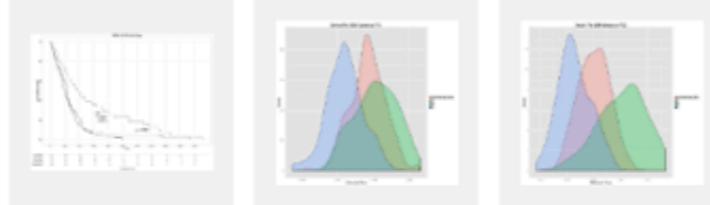
Project Contents

All Contents | Study | Data | Code | Link | Analysis | RObject | PhenotypeData | ExpressionData |

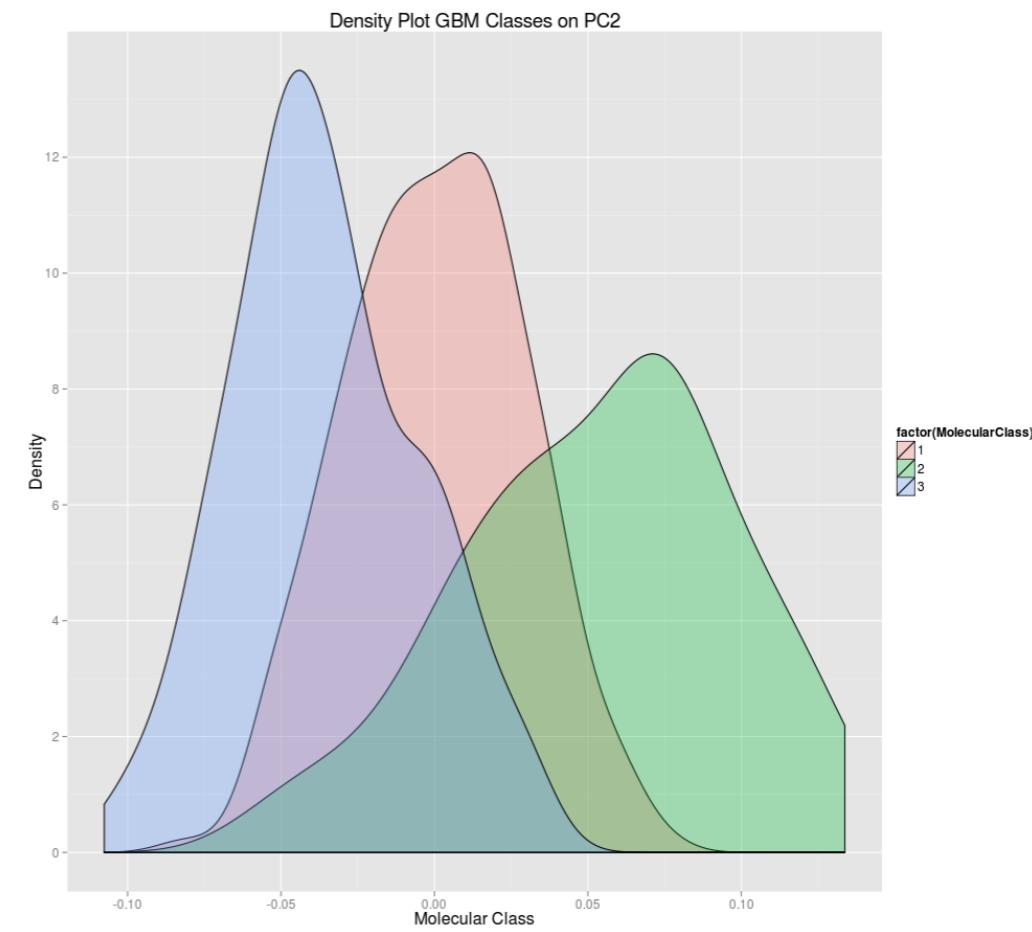
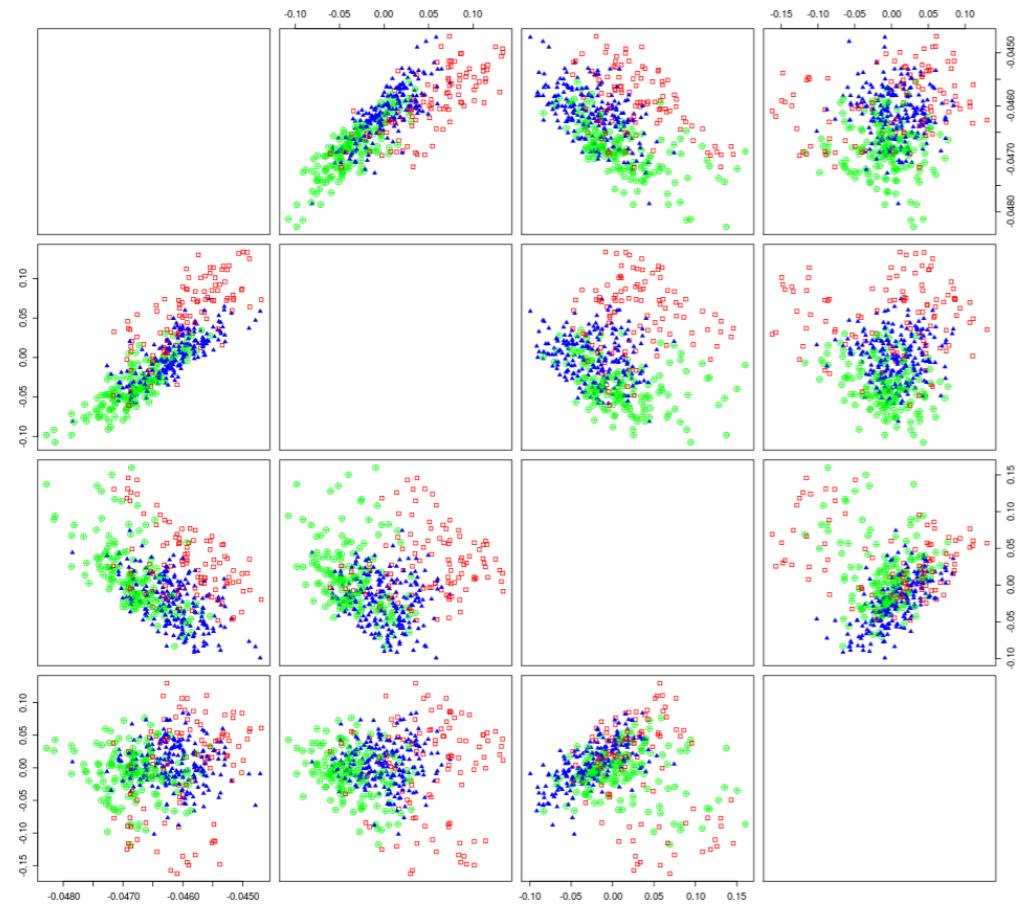
- TCGA Glioblastoma multiforme
- populate gbm data
- gbm survival modeling
- high dimensional gbm classification modeling
- intermediate results a. data preparation
- intermediate results b. results of association of expression with survival
- gbm classification visualization
- intermediate data c. results of high dimensional classification method

Right click on an item in the list to Edit or Delete.

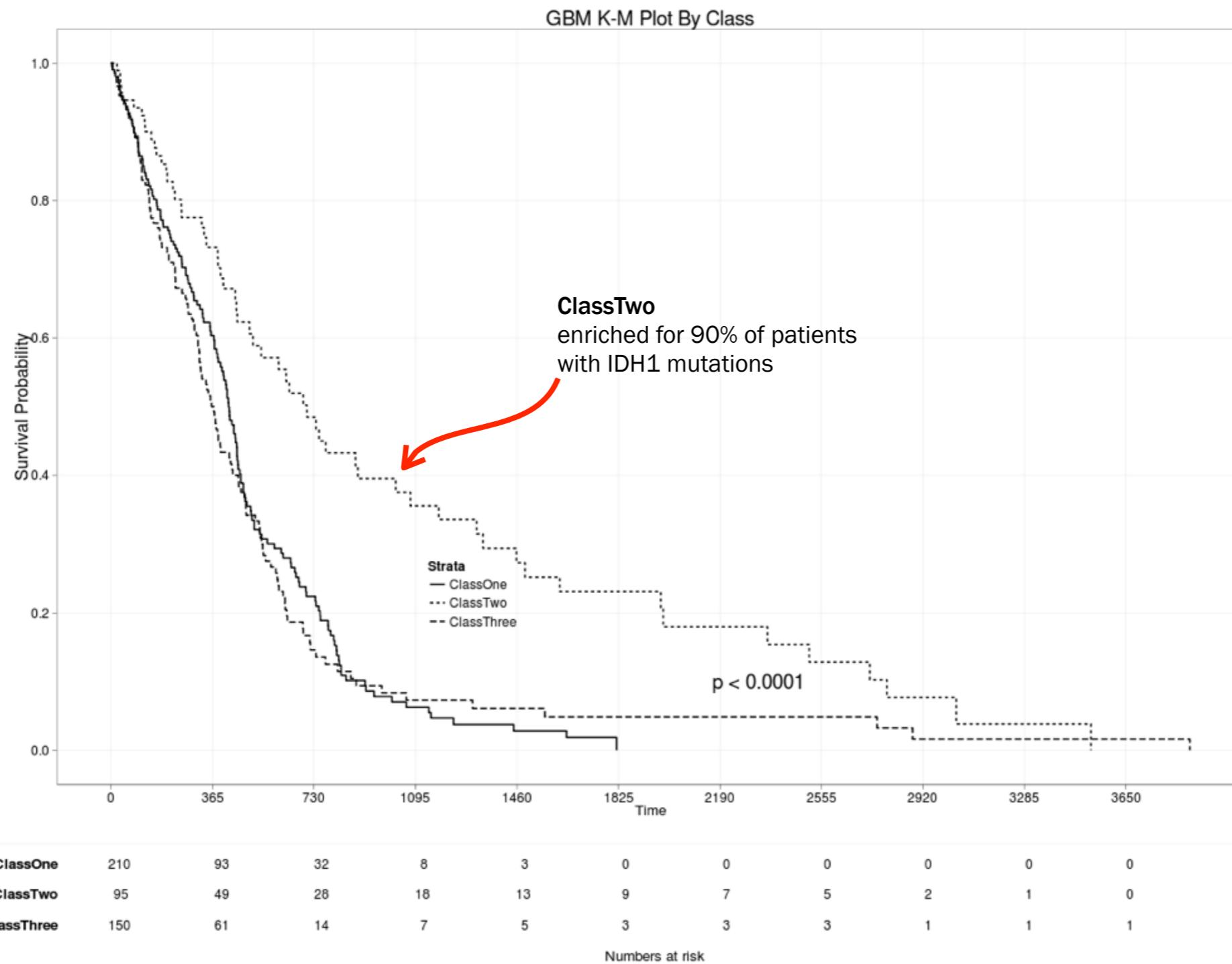
Visual Attachments



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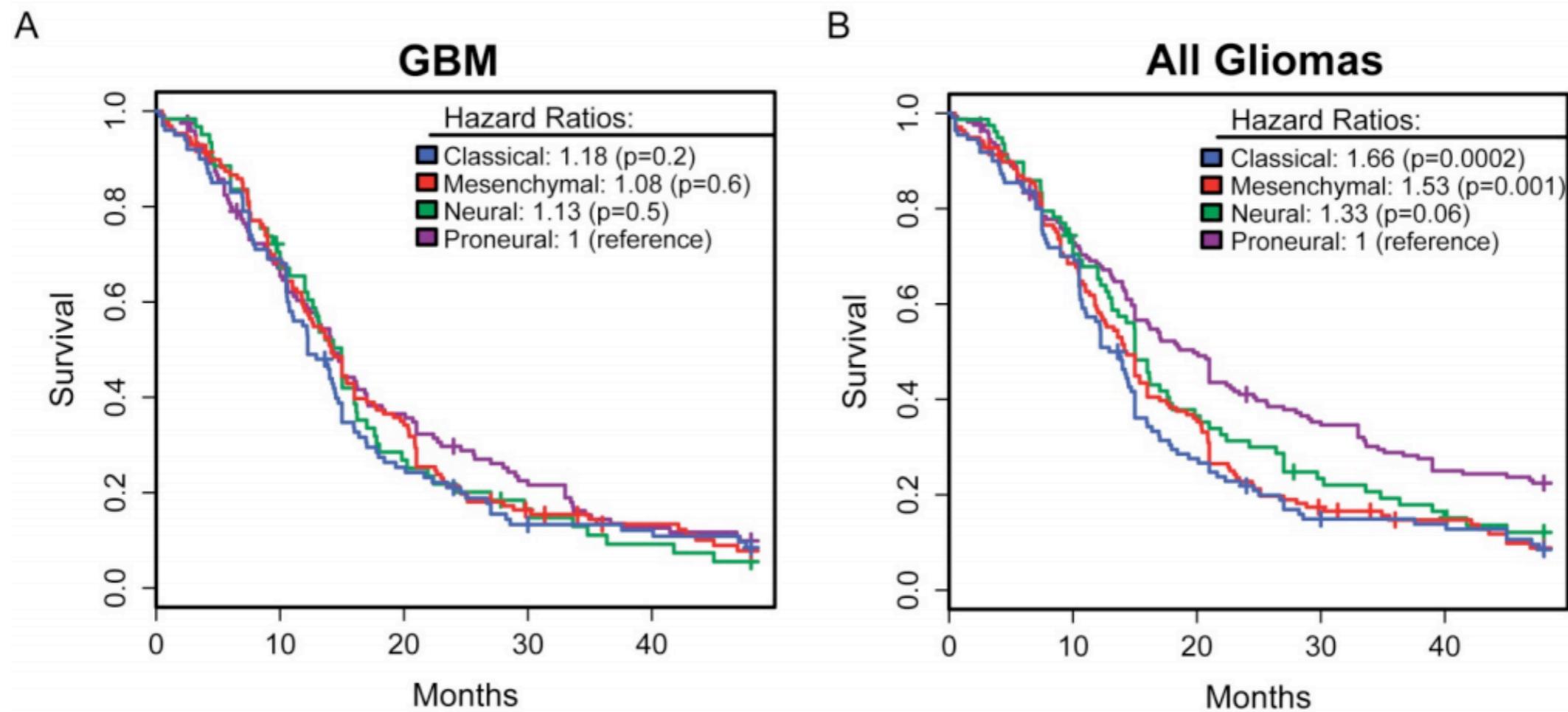


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Verhaak et al., Figure S7



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Screenshot of a web browser showing the clearScience prototype project abstract page.

The page title is "clearScience | Technical Demo: Modeling ER Status in Breast Cancer".

The main content area displays the "project abstract" with a "go to narrative" link.

A diagram illustrates the data flow:

```
graph TD; A[TRANSBIG Ext. DATA SYN 163017] --> B(Cohort Assignment CODE GITHUB v0.9-18); B --> C(TRAIN DATA SYN 163002); B --> D(VALID DATA SYN 163004); C --> E(ER RF Model Generation CODE GITHUB v0.9-18); D --> F(Validation Boxplot MEDIA SYN 163010)
```

The "project tag" is listed as "version 0.9-10".

The right side of the page features a sidebar titled "synapse powered building blocks" with sections for "code", "data", "models", and "figures".

code
code entities are executable blocks of code stored and keyed in synapse. their synapse web page can be accessed, or they can be brought directly into a web-accessible virtual machine:

- ☐ Cohort Assignment: [onWeb](#), or in [RStudio](#)
- ☐ Model Build & Validation: [onWeb](#) or in [RStudio](#)

data
data entities are both primary and secondary scientific data stored and keyed in synapse. their synapse web page can be accessed, or they can be brought directly into a web-accessible virtual machine

- ☐ TRANSBIG Data: [onWeb](#), in [RStudio](#)
- ☐ Training Data: [onWeb](#), in [RStudio](#)
- ☐ Validation Data: [onWeb](#), in [RStudio](#)
- ☐ Prediction Vector: [onWeb](#), in [RStudio](#)

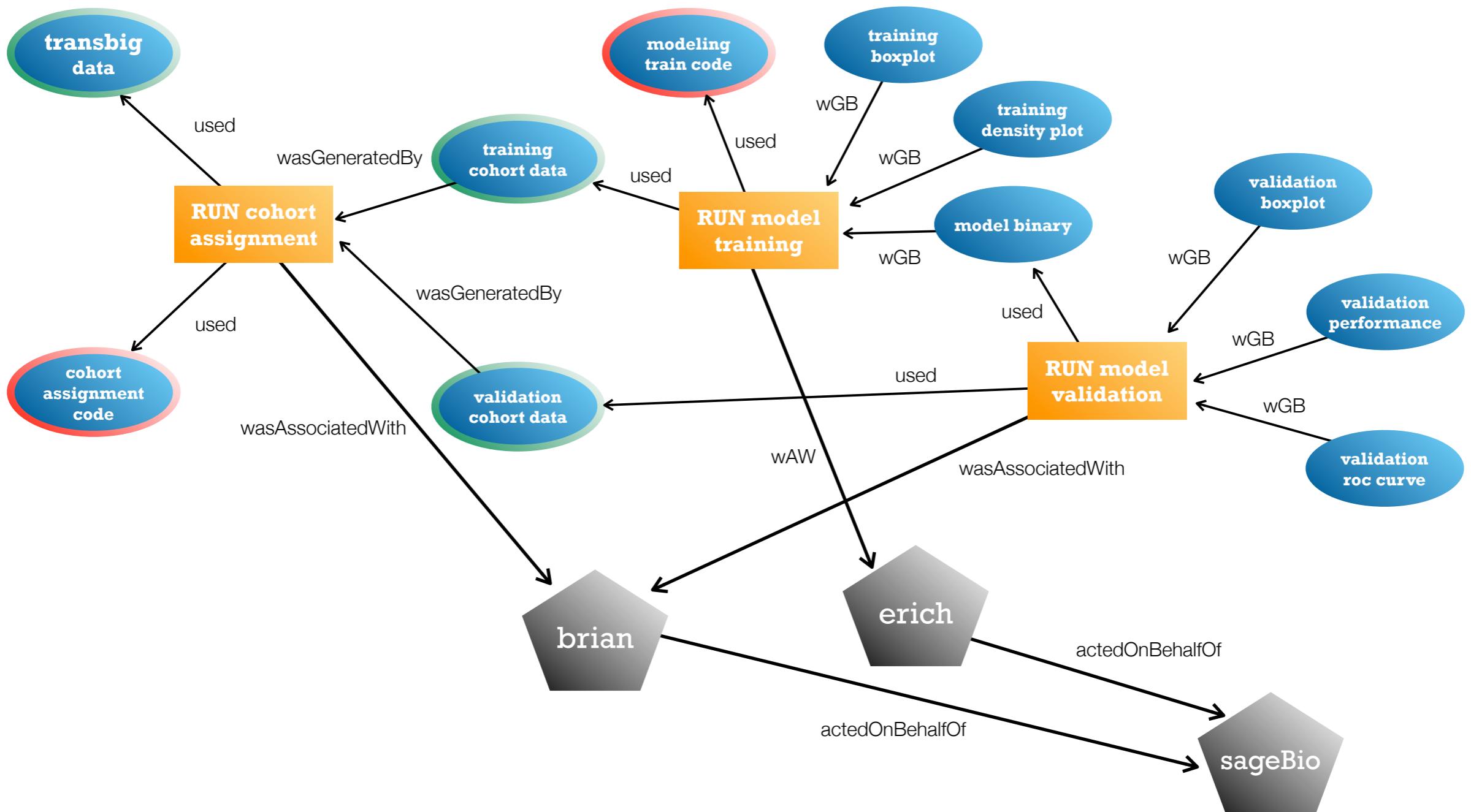
models
model entities are binaries generated by an analysis that will take data inputs and provide predictions. their synapse web page can be accessed, or they can be brought directly into a web-accessible virtual machine

- 🔊 Random Forest Model of ER Status: [onWeb](#), in [RStudio](#)

figures
figure entities are stored and keyed in synapse. their synapse web page can be accessed, or they can be

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World Wide Web Consortium
Provenance Model



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Sage-Bionetworks/Glioblastoma-Exploration

github

Sage-Bionetworks / Glioblastoma-Exploration

Code Network Pull Requests 0 Issues 0 Wiki Graphs Admin

Scouring the Glioblastoma (GBM) TCGA expression data for molecular signatures indicative of survival benefit — [Read more](#)

Clone in Mac ZIP HTTP SSH Git Read-Only https://github.com/Sage-Bionetworks/Glioblastoma Read+Write access

branch: master Files Commits Branches 1 Tags 1 Downloads

Latest commit to the master branch

Working on another bug.

erichhuang authored 4 months ago commit 5871d7c02a

name	age	message	history
plots	4 months ago	Move output visualization to subdirectory called "plots" [brian-bot]	
.gitignore	4 months ago	Bugfixes for visualizeGBMClasses.R [erichhuang]	
Glioblastoma-Exploration.Rproj	4 months ago	Bugfixes for visualizeGBMClasses.R [erichhuang]	
README	4 months ago	Updates of README for overview of study [brian-bot]	
hdClassDiscovery.R	4 months ago	Cleaning up and reconciling code entities and intermediate layers. [erichhuang]	
populateGBMdata.R	4 months ago	Further functionalizing and interactivity improvements. [erichhuang]	
survivalModels.R	4 months ago	Cleaning up and reconciling code entities and intermediate layers. [erichhuang]	
visualizeGBMClasses.R	4 months ago	Working on another bug. [erichhuang]	

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Betty Jones

36 years old

Recurrent triple negative breast cancer

How can we help others in her predicament?