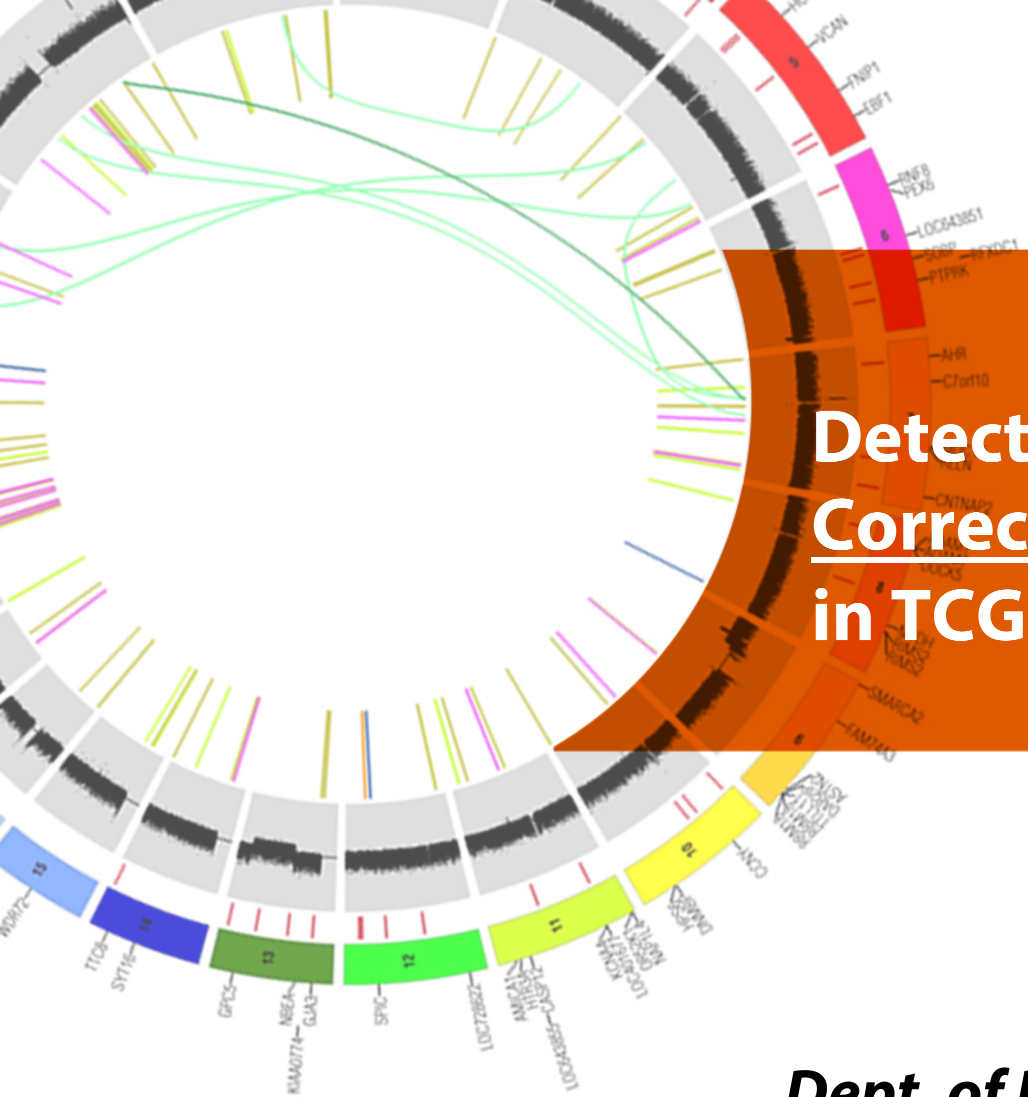
The Cancer Genome Atlas



Detection, Diagnosis and Correction of Batch Effects in TCGA Data

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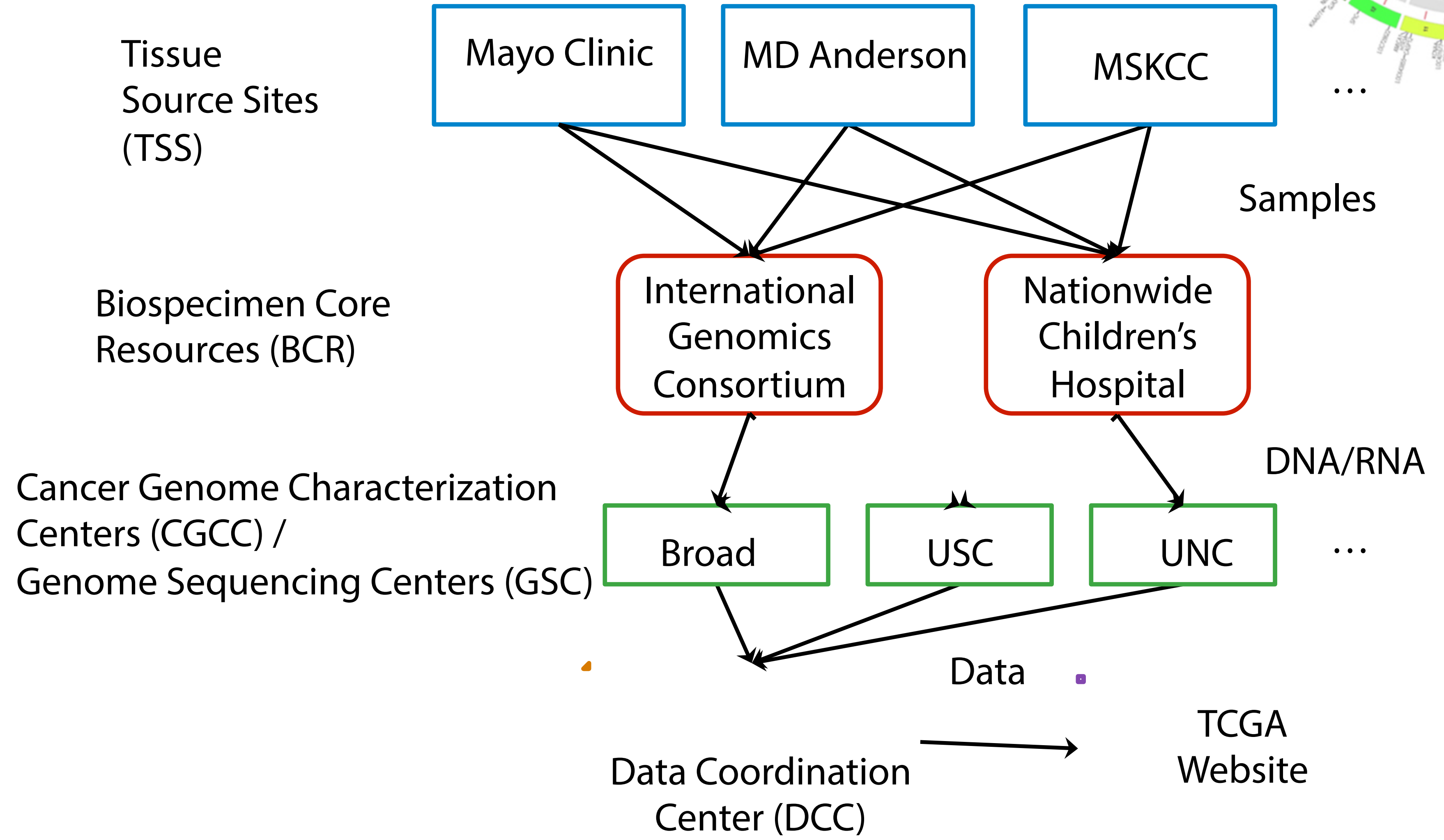
UT MD Anderson Cancer Center

THE UNIVERSITY OF TEXAS
MD Anderson
~~Cancer~~ Center

Simplified Flow Diagram for TCGA


Tissue Source Sites (TSS)
Mayo Clinic
MD Anderson
MSKCC
…
Samples
Biospecimen Core Resources (BCR)
International Genomics Consortium
Nationwide Children's Hospital
DNA/RNA
Cancer Genome Characterization Centers (CGCC) / Genome Sequencing Centers (GSC)
Broad
USC
UNC
…
Data
Data Coordination Center (DCC)
TCGA Website

Step 1: Batch effects diagnoses

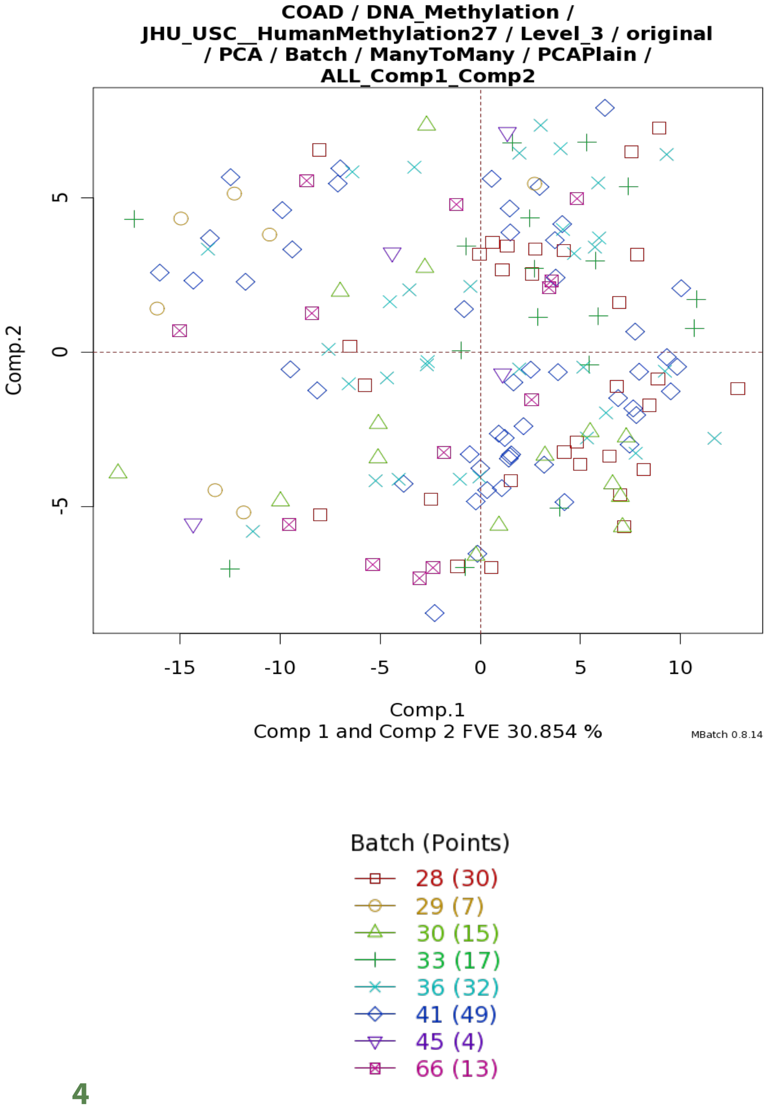
- Objectives
  - Detect / quantify batch effects
  - Identify source(s) of batch effects
- Tools / algorithms for diagnoses – MBatch R package

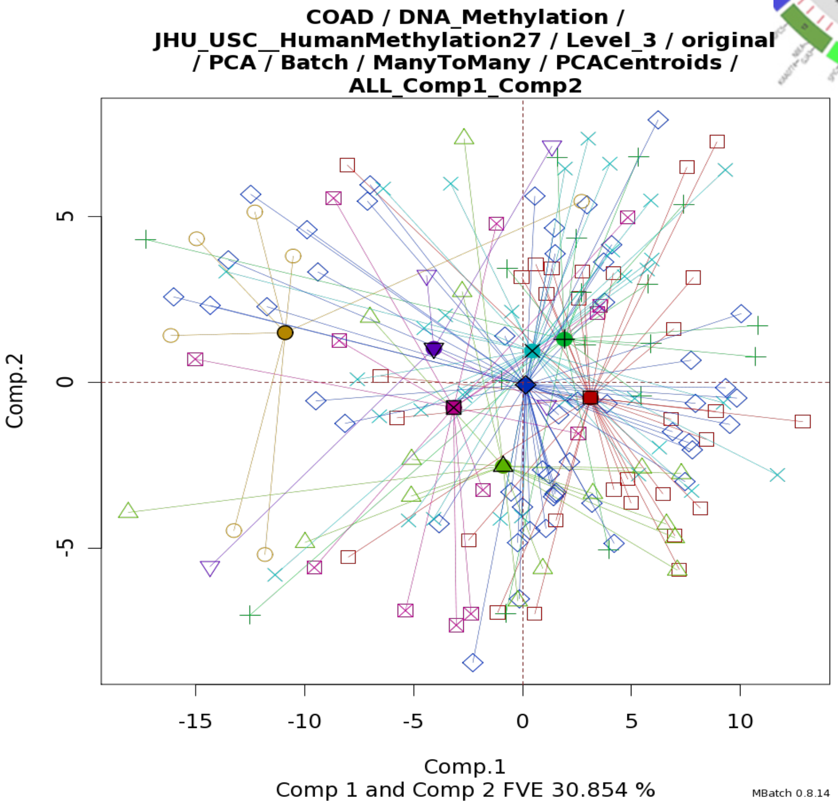
  http://bioinformatics.mdanderson.org/tcgabatcheffects/

  1. PCA-Plus plots (novel)
  2. BatchCorr algorithm (novel)
  3. Hierarchical clustering
  4. Clinical correlates
  5. Box plots
  6. ANOVA / MANOVA
- Disclaimer: No substitute for human input

1. PCA-Plus

http://bioinformatics.mdanderson.org/tcgabatcheffects/


COAD / DNA_Methylation / JHU_USC__HumanMethylation27 / Level_3 / original / PCA / Batch / ManyToMany / PCAPlain / ALL_Comp1_Comp2


COAD / DNA_Methylation / JHU_USC__HumanMethylation27 / Level_3 / original / PCA / Batch / ManyToMany / PCACentroids / ALL_Comp1_Comp2

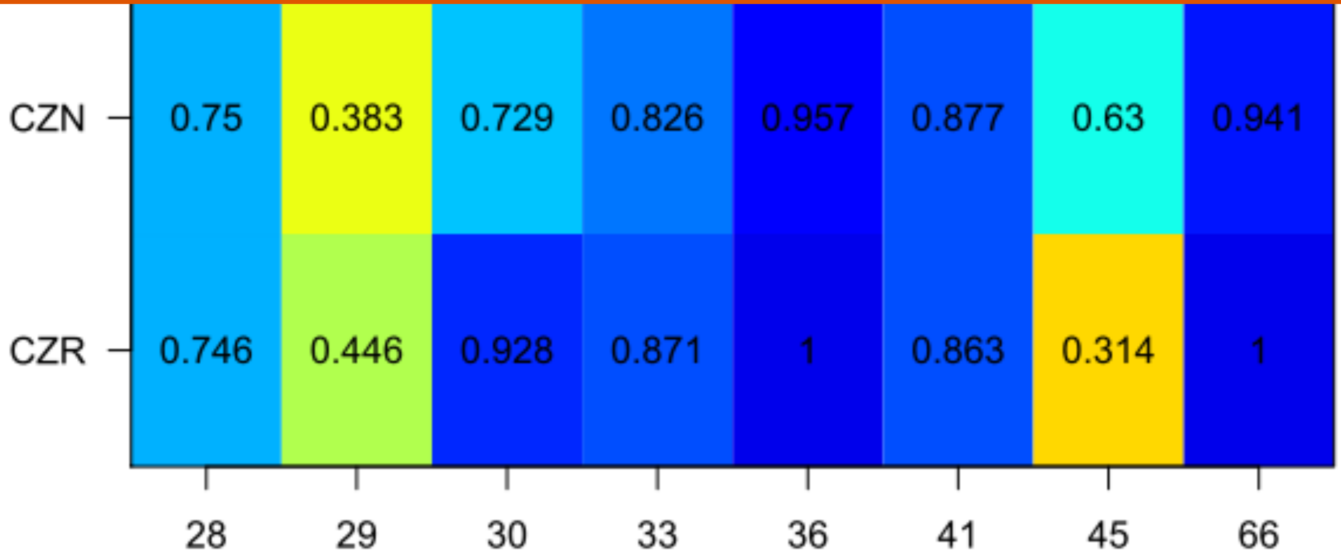
Dispersion Metrics

First PCA Component: 1
First Component FVE (%): 22.972
Second PCA Component: 2
Second Component FVE (%): 7.882

DSC(1,2): 0.411
Dw(1,2): 7.51
Db(1,2): 3.087
DSC pvalue(1,2): 0

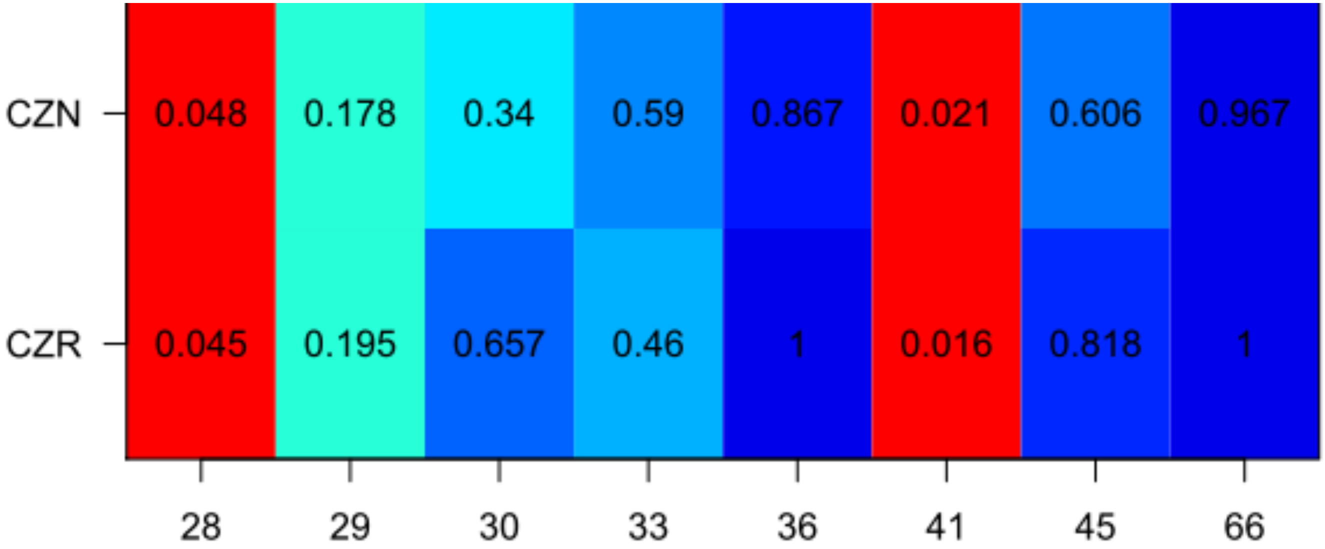
DSC: 0.299
Dw: 14.003
Db: 4.193
DSC pvalue: 0

2. BatchCorr



	28	29	30	33	36	41	45	66
CZN	0.75	0.383	0.729	0.826	0.957	0.877	0.63	0.941
CZR	0.746	0.446	0.928	0.871	1	0.863	0.314	1

BatchCorr value



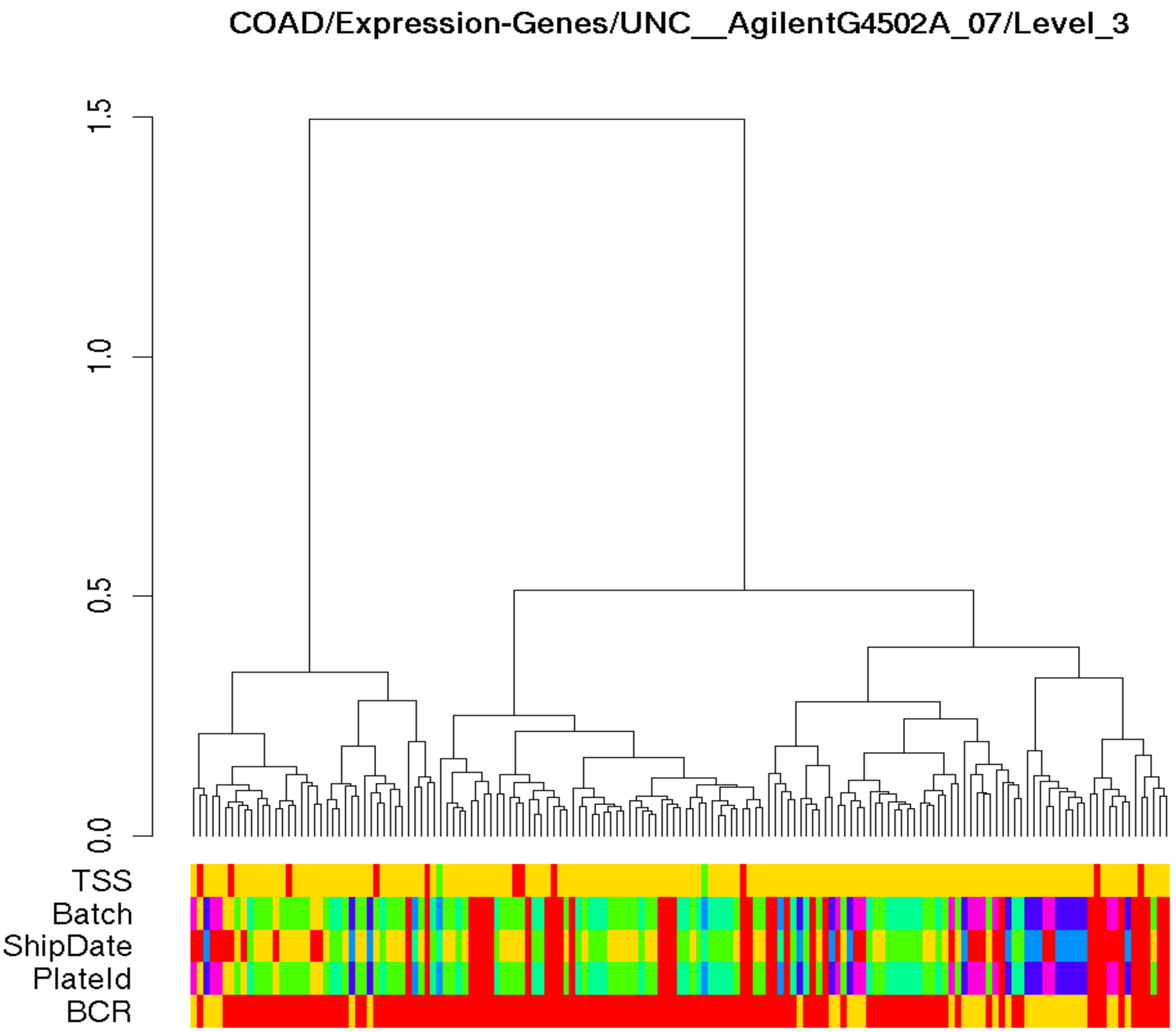
	28	29	30	33	36	41	45	66
CZN	0.048	0.178	0.34	0.59	0.867	0.021	0.606	0.967
CZR	0.045	0.195	0.657	0.46	1	0.016	0.818	1

p-values

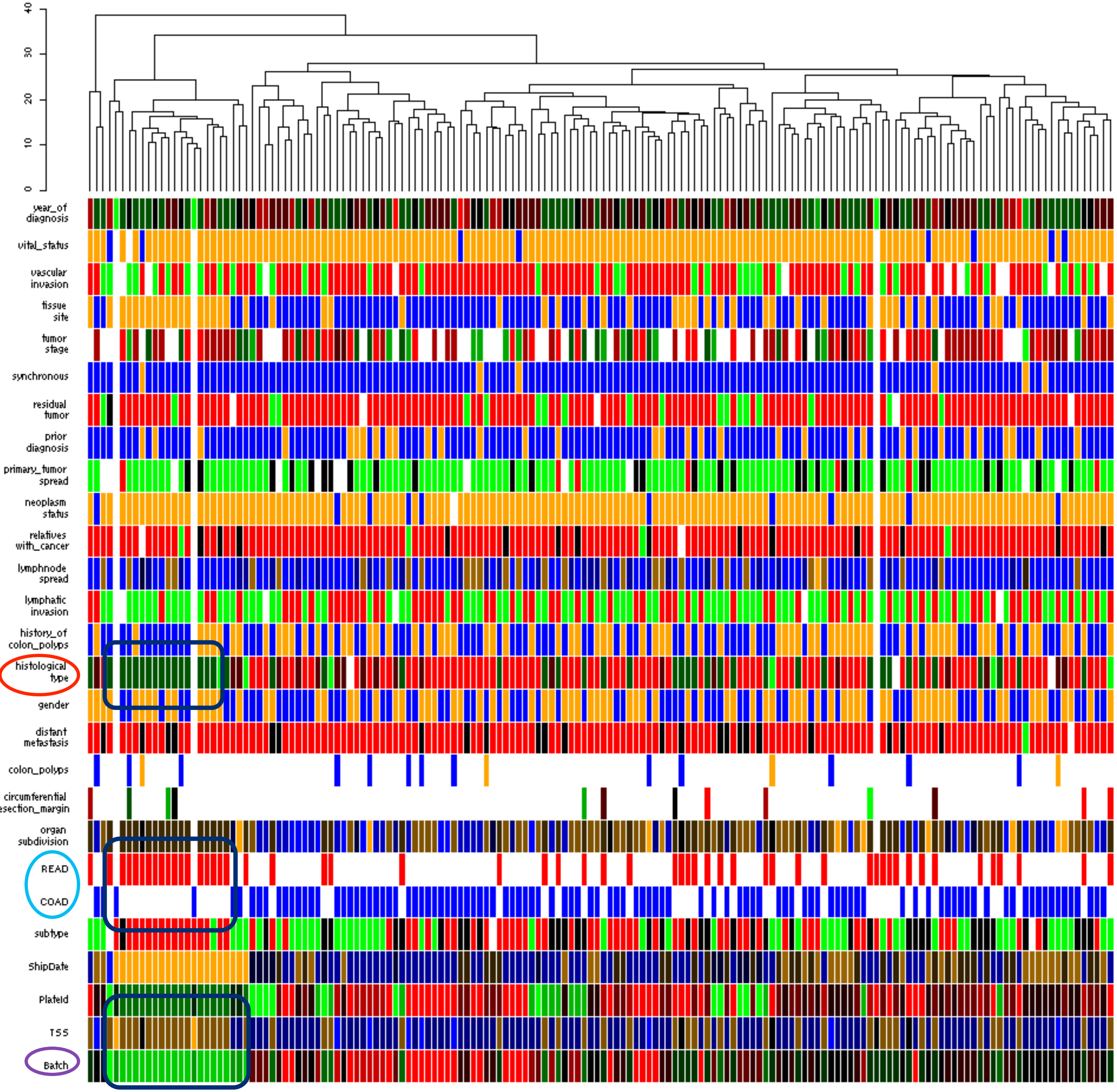
Batch effects present:

BatchCorr < 0.7 AND
p-value < 0.05

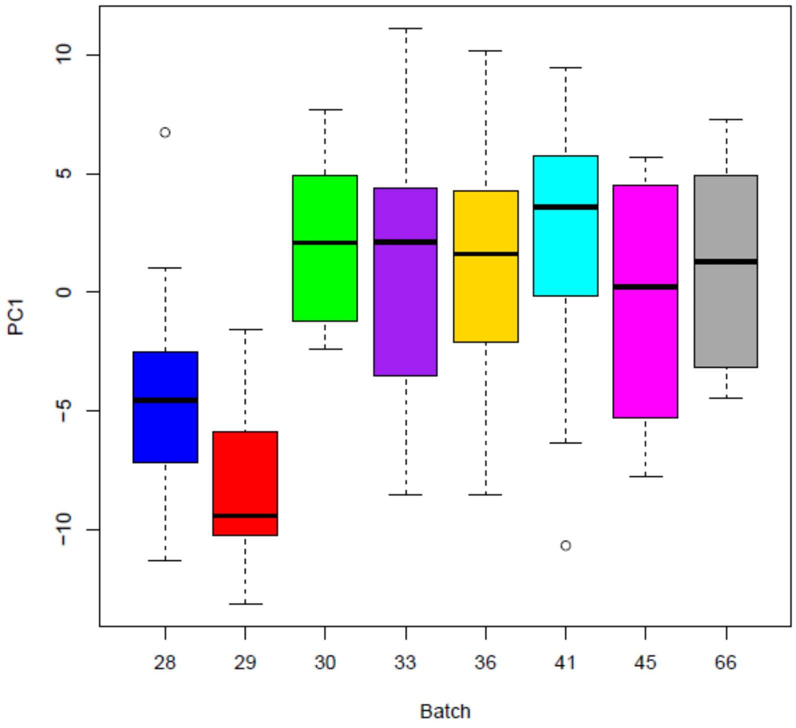
3. Hierarchical Clustering



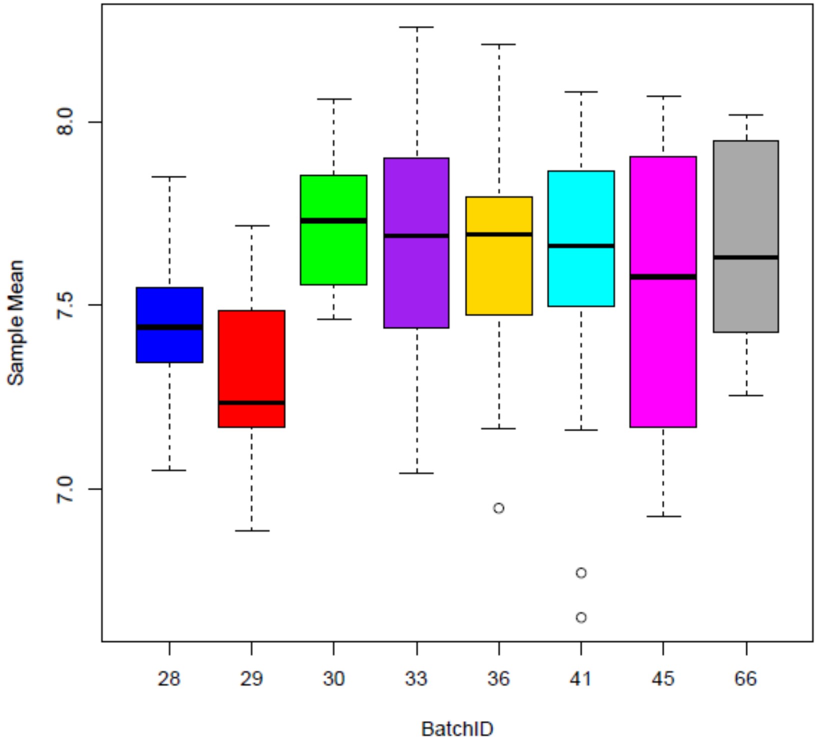
4. Clinical Correlates COAD/ READ miRNA



5. Box plots

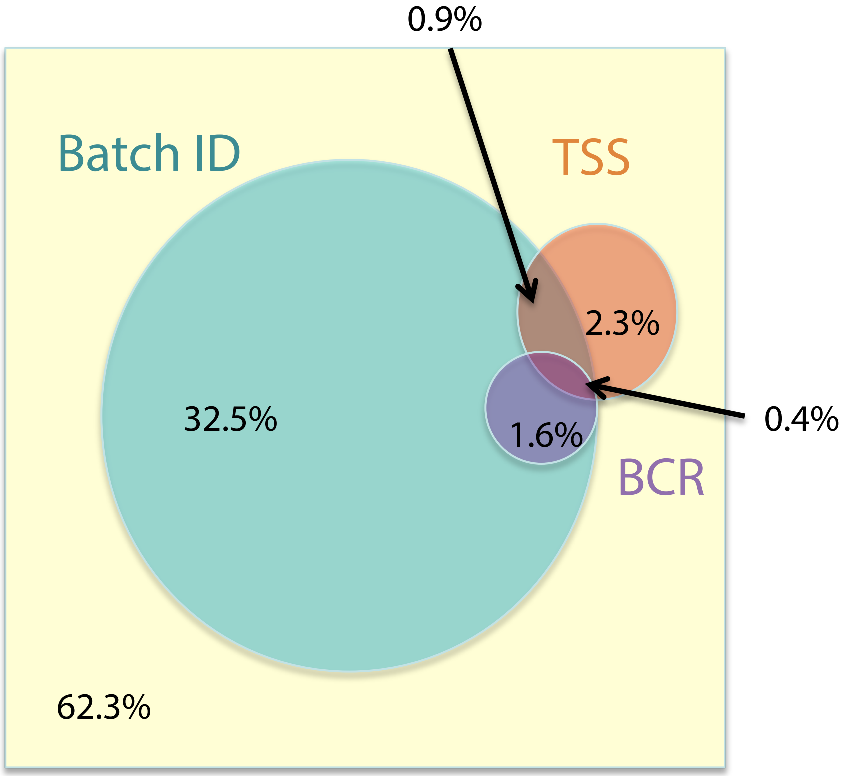


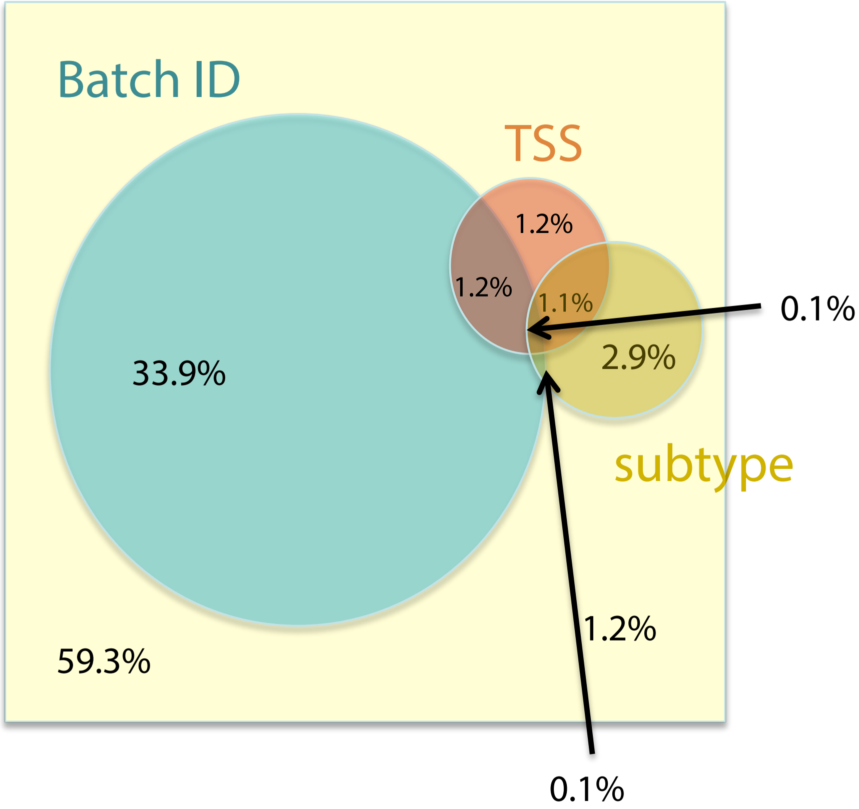
Batch medians



Batch means

6. ANOVA / MANOVA

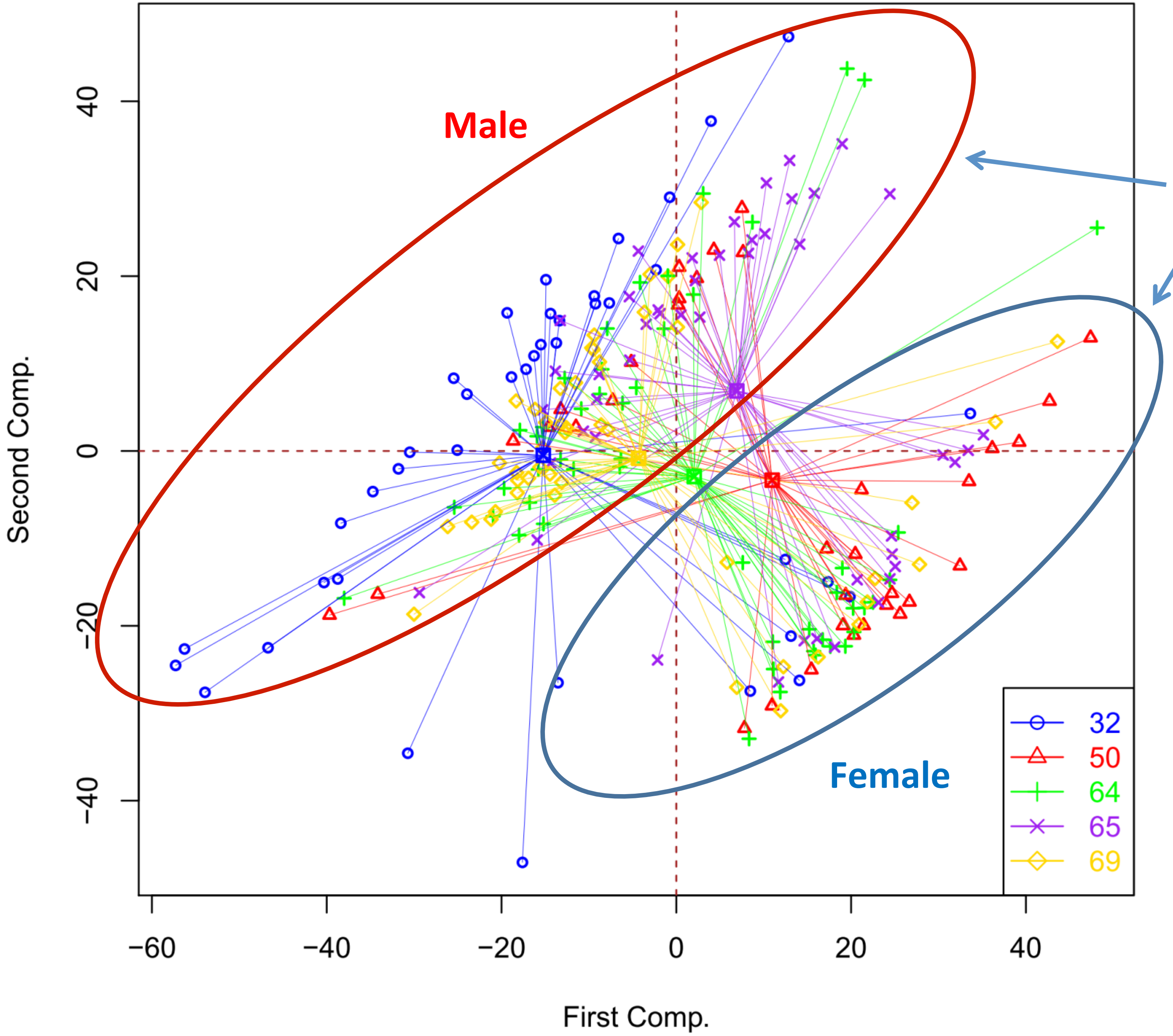




Step 2: Batch effects correction

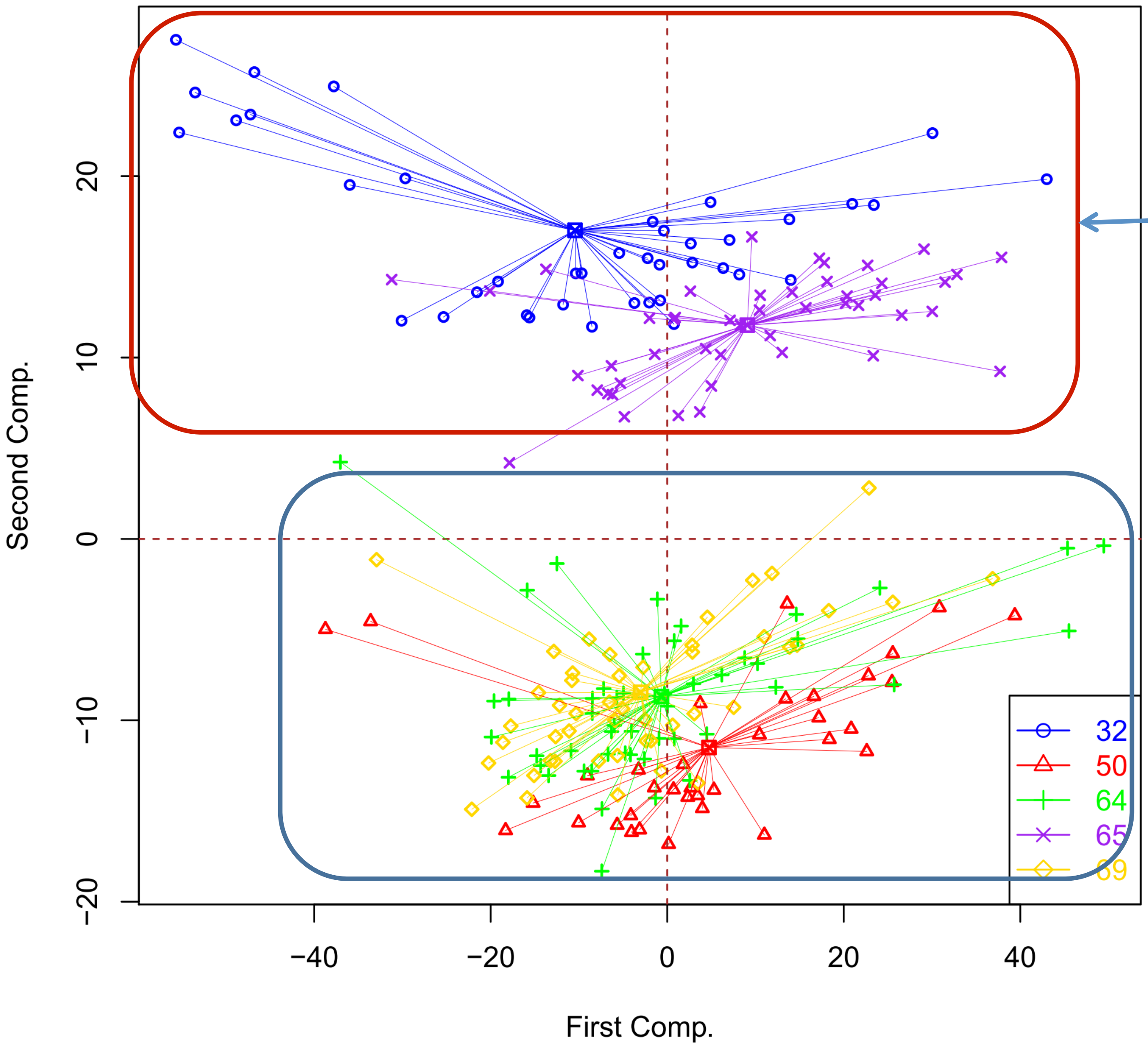
- Correct the source of the problem whenever possible
- When not possible, or source unknown, algorithms can be used
- Some algorithms for correction:
  - ComBat (aka Empirical Bayes)
  - ANOVA
  - Median Polish
- Included in MBatch R package
  http://bioinformatics.mdanderson.org/tcgabatcheffects/

Kidney cancer (KIRC) DNA methylation data (27k)



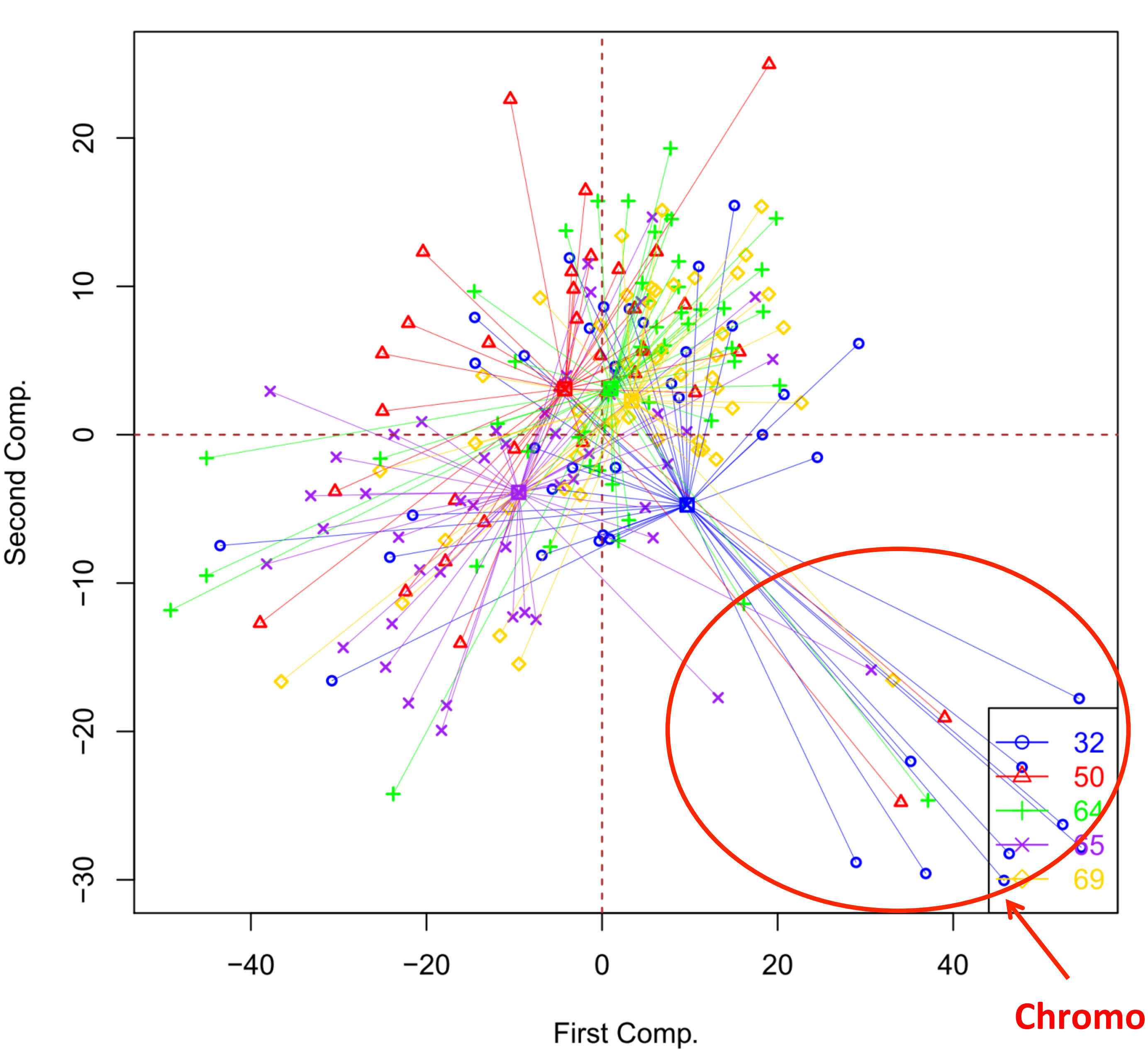
Dichotomy observed

After removing sex chromosomes



New dichotomy based on batch ID appears

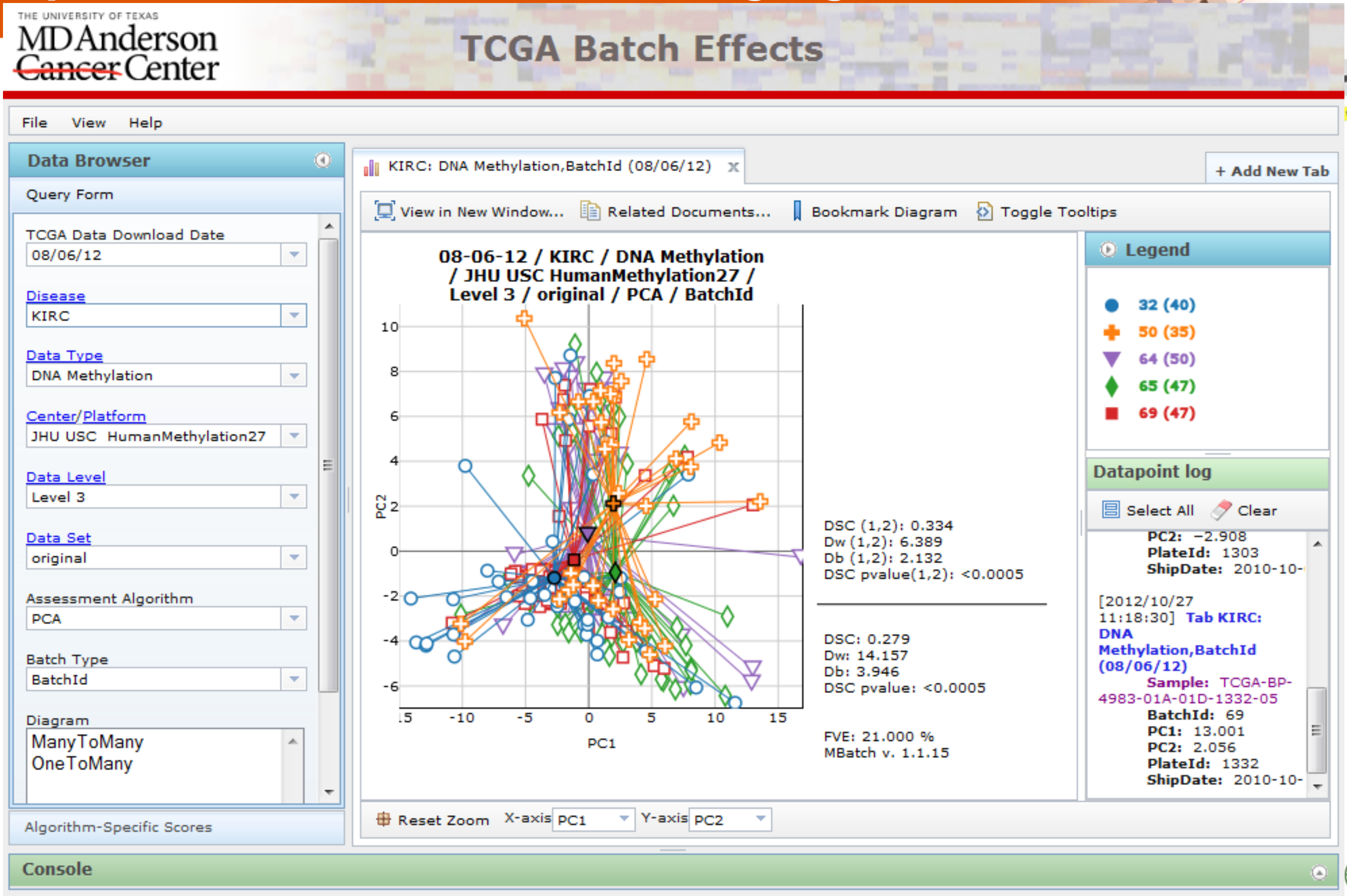
After removing chad probes



Chromophobes

TCGA MBatch website

http://bioinformatics.mdanderson.org/tcgabatcheffects/



TCGA Data Download Date: 08/06/12

Disease: KIRC

Data Type: DNA Methylation

Center/Platform: JHU USC HumanMethylation27

Data Level: Level 3

Data Set: original

Assessment Algorithm: PCA

Batch Type: BatchId

Diagram:
ManyToMany
OneToMany

08-06-12 / KIRC / DNA Methylation / JHU USC HumanMethylation27 / Level 3 / original / PCA / BatchId

DSC (1,2): 0.334
Dw (1,2): 6.389
Db (1,2): 2.132
DSC pvalue(1,2): <0.0005

DSC: 0.279
Dw: 14.157
Db: 3.946
DSC pvalue: <0.0005

FVE: 21.000 %
MBatch v. 1.1.15

Legend:
- ● 32 (40)
- ✚ 50 (35)
- ▼ 64 (50)
- ◆ 65 (47)
- ■ 69 (47)

Datapoint log:

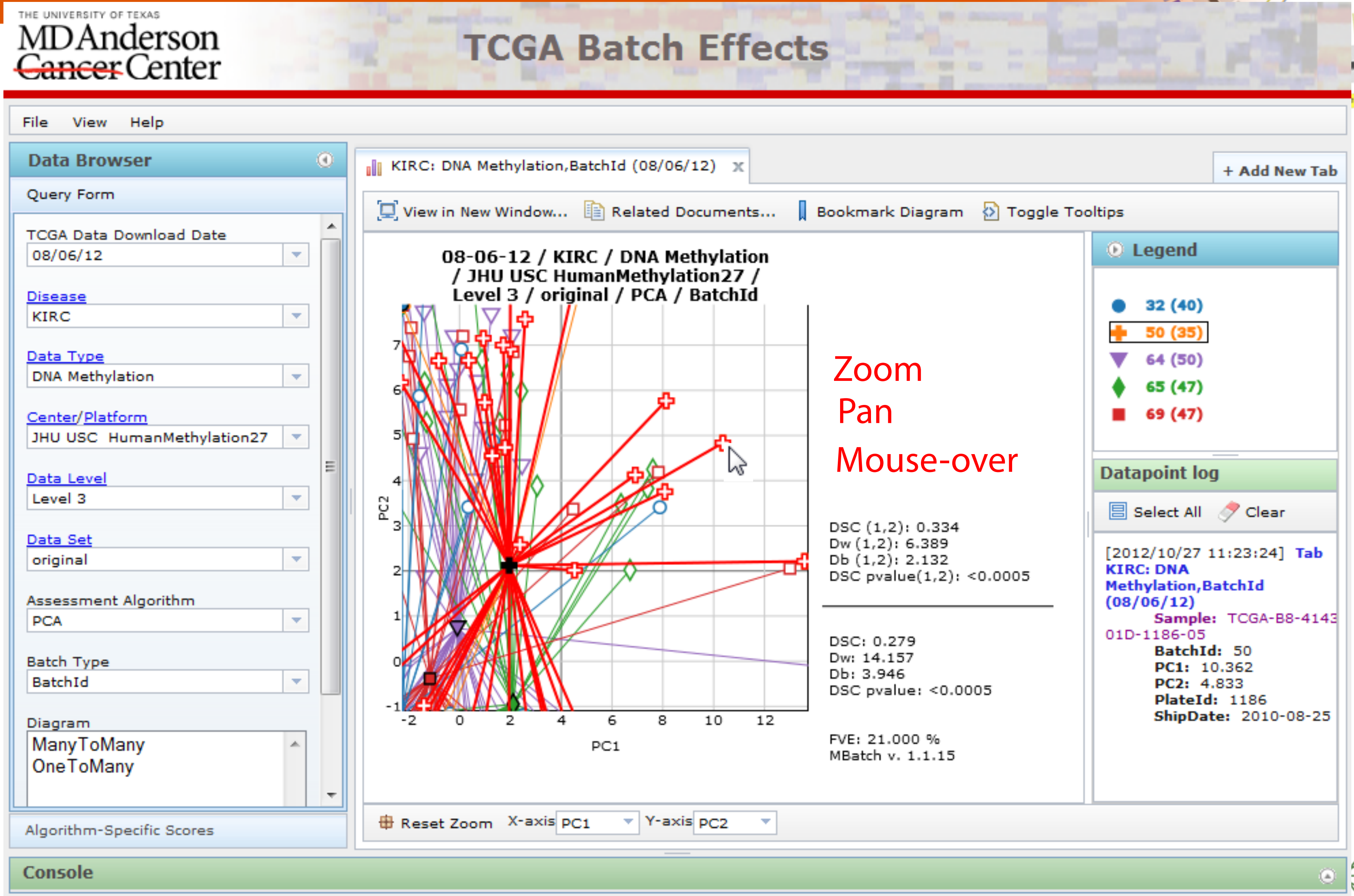
PC2: −2.908
PlateId: 1303
ShipDate: 2010-10-

[2012/10/27 11:18:30] **Tab KIRC: DNA Methylation,BatchId (08/06/12)**
Sample: TCGA-BP-4983-01A-01D-1332-05
BatchId: 69
PC1: 13.001
PC2: 2.056
PlateId: 1332
ShipDate: 2010-10-

X-axis: PC1 Y-axis: PC2

TCGA MBatch website

http://bioinformatics.mdanderson.org/tcgabatcheffects/



TCGA Data Download Date: 08/06/12

Disease: KIRC

Data Type: DNA Methylation

Center/Platform: JHU USC HumanMethylation27

Data Level: Level 3

Data Set: original

Assessment Algorithm: PCA

Batch Type: BatchId

Diagram:
ManyToMany
OneToMany

X-axis: PC1
Y-axis: PC2

```
DSC (1,2): 0.334
Dw (1,2): 6.389
Db (1,2): 2.132
DSC pvalue(1,2): <0.0005

DSC: 0.279
Dw: 14.157
Db: 3.946
DSC pvalue: <0.0005

FVE: 21.000 %
MBatch v. 1.1.15
```

```
[2012/10/27 11:23:24] Tab
KIRC: DNA
Methylation,BatchId
(08/06/12)
     Sample:  TCGA-B8-4143
01D-1186-05
     BatchId:  50
     PC1:  10.362
     PC2:  4.833
     PlateId:  1186
     ShipDate:  2010-08-25
```

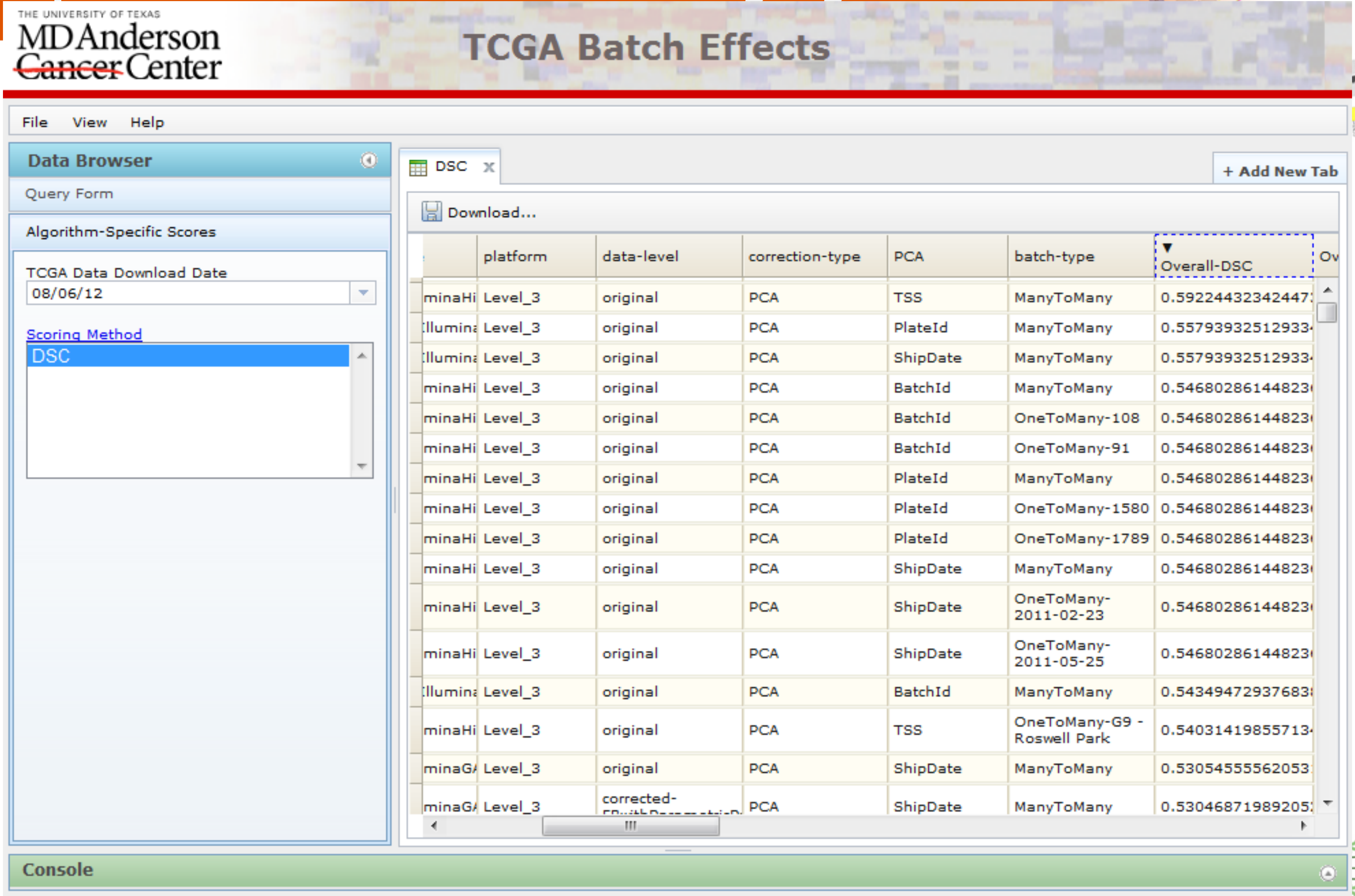
Zoom

Pan

Mouse-over

TCGA MBatch website

http://bioinformatics.mdanderson.org/tcgabatcheffects/



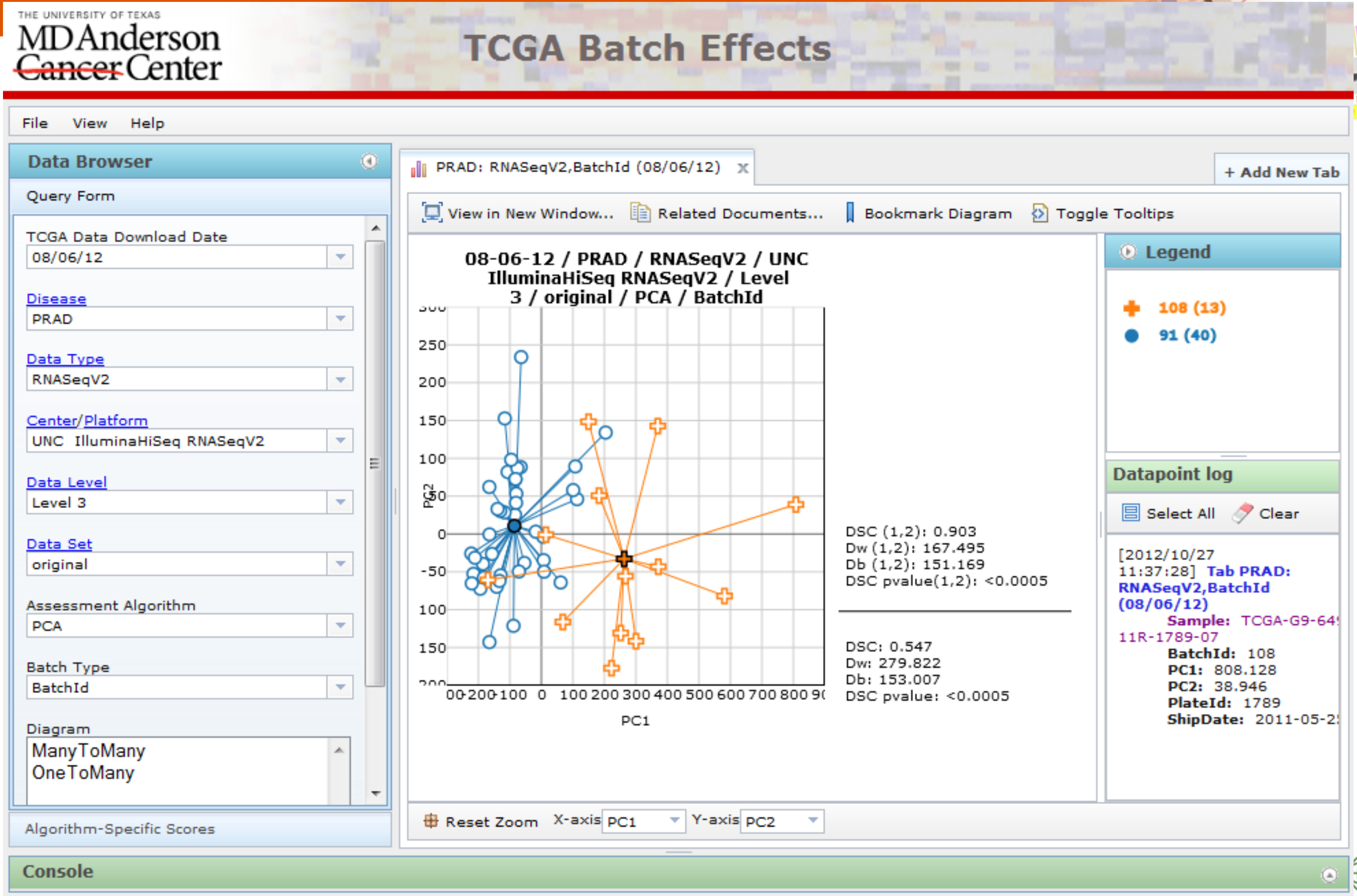
TCGA Data Download Date: 08/06/12

Scoring Method: DSC

	platform	data-level	correction-type	PCA	batch-type	Overall-DSC	Ov
minaHi	Level_3	original	PCA	TSS	ManyToMany	0.59224432342447	
Illumina	Level_3	original	PCA	PlateId	ManyToMany	0.55793932512933	
Illumina	Level_3	original	PCA	ShipDate	ManyToMany	0.55793932512933	
minaHi	Level_3	original	PCA	BatchId	ManyToMany	0.54680286144823	
minaHi	Level_3	original	PCA	BatchId	OneToMany-108	0.54680286144823	
minaHi	Level_3	original	PCA	BatchId	OneToMany-91	0.54680286144823	
minaHi	Level_3	original	PCA	PlateId	ManyToMany	0.54680286144823	
minaHi	Level_3	original	PCA	PlateId	OneToMany-1580	0.54680286144823	
minaHi	Level_3	original	PCA	PlateId	OneToMany-1789	0.54680286144823	
minaHi	Level_3	original	PCA	ShipDate	ManyToMany	0.54680286144823	
minaHi	Level_3	original	PCA	ShipDate	OneToMany-2011-02-23	0.54680286144823	
minaHi	Level_3	original	PCA	ShipDate	OneToMany-2011-05-25	0.54680286144823	
Illumina	Level_3	original	PCA	BatchId	ManyToMany	0.54349472937683	
minaHi	Level_3	original	PCA	TSS	OneToMany-G9 - Roswell Park	0.54031419855713	
minaGA	Level_3	original	PCA	ShipDate	ManyToMany	0.53054555562053	
minaGA	Level_3	corrected-	PCA	ShipDate	ManyToMany	0.53046871989205	

TCGA MBatch website

http://bioinformatics.mdanderson.org/tcgabatcheffects/



TCGA Data Download Date: 08/06/12

Disease: PRAD

Data Type: RNASeqV2

Center/Platform: UNC IlluminaHiSeq RNASeqV2

Data Level: Level 3

Data Set: original

Assessment Algorithm: PCA

Batch Type: BatchId

Diagram:
ManyToMany
OneToMany

08-06-12 / PRAD / RNASeqV2 / UNC IlluminaHiSeq RNASeqV2 / Level 3 / original / PCA / BatchId

✚ 108 (13)
● 91 (40)

DSC (1,2): 0.903
Dw (1,2): 167.495
Db (1,2): 151.169
DSC pvalue(1,2): <0.0005

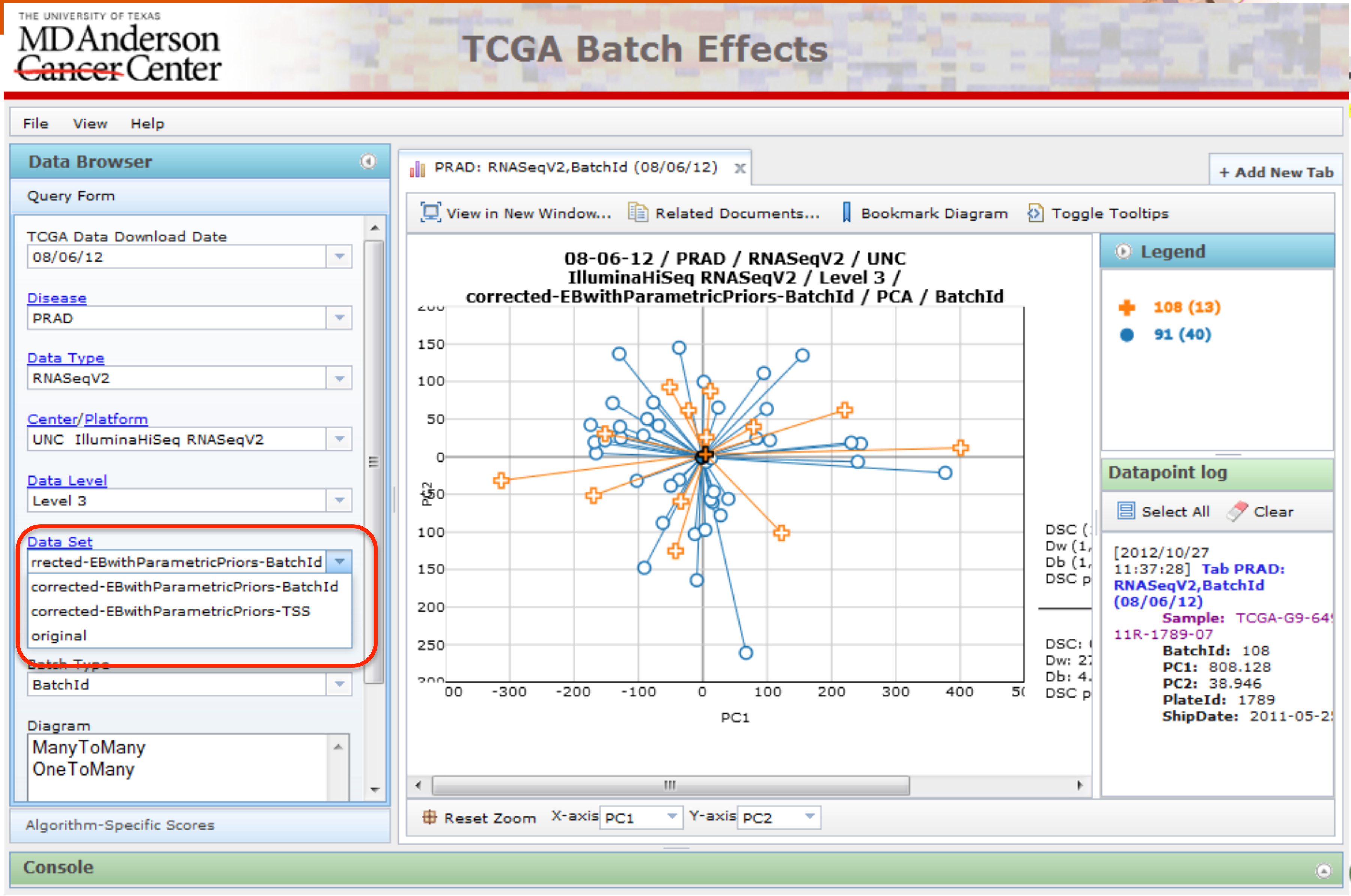
DSC: 0.547
Dw: 279.822
Db: 153.007
DSC pvalue: <0.0005

[2012/10/27 11:37:28] Tab PRAD: RNASeqV2,BatchId (08/06/12)
Sample: TCGA-G9-64
11R-1789-07
BatchId: 108
PC1: 808.128
PC2: 38.946
PlateId: 1789
ShipDate: 2011-05-2

X-axis PC1
Y-axis PC2

TCGA MBatch website

http://bioinformatics.mdanderson.org/tcgabatcheffects/



TCGA Data Download Date
08/06/12

Disease
PRAD

Data Type
RNASeqV2

Center/Platform
UNC IlluminaHiSeq RNASeqV2

Data Level
Level 3

Data Set
rrected-EBwithParametricPriors-BatchId
corrected-EBwithParametricPriors-BatchId
corrected-EBwithParametricPriors-TSS
original

Batch Type
BatchId

Diagram
ManyToMany
OneToMany

08-06-12 / PRAD / RNASeqV2 / UNC IlluminaHiSeq RNASeqV2 / Level 3 / corrected-EBwithParametricPriors-BatchId / PCA / BatchId

✚ 108 (13)
● 91 (40)

[2012/10/27 11:37:28] Tab PRAD: RNASeqV2,BatchId (08/06/12)
Sample: TCGA-G9-64
11R-1789-07
BatchId: 108
PC1: 808.128
PC2: 38.946
PlateId: 1789
ShipDate: 2011-05-2

X-axis PC1
Y-axis PC2

Acknowledgments

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In-Silico

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- Andy Wong
- Mike Ryan

Poster # 50