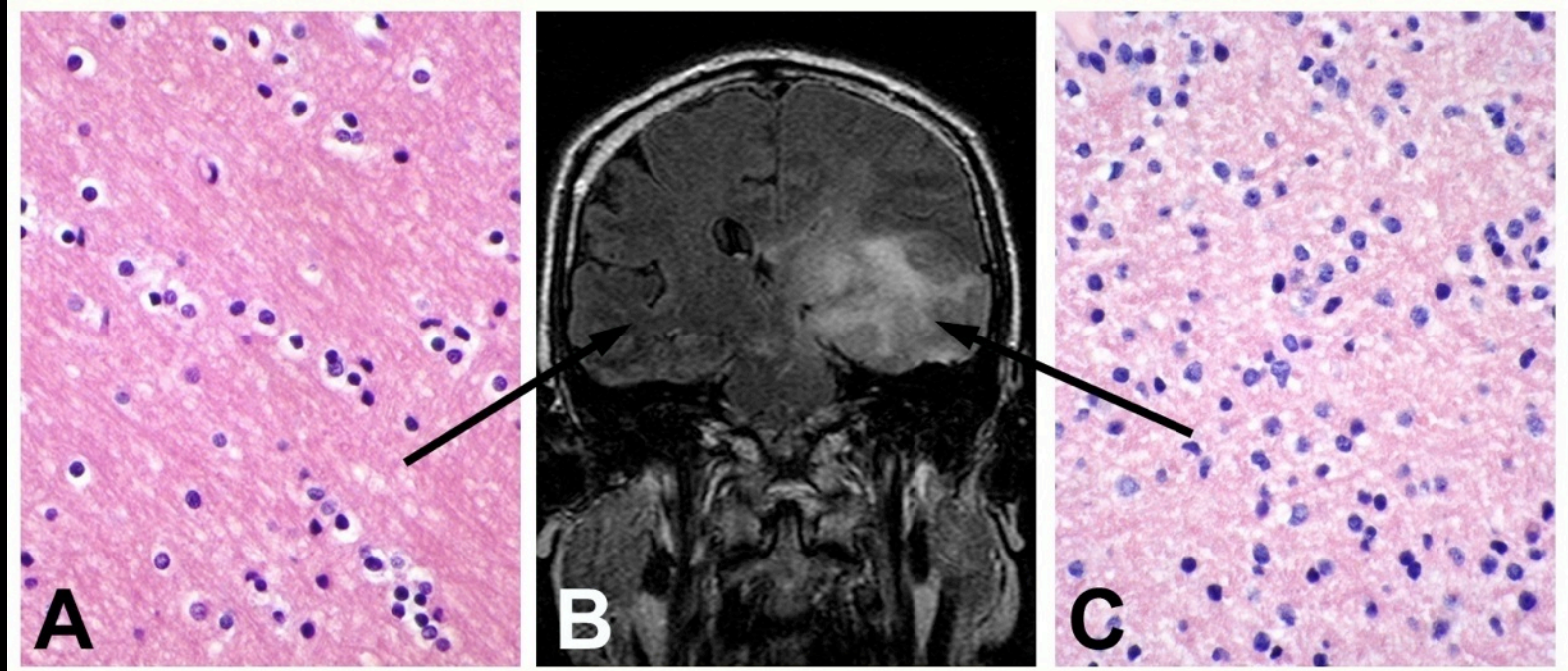# Integrative Genomic Characterization of Lower Grade Gliomas

Daniel J. Brat MD, PhD
Emory University School of Medicine

On behalf of the TCGA Lower Grade Gliomas Analysis Working Group

Diffuse Gliomas: 2007 WHO Classification

Astrocytomas
Infiltrating Astrocytoma (WHO grade II)
Anaplastic Astrocytoma (WHO grade III)
Glioblastoma (WHO grade IV)

Oligodendrogliomas
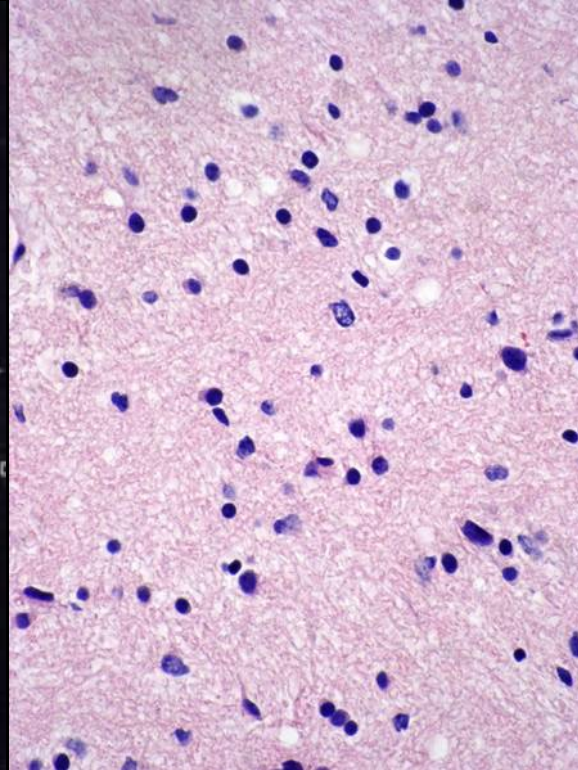**Oligodendroglioma (WHO grade II)**
Anaplastic Oligodendroglioma (WHO grade III)

Mixed Oligoastrocytomas
Oligoastrocytoma (WHO grade II)
Anaplastic Oligoastrocytoma (WHO grade III)
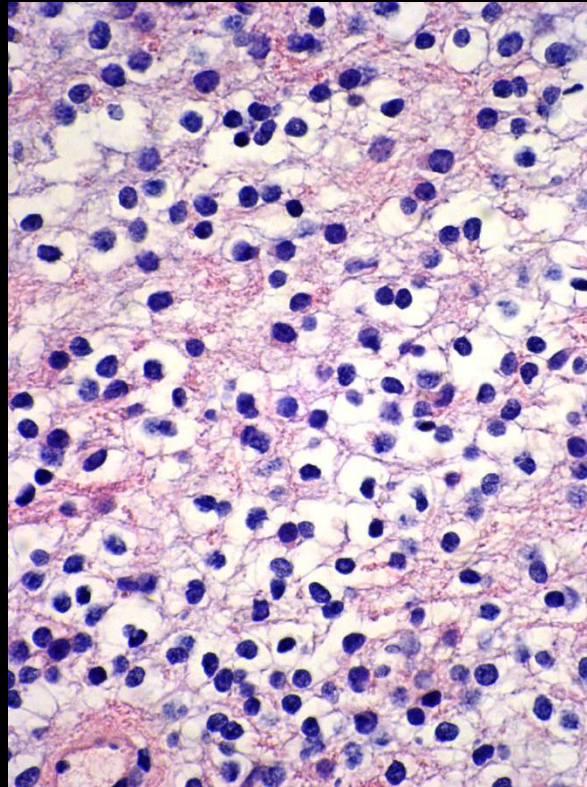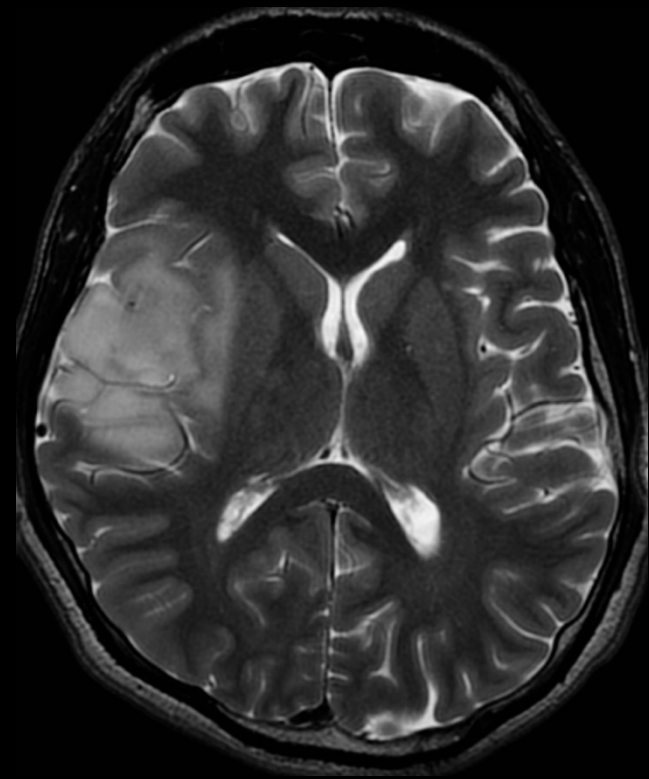
Astrocytoma (WHO grade II and III)

IDH, TP53, ATRX mutations

Median Survival:
Grade II: 60 mo
Grade III: 36 mo

Progress to GBM
(Secondary GBM)
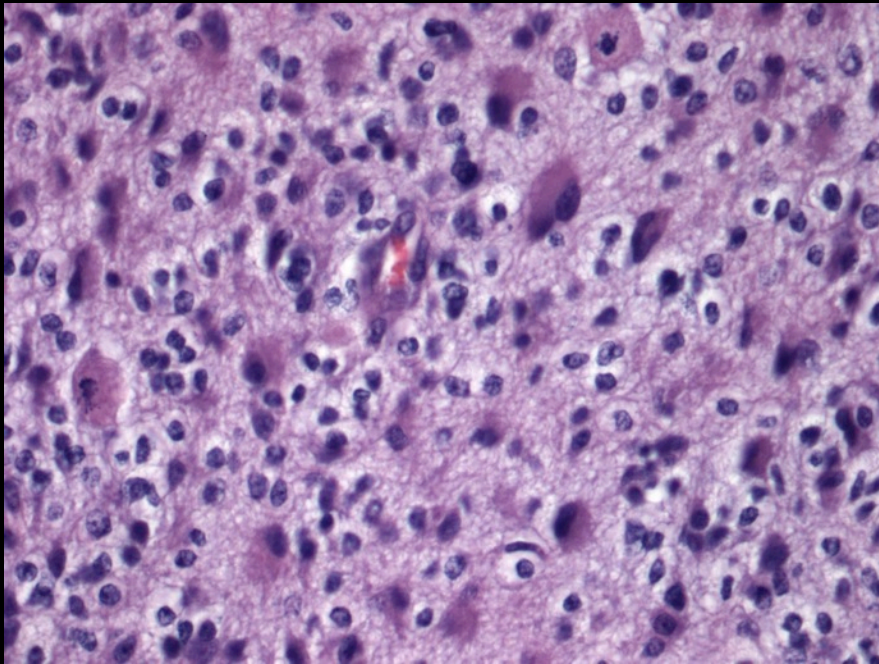
Oligodendroglioma (WHO grade II and III)

1p/19q co-deletion
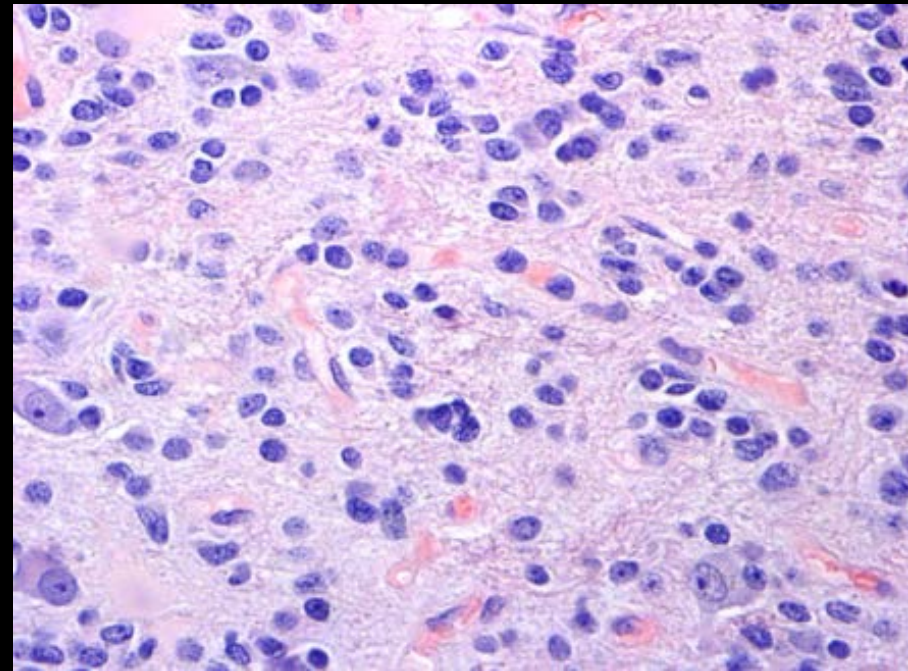*IDH, CIC, FUBP1, TERT* promoter

Median Survival:
Grade II: 120 mo
Grade III: 60 mo
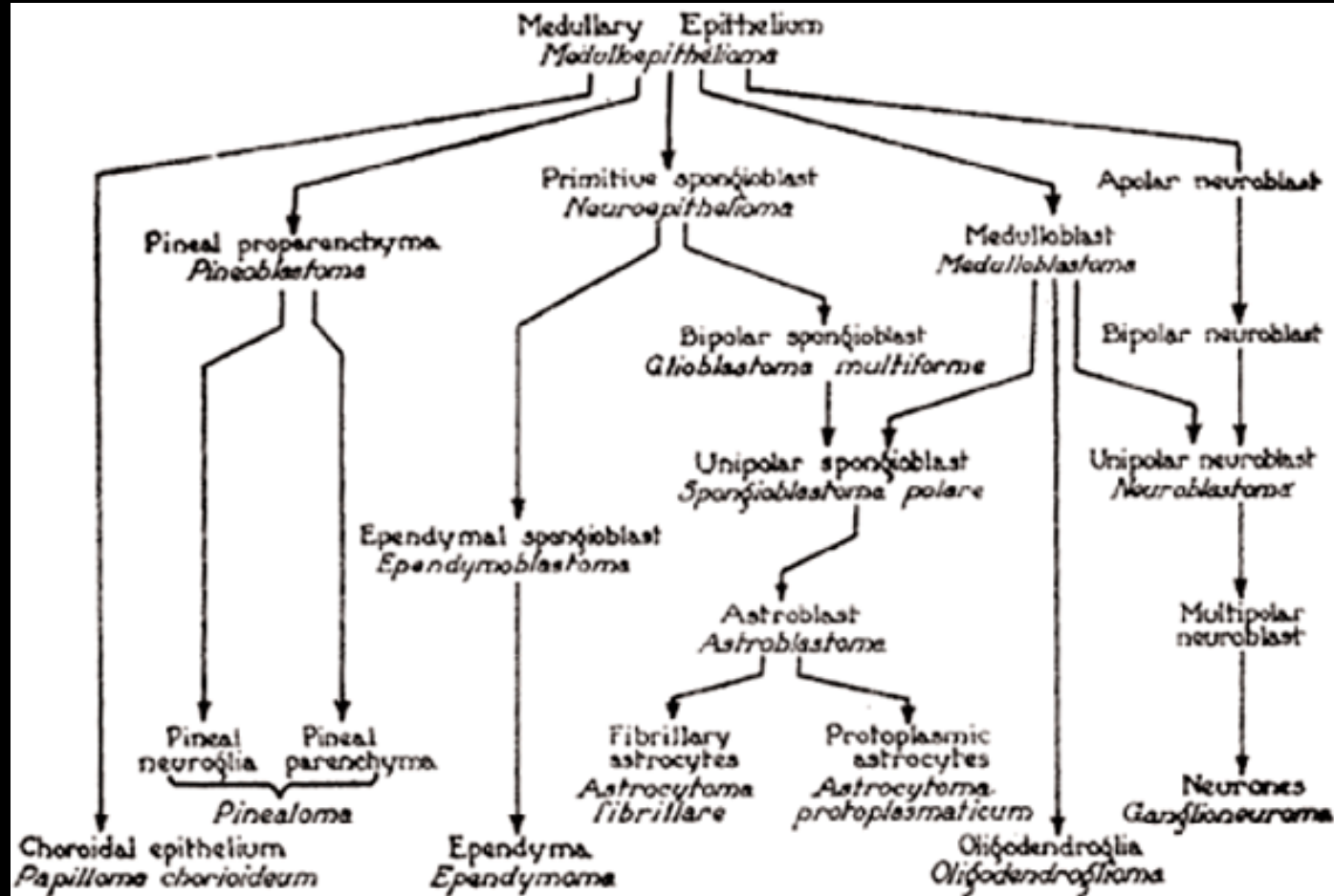
Chemosensitive

Oligoastrocytoma
(WHO grade II and III)

Ambiguous
Morphology

Brain Tumor Histogenesis

**Harvey Cushing
Percival Bailey
1926**

Distinguishing Among the Gliomas

"There are also many cells which appear to be transitions between gigantic oligodendroglia and astrocytes. It is impossible to classify them as belonging in either group"

Bailey P, Bucy PC. *Oligodendrogliomas of the brain.* J Pathol Bacteriol 1929: 32:735

60-70% concordance among neuropathologists in the diagnosis of diffuse gliomas

Coons SW et al. Cancer. 1997;79:1381

Interobserver variation of the histopathological diagnosis in clinical trials on glioma: a clinician's perspective

Martin J. van den Bent

Tumor type	Standard of care
Glioblastoma multiforme	Combined chemo-irradiation (60 Gy) with temozolomide
Grade III tumors	Radiotherapy 60 Gy, value of adjuvant chemotherapy and of combined chemo-irradiation unproven
Low grade glioma	Radiotherapy 45–55 Gy, higher dosages of RT correlated with more toxicity, unproven role for upfront chemotherapy alone
Oligodendroglial tumors	Initial management with upfront chemotherapy widely accepted, regardless of tumor grade

Table 1 Standard of care in gliomas

TCGA Research Network
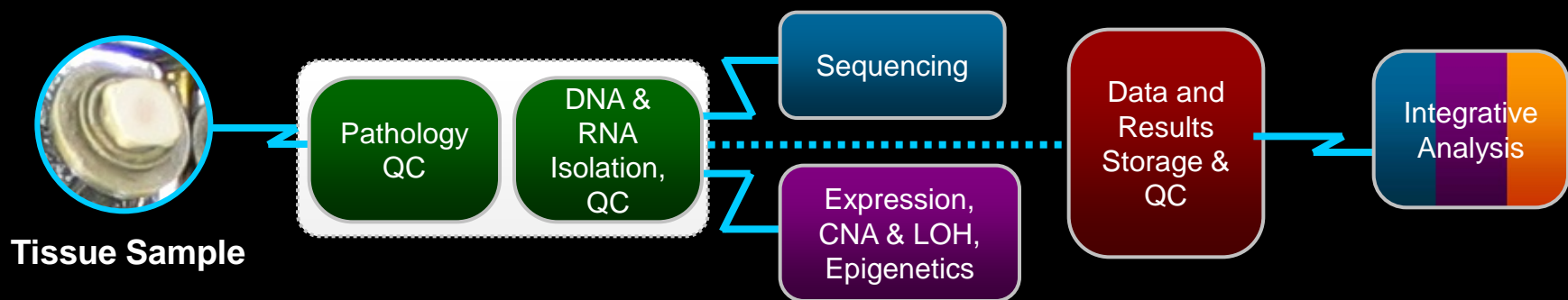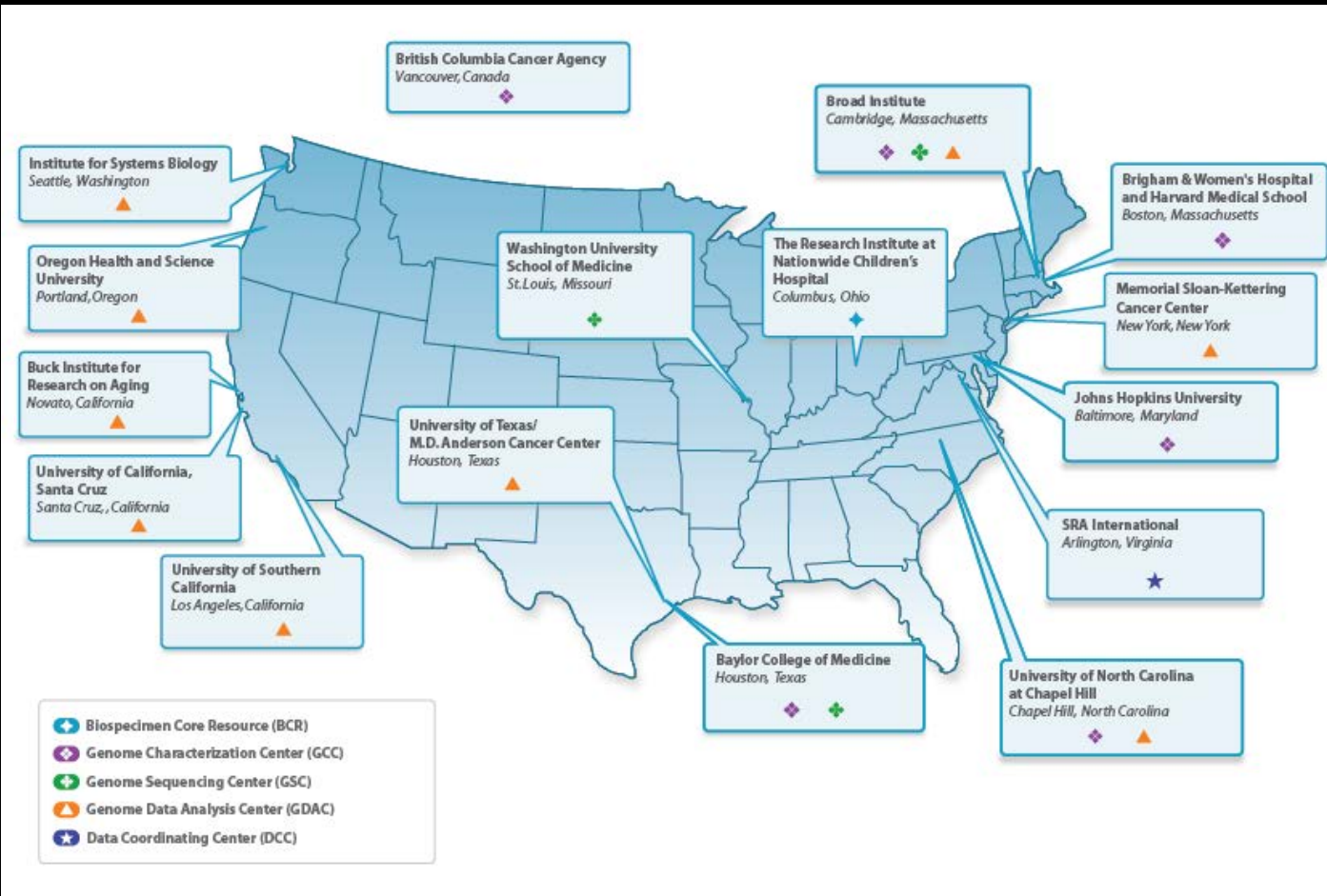
Comprehensive Analysis of 500 Lower Grade Gliomas

Data type	Platform	Center
Somatic mutations	Whole exome Whole genome	Broad Institute
DNA copy-number	Affymetrix SNP6	Broad Institute
mRNA expression (incl. fusions)	RNA-Seq (Illumina HiSeq)	UNC
DNA methylation	Infinium 450	USC
microRNA expression	miRNA-Seq	BCGCS
Protein levels & phosphorylation	RPPA	MD Anderson
DNA copy-number / rearrangements	Low-pass whole genome sequencing	Harvard

TCGA Lower Grade Gliomas:
Data Freeze for Biomarker Manuscript

Data type	Platform	# samples
Exome sequencing	Illumina	290
Whole genome sequencing	Illumina	23
DNA copy number	Affymetrix SNP6	271
DNA copy number	Low pass whole genome	43
mRNA	RNA-Seq	269
DNA methylation	Infinium 450	268
microRNA expression	miRNA-Seq	295
Protein levels	RPPA	241

293 cases, with overlapping data on 254 for major platforms

Troy Shelton

MutSigCV Identifies Significantly Mutated Genes and Reveals Mutation Classes

Esther Rheinbay
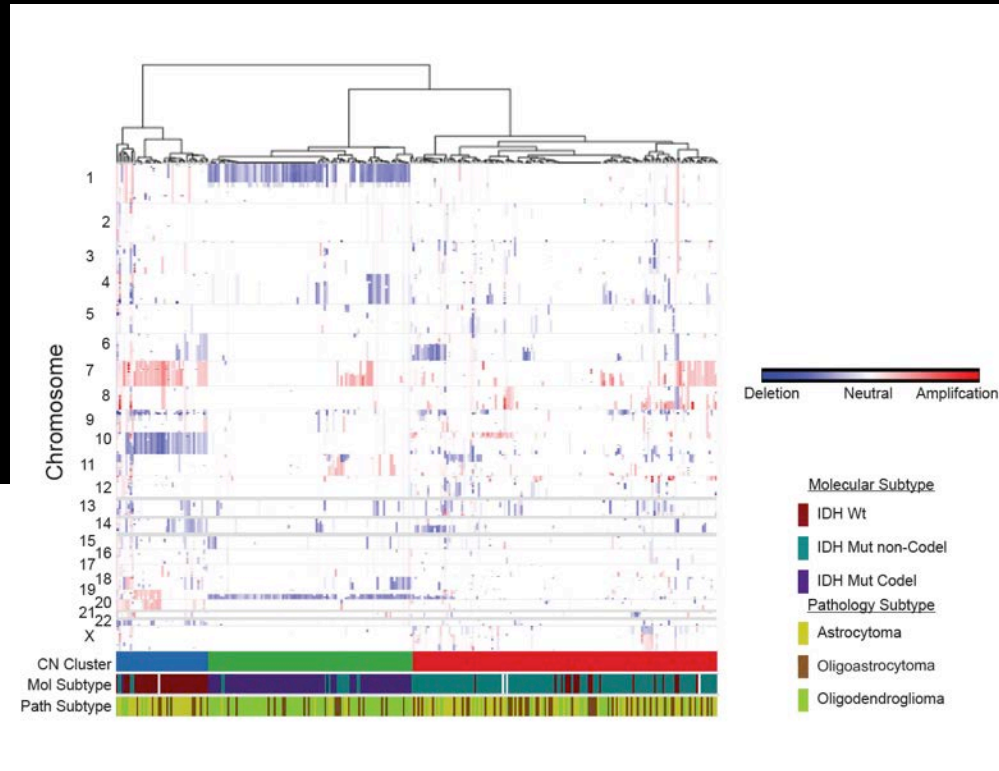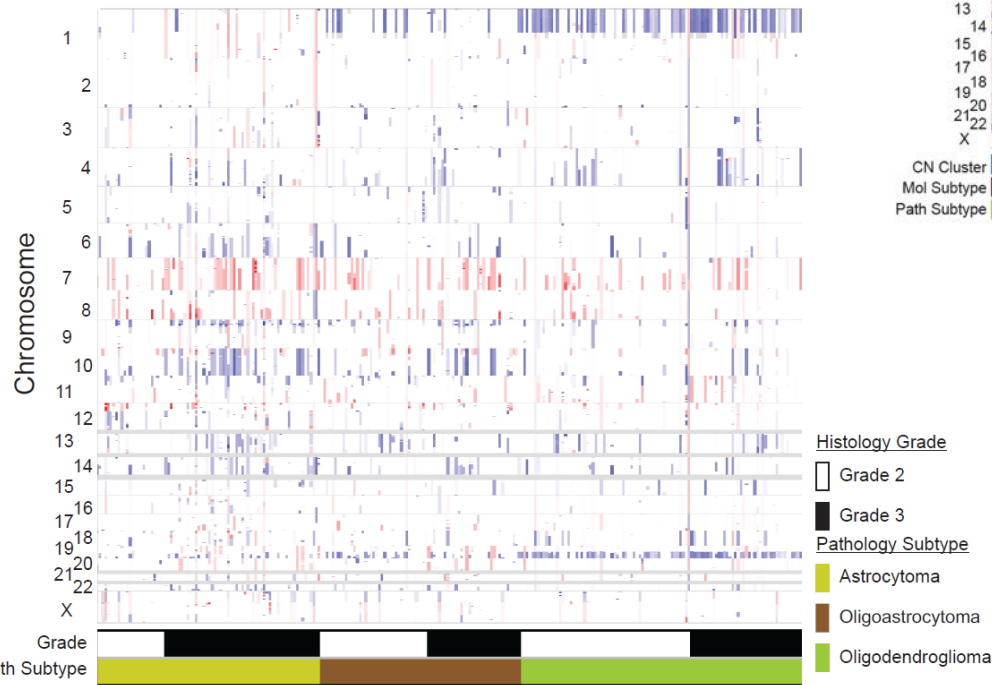Hailei Zhang
Jaegil Kim
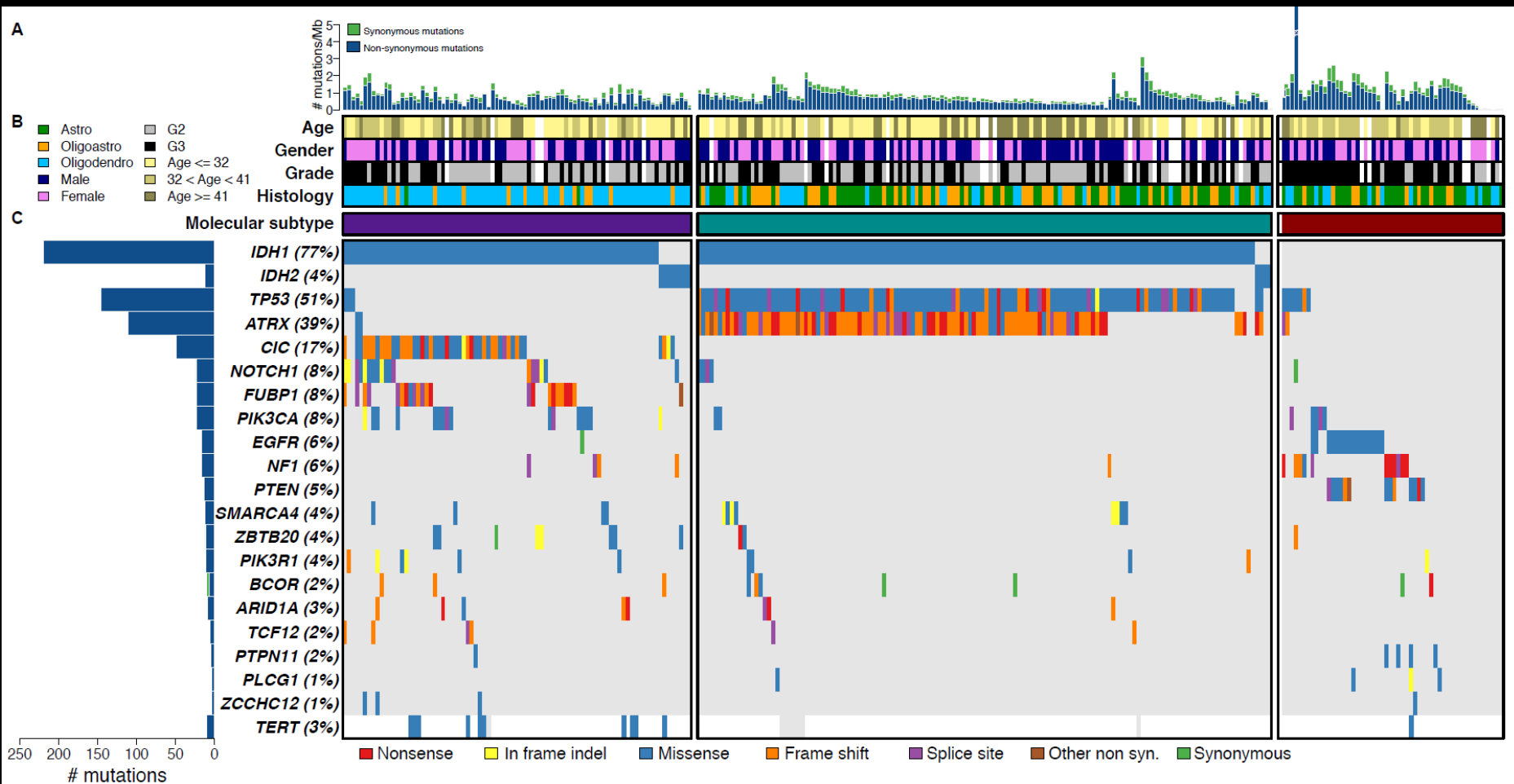
IDH mutations occur in ~80% of LGGs
1) CIC, FUBP1, Notch1, PIK3CA mutations (mostly oligo)
2) TP53 and ATRX mutations (mostly astro and oligoastro)
IDH wt LGG have mutations similar to GBM

LGG: Copy Number Alterations

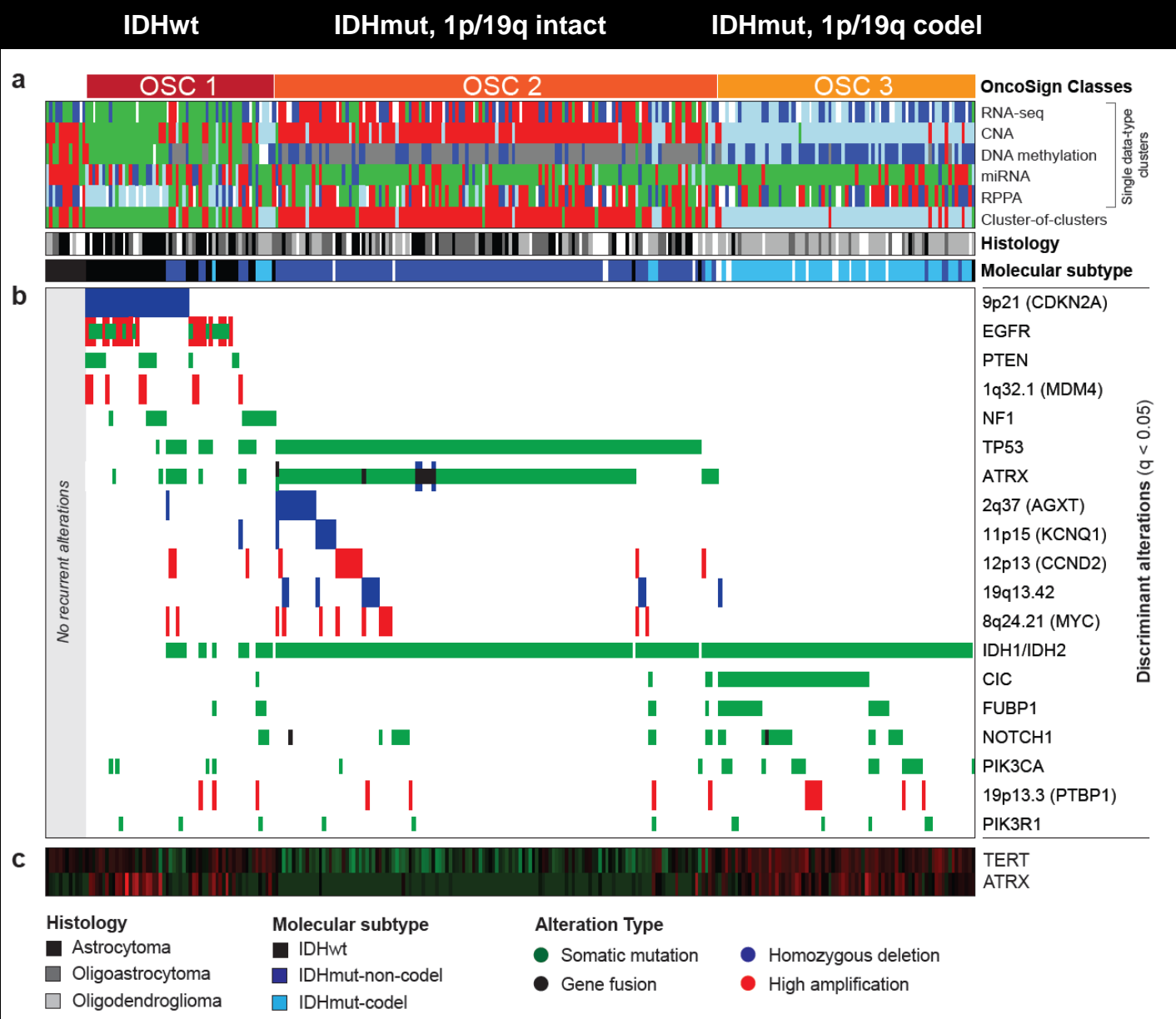By Histology

NMF Clustering

Hailei Zhang
Andrew Cherniack
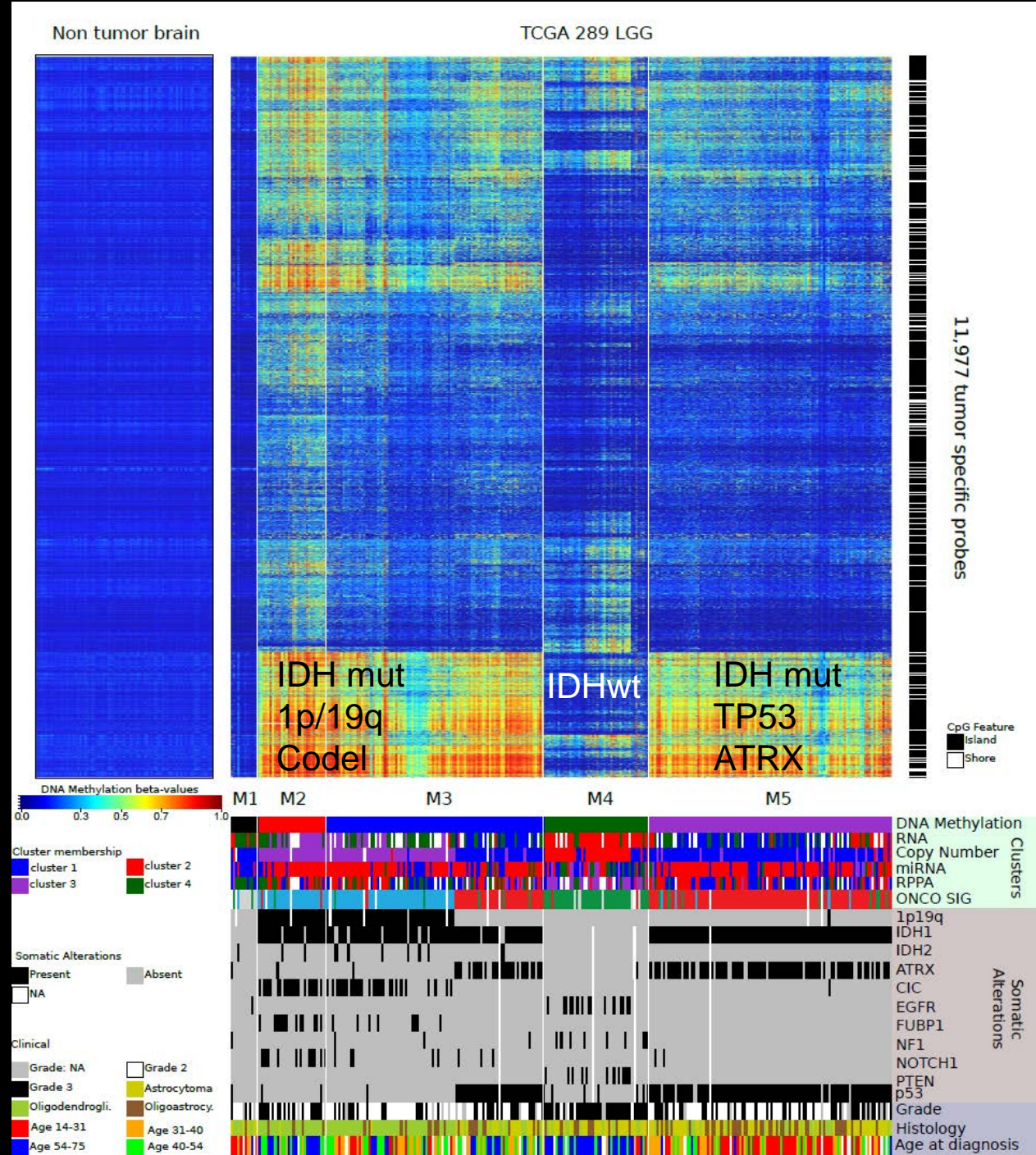
OncoSign
(Oncogenic Signatures)
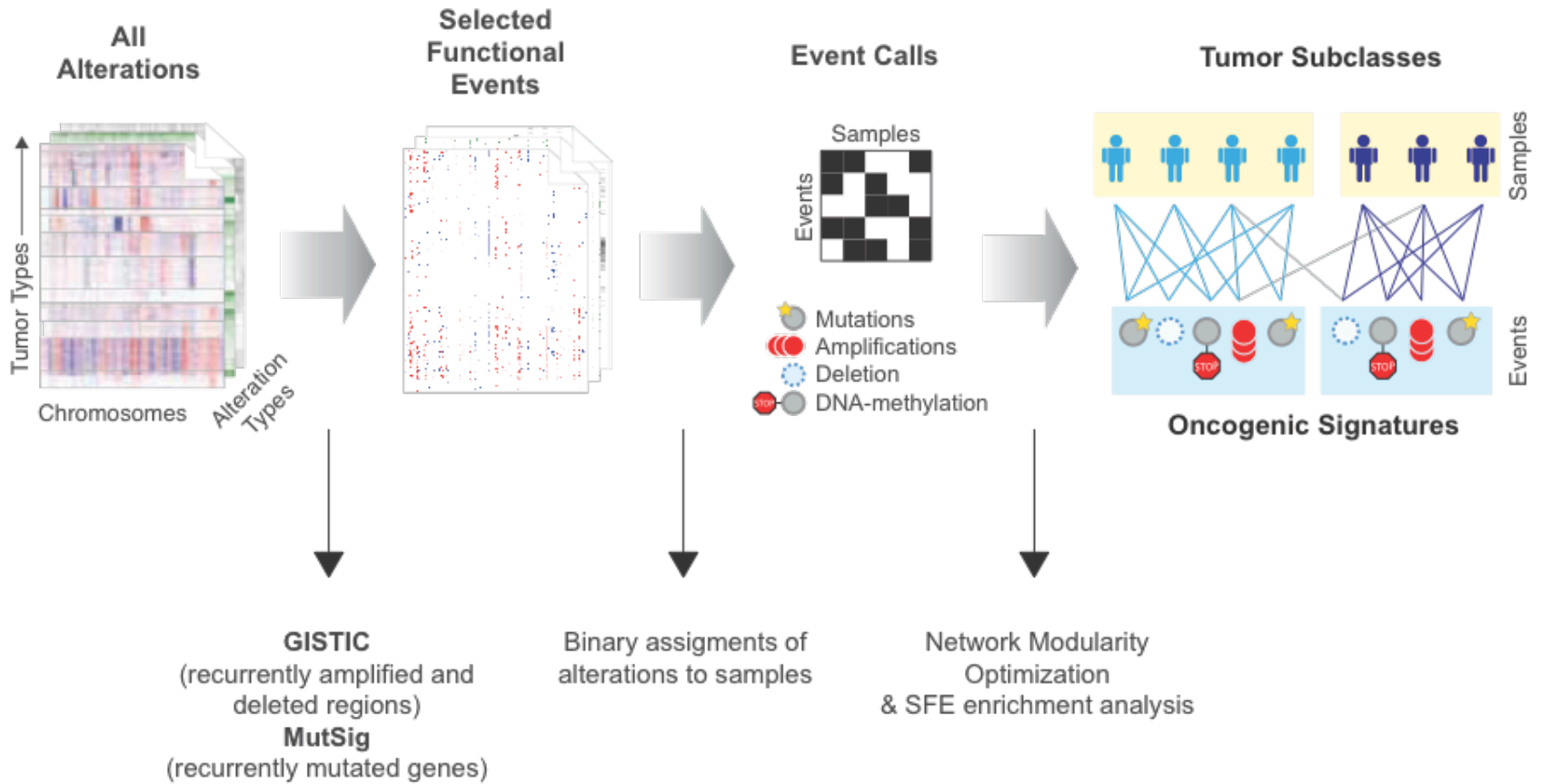
OncoSign Identifies 3 Molecular Classes Largely Based on IDH and 1p/19q status

Giovanni Ciriello
Jason Huse

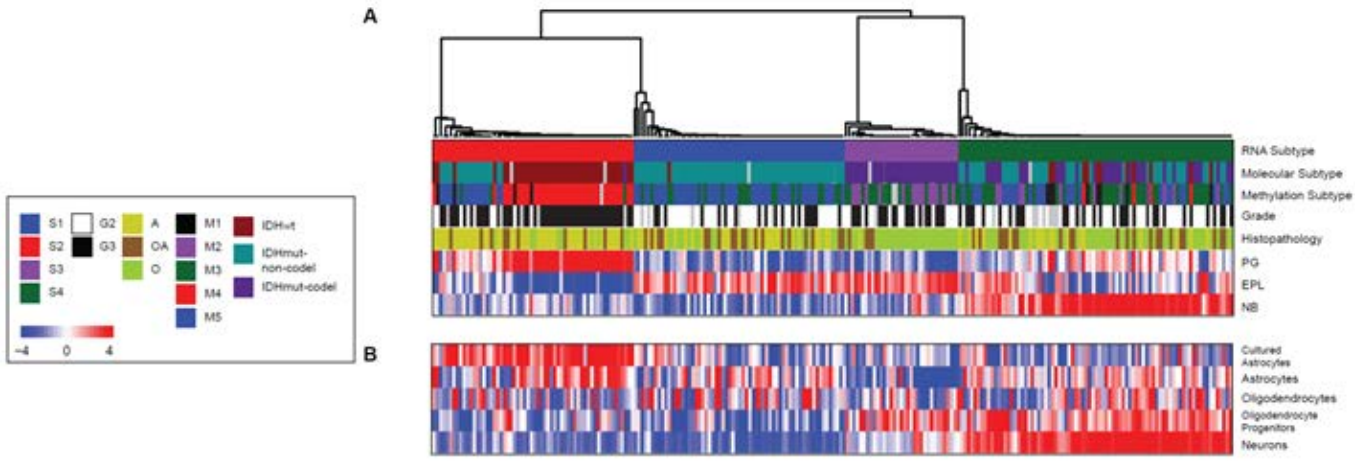# DNA Methylation Status
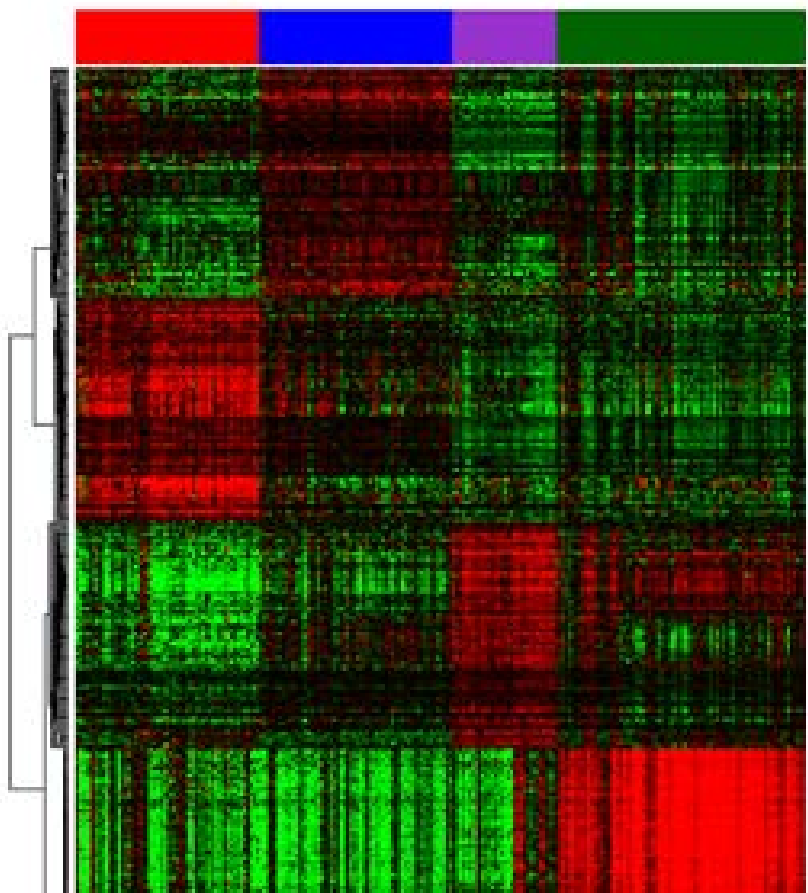

Houtan Noushmehr
Peter Laird

mRNA Expression Clustering
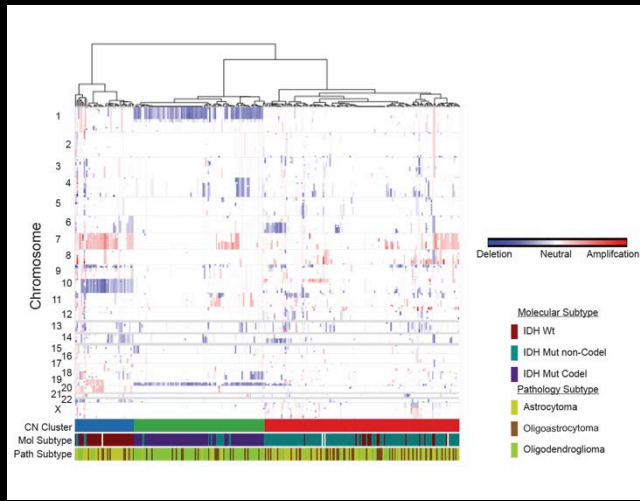
1500 most variable genes selected by MAD.

Consensus Heirarchical Clustering (Pearson).
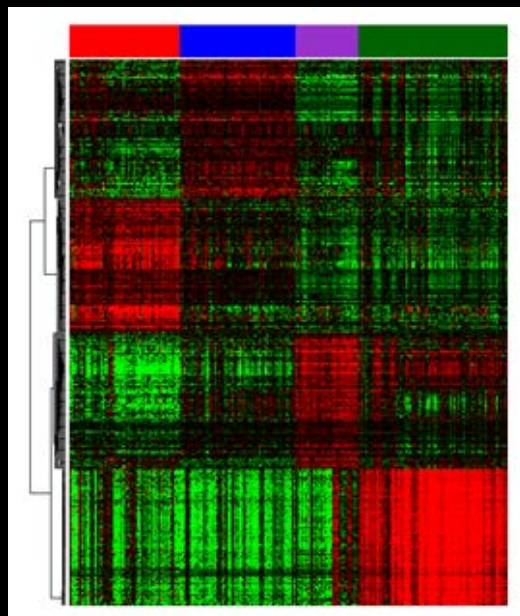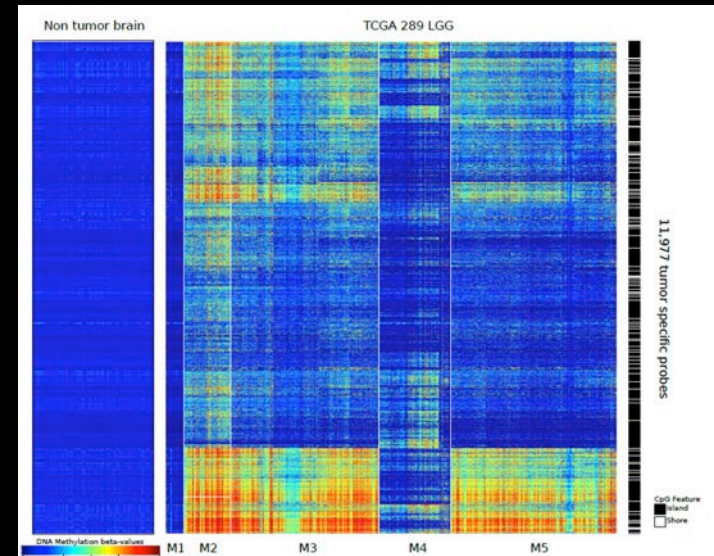
At k=6, 4 large clusters.

Mark Vitucci
Ryan Miller

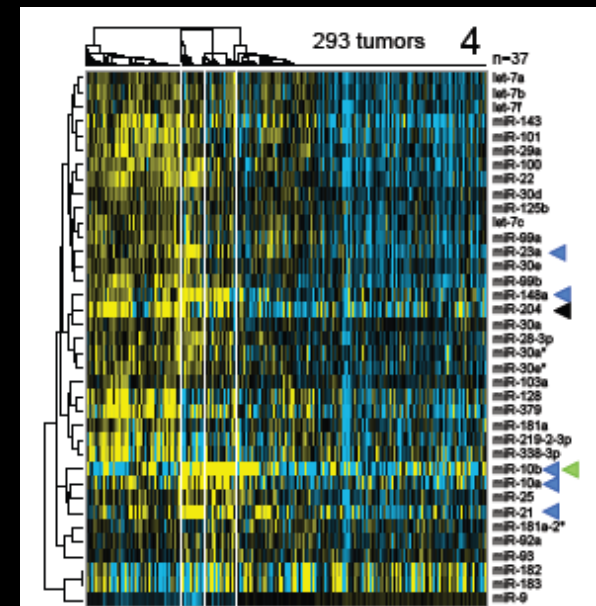# Clustering of molecular data (Copy Number, mRNA, miRNA, methylation) identifies 3-5 subtypes
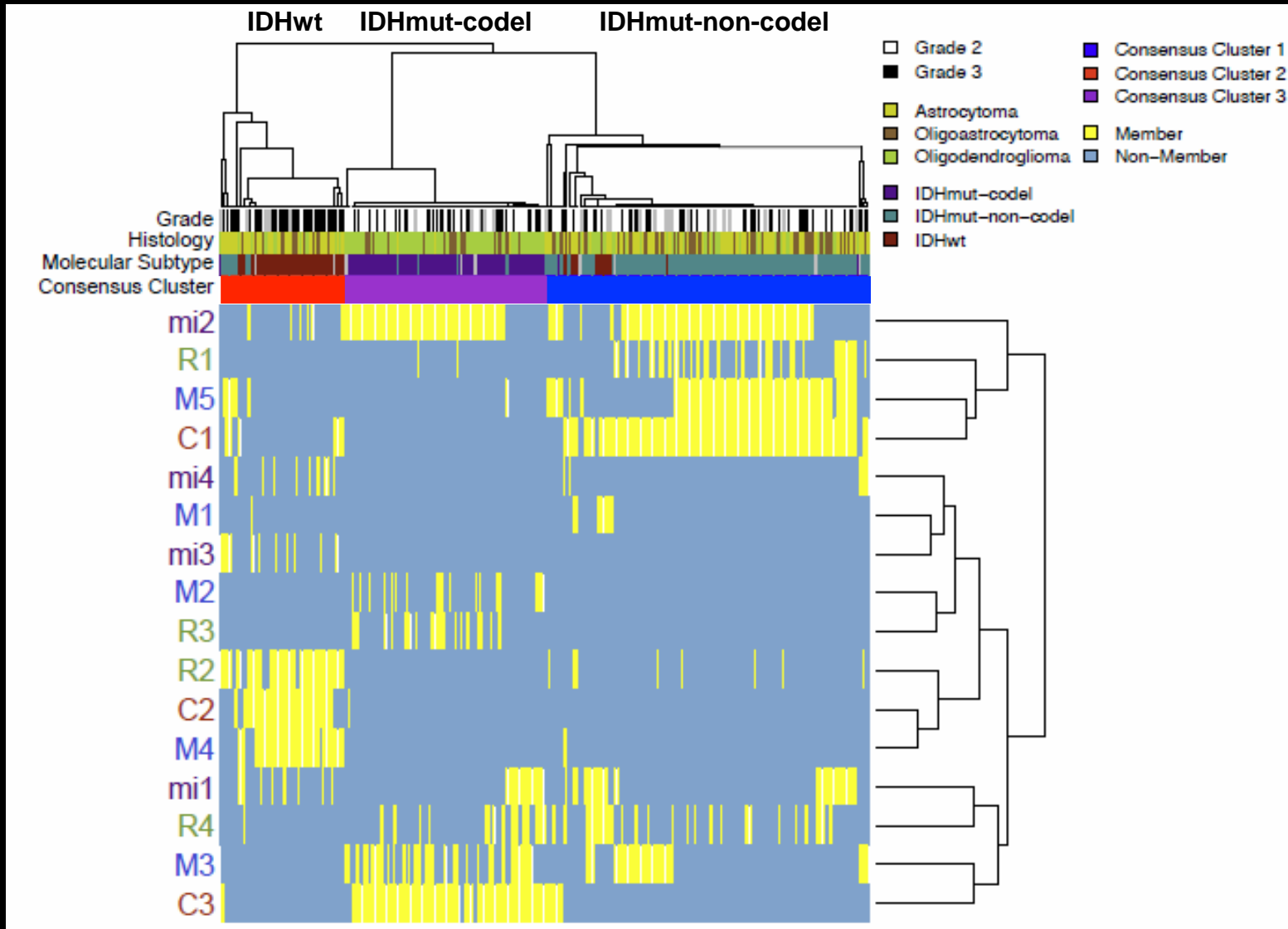

Andy Cherniak

Houtan Noushmehr

Mark Vitucci

Gordon Robertson

Clustering of Clusters **Identifies 3 Molecular Classes**
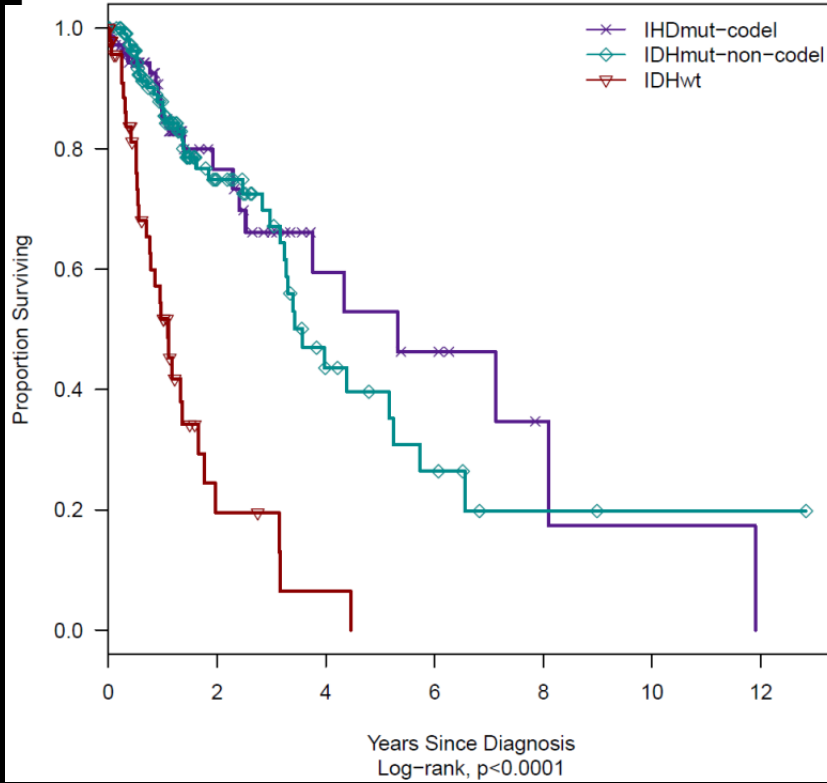## Largely Based on IDH and 1p/19q status

Three Robust, Non-overlapping LGG Classes

IDHmut-codel	IDHmut-non-codel	IDHwt
IDH mutant	IDH mutant	IDH wt
1p/19q del	1p/19q intact	+7, -10
CIC mut	TP53 mut	EGFR amp
FUBP1 mut	ATRX mut	PTEN mut
TERT mut	8q24 amp	NF1 mut
Notch1 mut		

Clinical Outcomes

Laila Poisson
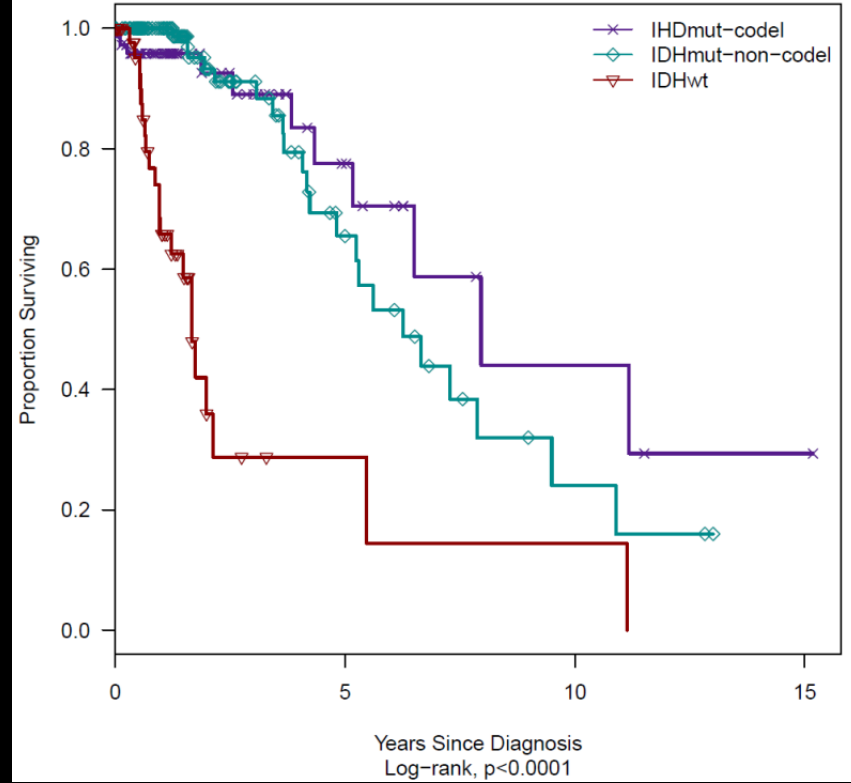
IDHwt LGGs have Mutation Frequencies Similar to Glioblastoma

Mia Gifford
Olena Morozova
Sofie Salama
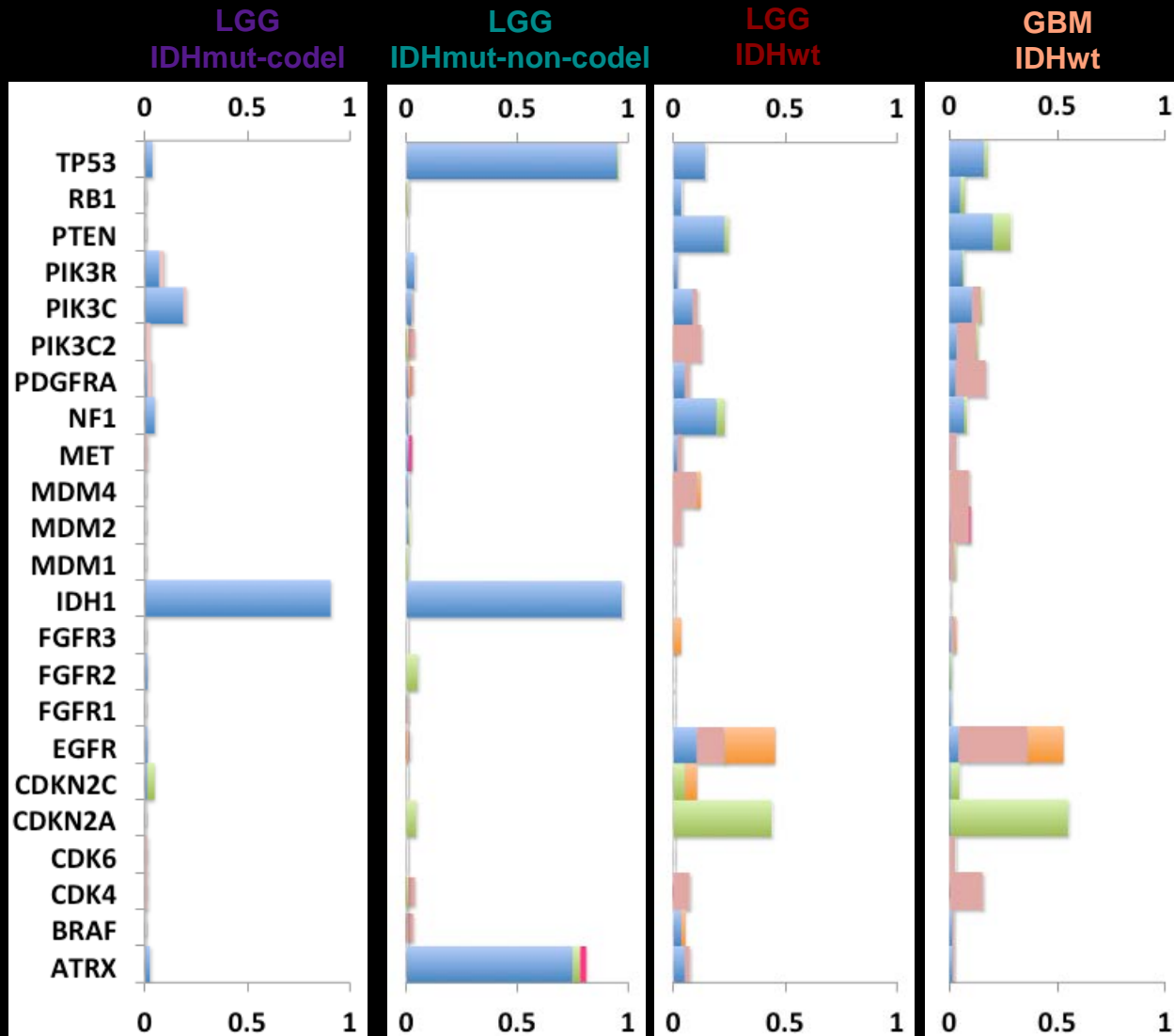
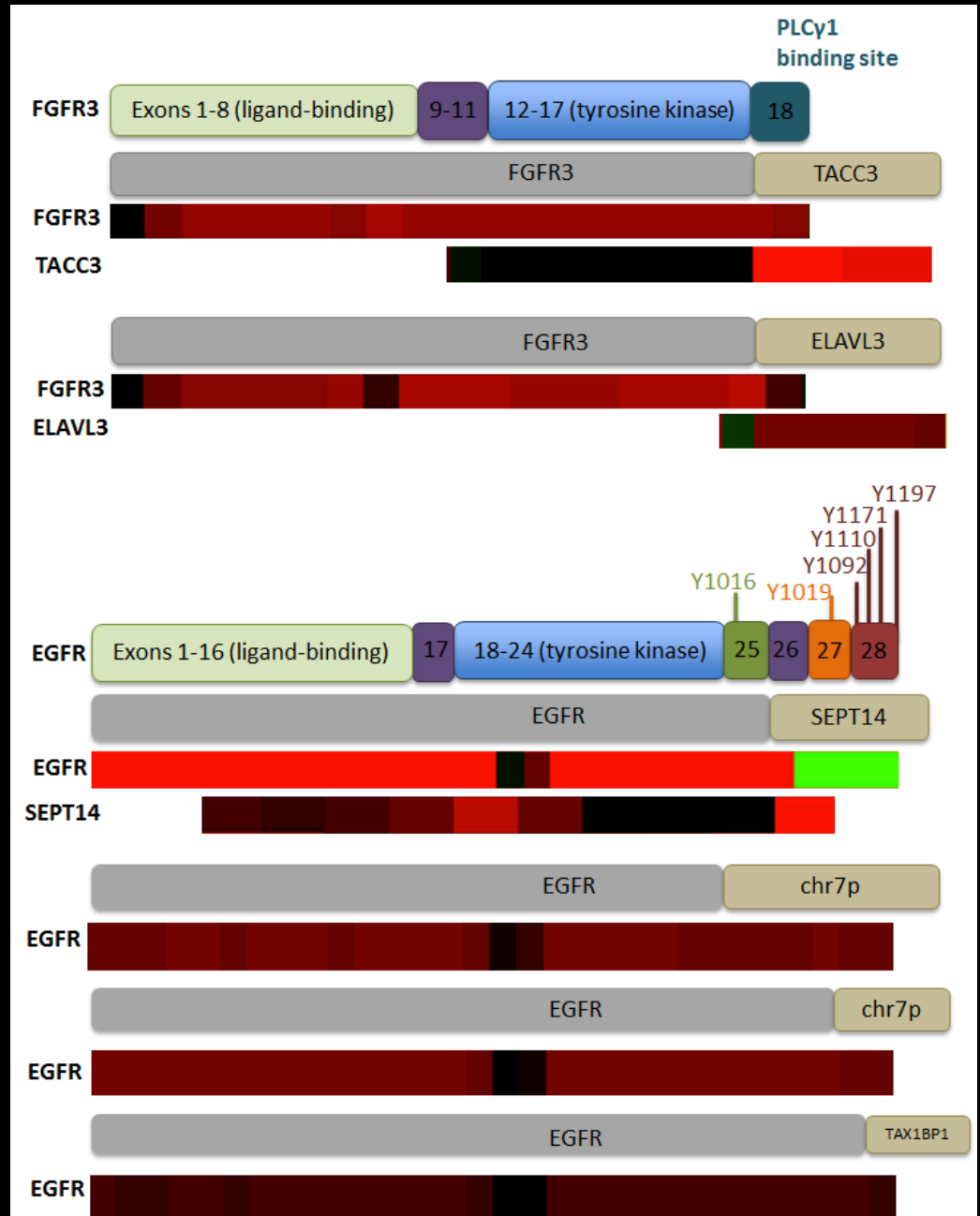Fraction of samples with specific alteration in gene

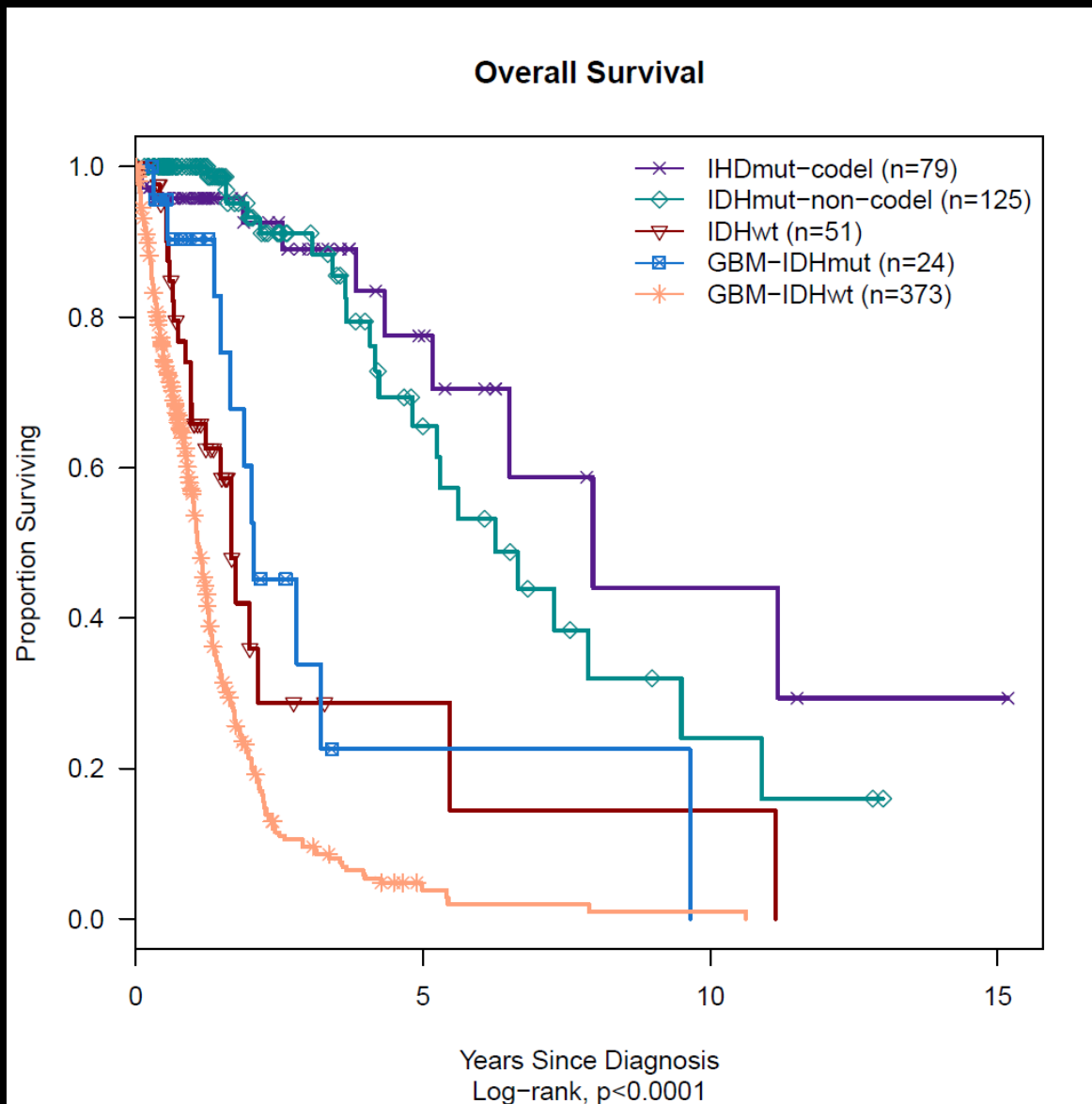■ SNV/indel ■ Amplification ■ Deletion ☐ SV ■ Fusion ■ Two or more aberrations

IDHwt LGGs have Oncogenic Gene Fusions Similar to Glioblastoma
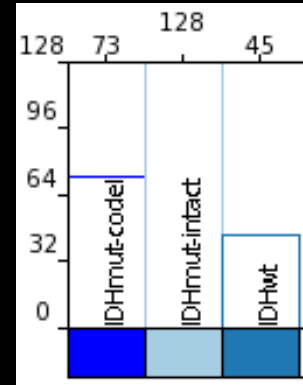

Olena Morozova
Sofie Salama
Roel Verhaak

IDHwt LGGs have Clinical Outcomes Similar to Glioblastoma

Overall Survival

IHDmut–codel (n=79)
IDHmut–non–codel (n=125)
IDHwt (n=51)
GBM–IDHmut (n=24)
GBM–IDHwt (n=373)

Proportion Surviving

Years Since Diagnosis
Log–rank, p<0.0001

Laila Poisson

RPPA: Supervised clustering
189 Antibodies

Rehan Akbani and Gordon B. Mills
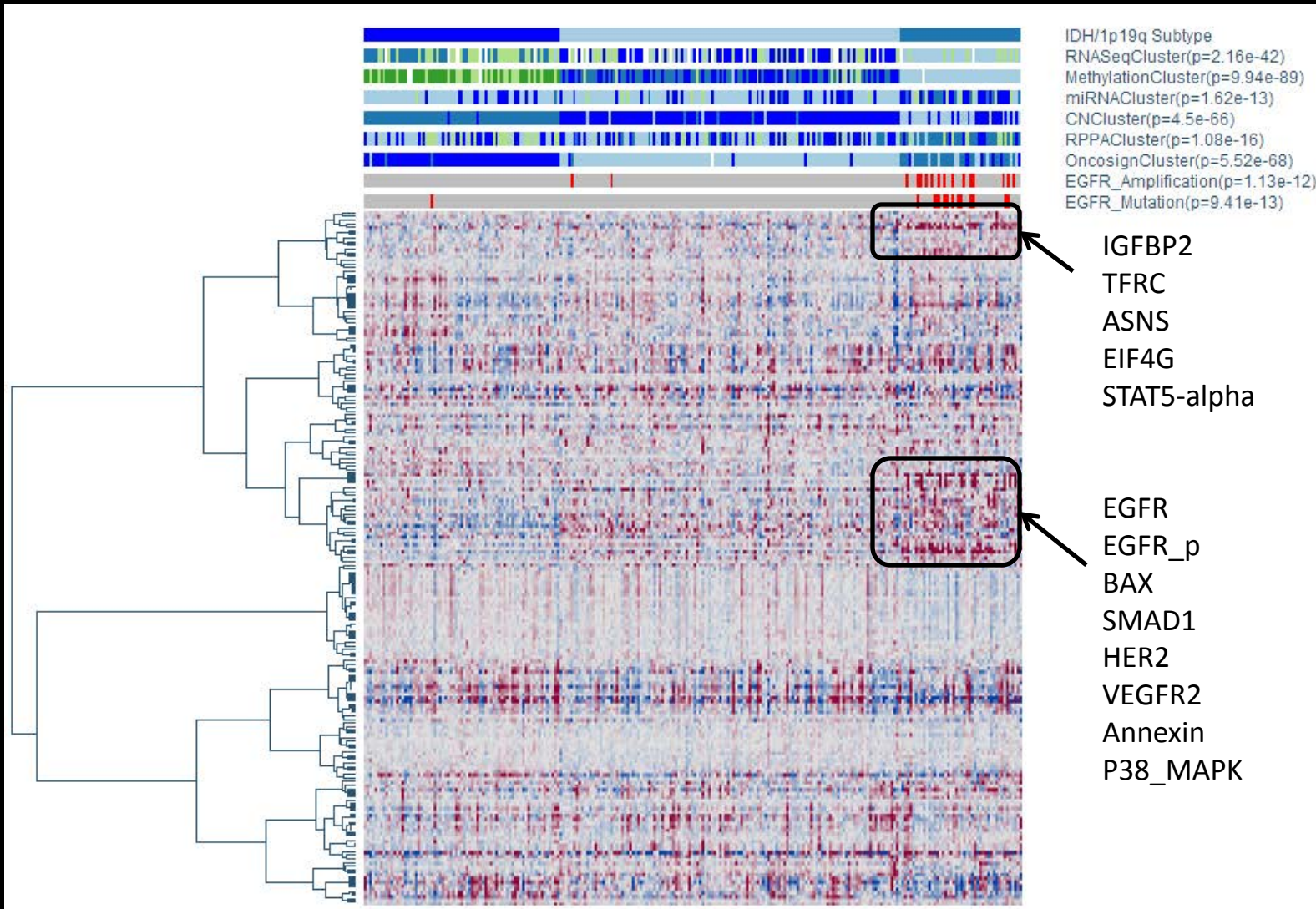
RPPA: Supervised clustering
14 Tyrosine Kinase Antibodies

Rehan Akbani and Gordon B. Mills
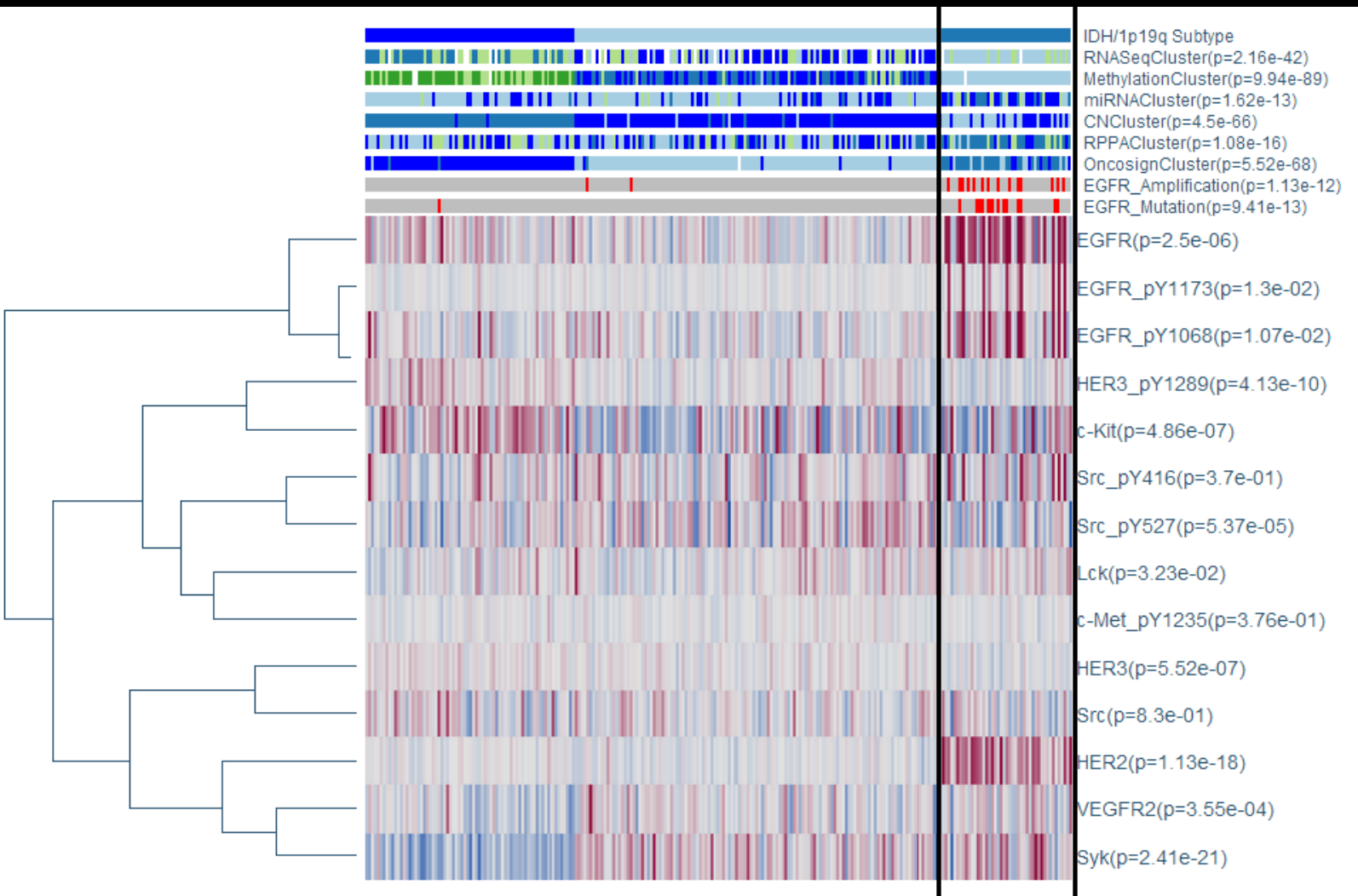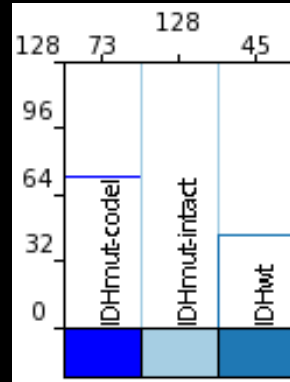
Summary

6 histopathologic diagnoses can be distilled into
3 robust, clinically relevant molecular classes

IDH mutant, 1p/19q co-deleted gliomas: CIC, FUBP1, TERT promoter, Notch1 and PIK3CA mutations

IDH mutant, non-codel gliomas: TP53, ATRX, 8q24

IDH wild type LGG have molecular alterations and clinical behavior similar to GBM

Thank You!

**TCGA LGG
Analysis Working Group**

Co-Chairs: Dan Brat, Al Yung
Data Coordinator: Lee Cooper
Manuscript Coordinator: Ken Aldape
Analysis Coordinators: Roel Verhaak, Sofie Salama
DCC Representative: Joan Pontius
TCGA Program Office: Margi Sheth
                                            Kenna Shaw
                                            Jean Claude Zenklusen
                                            Carolyn Hutter