Case Western Reserve University | Case Comprehensive Cancer Center

NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

Advances in Brain Tumor Research: Leveraging BIG data for BIG discoveries

Jill Barnholtz-Sloan, PhD
Associate Professor & Associate Director for Bioinformatics and Translational Informatics
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University Hospitals Seidman Cancer Center | Case Western Reserve University Est. 1826 | Cleveland Clinic

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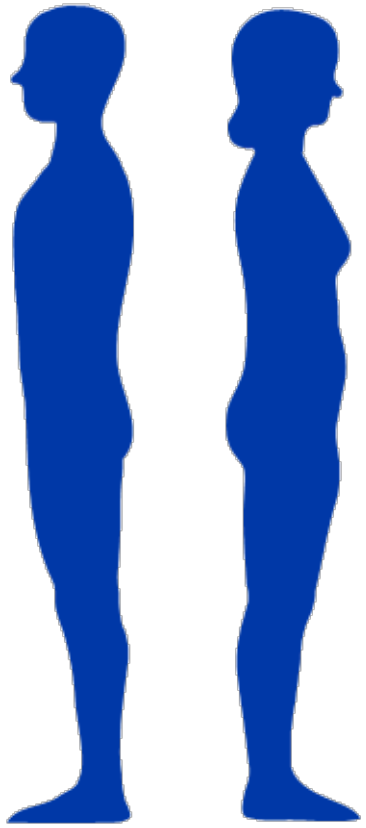
Estimated New US Cancer Cases 2016

Males 841,390	
Prostate	21%
Lung & bronchus	14%
Colon & rectum	8%
Urinary bladder	7%
Melanoma of skin	6%
Non-Hodgkin lymphoma	5%
Kidney & renal pelvis	5%
Oral cavity & pharynx	4%
Leukemia	4%
Liver & intrahepatic bile duct	3%
All other sites	22%



Females 843,820	
29%	Breast
13%	Lung & bronchus
8%	Colon & rectum
7%	Uterine corpus
6%	Thyroid
4%	Non-Hodgkin lymphoma
3%	Melanoma of skin
3%	Leukemia
3%	Pancreas
3%	Kidney & renal pelvis
21%	All other sites

ACS, 2016

*Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

Top US cancer deaths

Males: Lung (27%), prostate (8%), colorectal (8%)

Females: Lung (26%), breast (14%), colorectal (8%)

AACR, 2016
ACS, 2016

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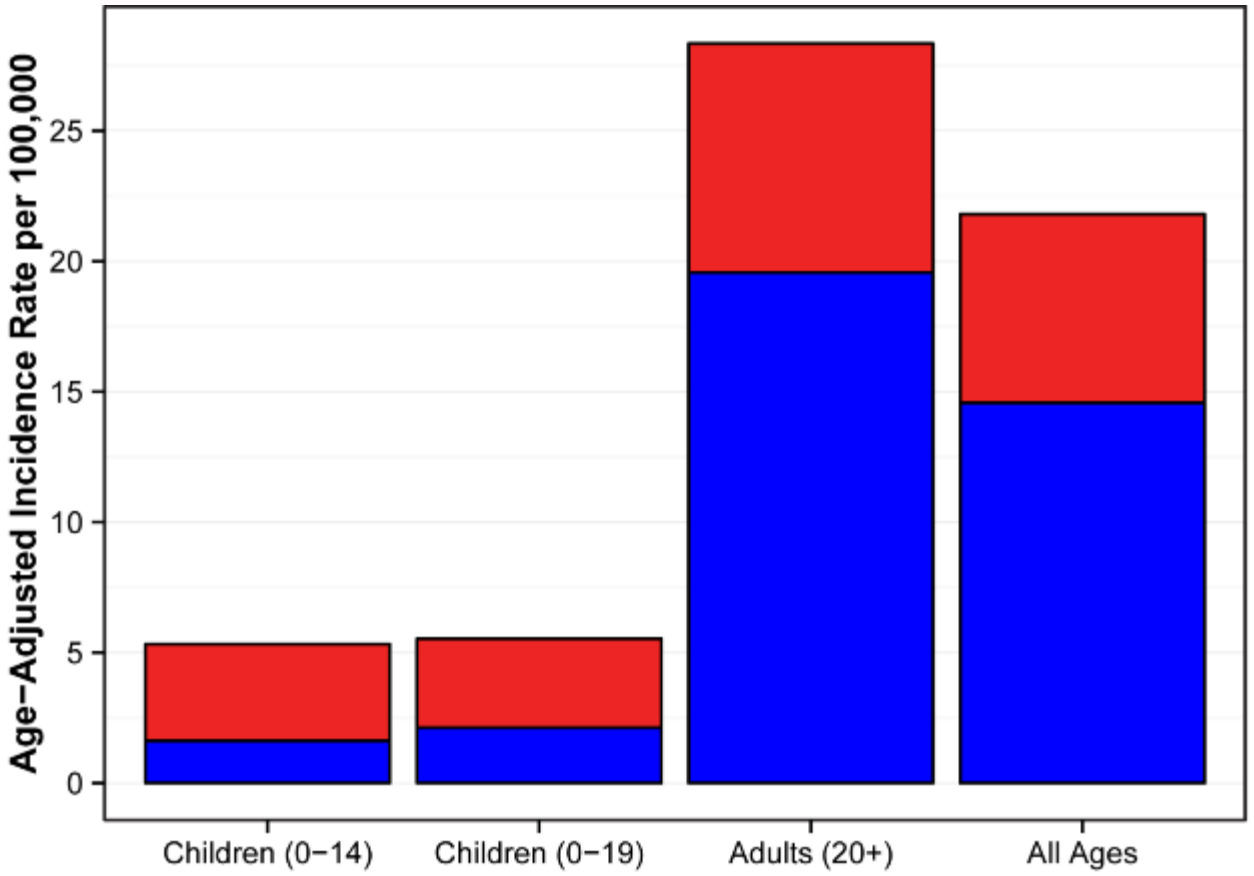
BTs account for 1-2% of all cancers



	Children (0−14)	Children (0−19)	Adults (20+)	All Ages
Non−Malignant	1.64	2.15	19.82	14.75
Malignant	3.73	3.42	8.76	7.23
Total	5.37	5.57	28.58	21.98

a. Rates per 100,000 and age-adjusted to the 2000 United States standard population.

CBTRUS, Neuro Oncology, 2015

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Most Common Primary Brain and CNS Tumors by Age

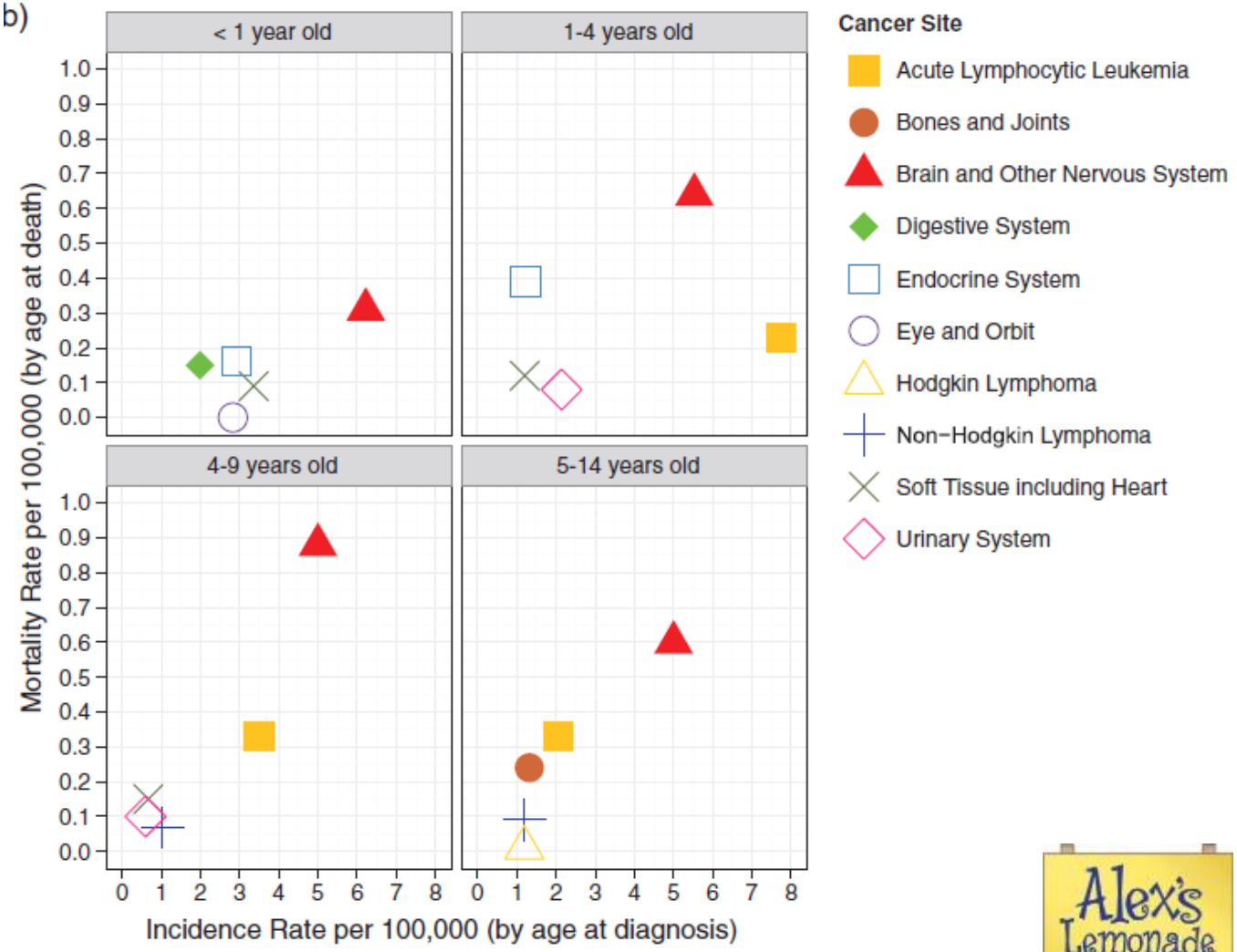
Age (years)	Most Common Histology			Second Most Common Histology		
	Histology	Rate[b]	(95% CI)	Histology	Rate	(95% CI)
0-4	Embryonal Tumors	1.24	(1.17-1.31)	Pilocytic Astrocytoma	1.03	(0.96-1.09)
5-9	Pilocytic Astrocytoma	1.01	(0.95-1.07)	Glioma Malignant, NOS	0.88	(0.82-0.94)
10-14	Pilocytic Astrocytoma	0.86	(0.81-0.92)	Glioma Malignant, NOS	0.51	(0.47-0.56)
15-19	Tumors of the Pituitary	1.66	(1.58-1.73)	Pilocytic Astrocytoma	0.60	(0.55-0.65)
20-34	Tumors of the Pituitary	3.16	(3.10-3.23)	Meningioma	1.39	(1.35-1.43)
35-44	Meningioma	4.82	(4.72-4.91)	Tumors of the Pituitary	4.36	(4.27-4.45)
45-54	Meningioma	9.02	(8.89-9.14)	Tumors of the Pituitary	4.64	(4.55-4.73)
55-64	Meningioma	14.77	(14.59-14.95)	Glioblastoma	8.08	(7.95-8.21)
65-74	Meningioma	25.96	(25.66-26.27)	Glioblastoma	13.05	(12.84-13.27)
75-84	Meningioma	38.70	(38.22-39.18)	Glioblastoma	15.24	(14.94-15.54)
85+	Meningioma	51.31	(50.47-52.16)	Glioblastoma	9.12	(8.77-9.48)
OVERALL	**Meningioma**	**7.86**	**(7.81-7.90)**	**Tumors of the Pituitary**	**3.49**	**(3.46-3.52)**

CBTRUS, Neuro Oncology, 2015

CBTRUS Infant and Childhood Report

published in Neuro Oncology 2015

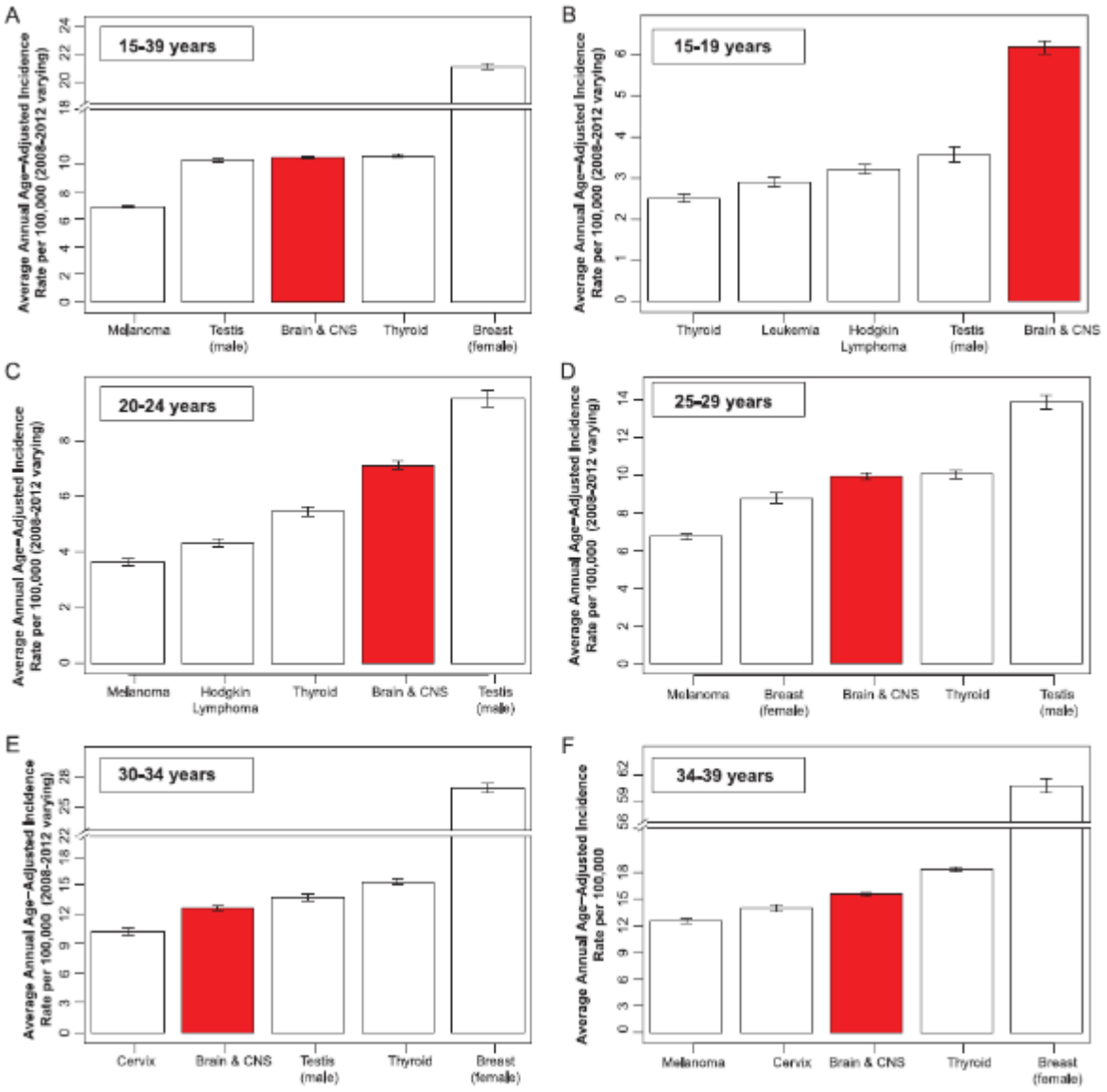
- Childhood brain tumors are the most common cancer in children 0-14.
- The most common types of brain tumors in children are gliomas (52.9%) and embryonal tumors (15.0%).
- Incidence of brain tumors is highest among infants < 1 year old



CBTRUS Adolescent and Young Adult Report

Published in Neuro Oncology 2016

- Brain tumors are the third common cancer in AYA 15-39.
- The most common types of brain tumors in AYA are tumors of the pituitary (29.9%) and meningioma (15.9%).
- Incidence of brain tumors is highest among adolescents 15-19 and mortality is highest among this same age group



American Brain Tumor Association®

Providing and pursuing answers®

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Incidence trends

Published in Cancer 2015, Presented at SNO

- In adults, there were decreases in incidence of colon, breast, lung, and prostate cancer, as well as malignant brain tumors.
- In adolescents(15-19), there were increases in incidence of malignant and non-malignant brain-tumors.
- In children(0-14), there were increases in incidence of acute lymphocytic leukemia, non-Hodgkin lymphoma, and malignant brain tumors.

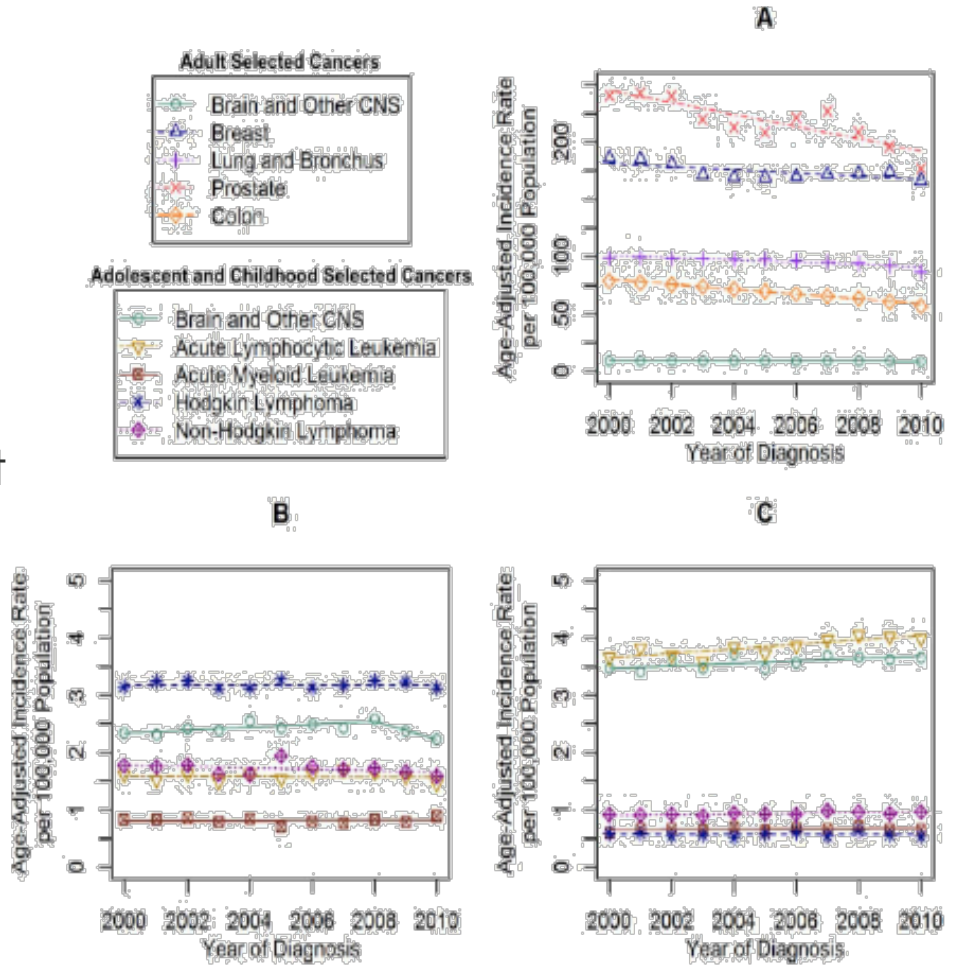

Figure 2. Malignant incidence time trends for selected cancers in (A) adults, (B) adolescents, and (C) children are shown based on the United States Cancer Statistics (USCS) publication for 2000 to 2010 and the Central Brain Tumor Registry of the United States (CBTRUS) for 2000 through 2010. Age-adjusted incidence rates per 100,000 population were plotted annually from 2000 through 2010 for selected common cancers in adults, adolescents, and children. Each time trend is accompanied by its respective Joinpoint trend line(s). CNS, central nervous system.

Searching for a cause….

- MANY environmental and genetic risk factors have been studied.
- No risk factor accounting for a large number of brain tumors has been identified.
  - Ionizing Radiation to the head
    - Israeli studies -- ~4 fold increased risk of meningioma; ~2 fold increased risk of gliomas
    - Childhood cancer survivor studies
  - Allergies, immune response
    - Decreased risk of brain tumor

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Unproven causes of brain tumors

Glioma

- Head trauma
- Dietary nitrate consumption
- Filtered cigarette smoking
- Diagnostic ionizing radiation

Childhood brain tumors

- Active or passive maternal tobacco smoking
- Residential electromagnetic field exposures
- Exposure to air pollutants
- Maternal cosmetic use

Unspecified for all brain tumor types

- Residential electromagnetic field exposures (many more positive than negative findings with "high" exposure occupations, but no consistent dose-response)
- Agricultural worker exposures
- Industrial Formaldehyde exposures
- Alcohol consumption
- Cell phone use
- Common drugs-fertility, oral contraceptives, sleeping pills, pain meds, headache meds, antihistamines

Wrensch et al, Neuro-oncology 2002

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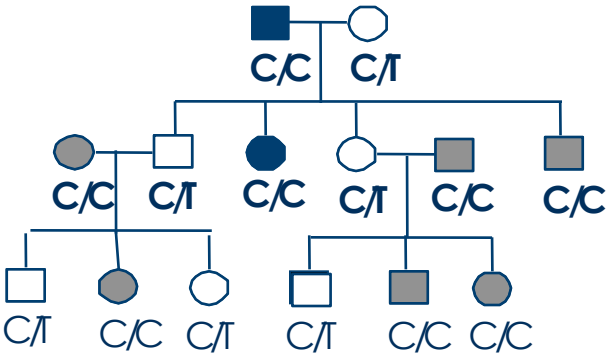
Strategies for finding genes that cause disease

FAMILIES

Linkage Studies



Simple Inheritance

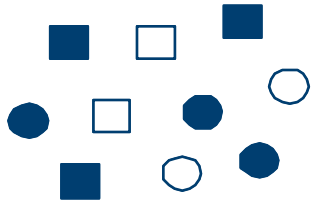
Single Gene

Rare Variants

~600 Short Tandem Repeat Markers

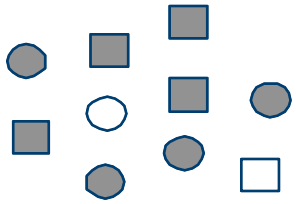
POPULATIONS

Association Studies (GWAS)



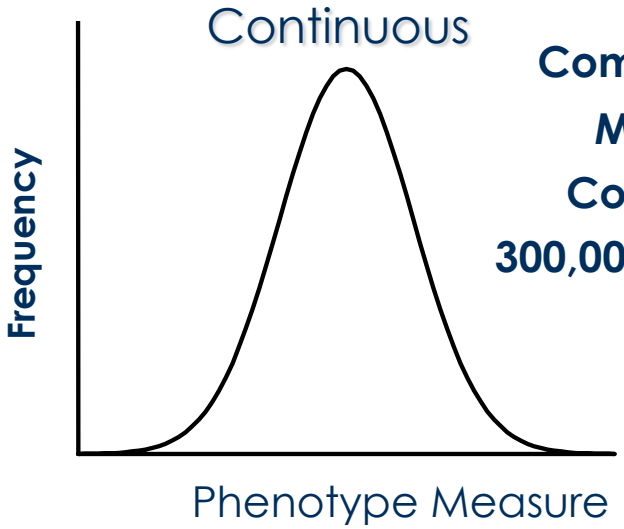
40% T , 60% C

Cases



15% T , 85% C

Controls



Complex Inheritance

Multiple Genes

Common Variants

300,000 -1,000,000 SNPs

Syndrome	**Type of Pediatric BT**	**Gene**	**Chromosomal Location**	**Overall Incidence** ***Pediatric BT incidence***
NF1	Neurofibroma/sarc Optic nerve glioma Astrocytoma	*NF1*	17q11	1:4000 *4-45%*
NF2	Schwannoma Meningioma Glioma Ependymoma	*NF2*	22q12	1:40,000 *Unknown*
Tuberous Sclerosis	Giant cell astrocytoma	*TSC1 / TSC2*	9q34 / 16p13	1:5000 *6-14%*
Von Hippel-Lindau	Hemangioblastoma	*VHL*	3p25	1:45,500 *2%*
Retinoblastoma	Retinoblastoma Pineoblastoma Malignant glioma	*RB1*	13q14	1:20,000 *Very rare*
Li-Fraumeni	Malignant glioma	*TP53*	17p13	Rare *2nd most common*
Turcots	Medulloblastoma Glioma	*APC / MMR*	5q21	Very rare *Very rare*
Nevoid basal cell carcinoma	Medulloblastoma	*PTCH*	9q22.3	1:57,000 *Unknown*

Adapted from Kleihues et al, 2000; Melean et al, 2004

Gene mapping in families for BTs

GLIOGENE studies (ABTA supported)

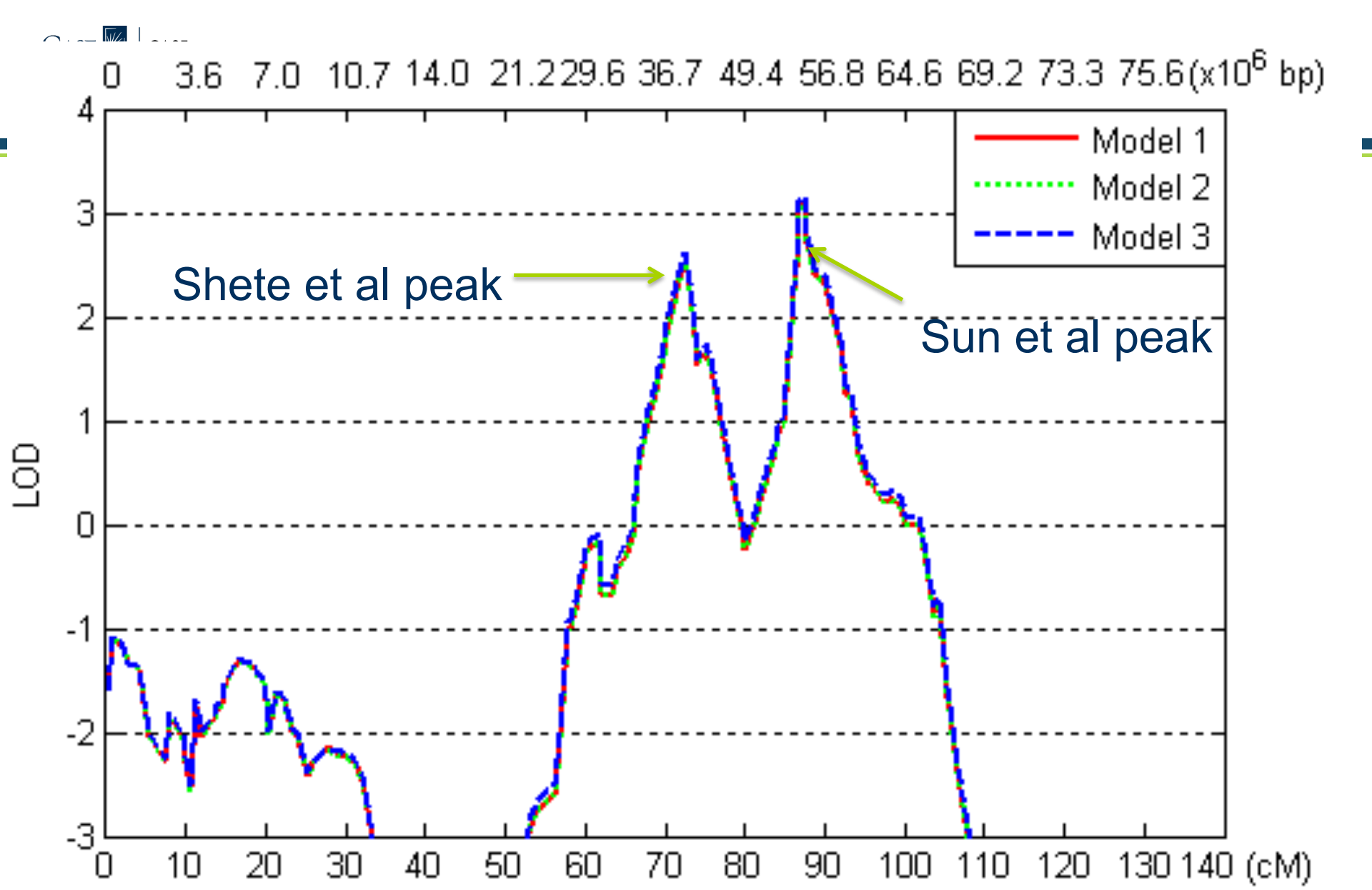
- Families with 2 or more gliomas
- Most gliomas occurred in clusters of 2

Shete, et al.

- Linkage search identifies susceptibility region on chromosome 17

Sun, et al.

- Narrowed chromosome 17 linkage peak identified in Shete, et al., using a new model-based approach



Chromosome 17

Sun et al., 2012

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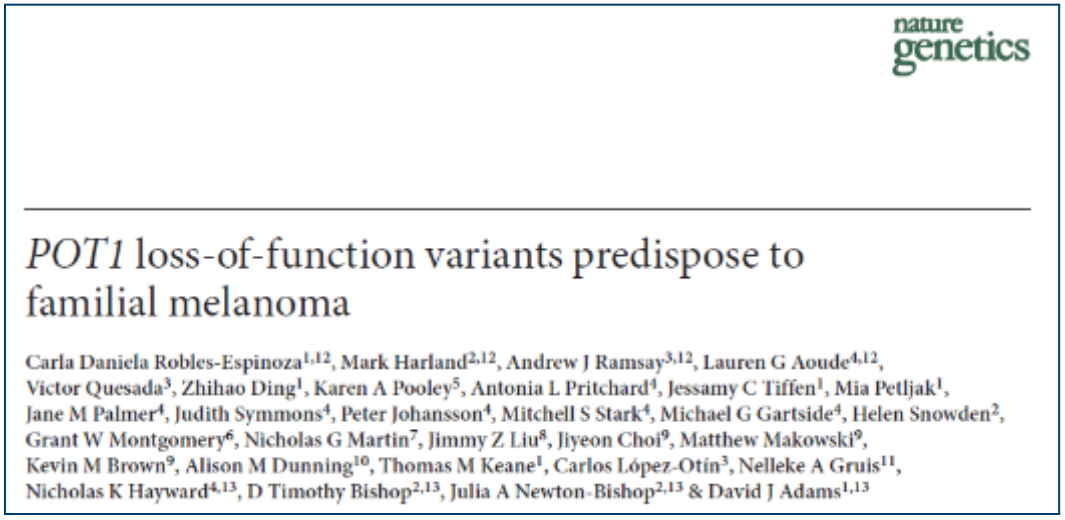
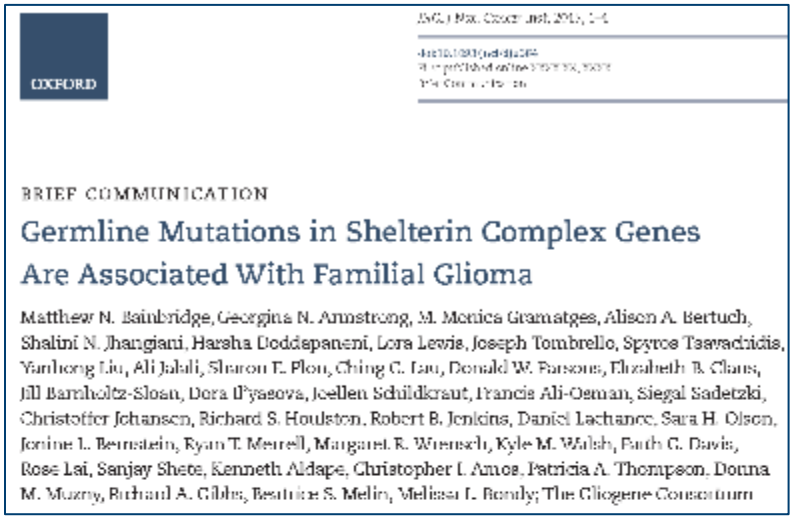
Protection of telomeres 1 gene (*POT1*) and familial melanoma and familial glioma



nature genetics

POT1 loss-of-function variants predispose to familial melanoma

Carla Daniela Robles-Espinoza[1,12], Mark Harland[2,12], Andrew J Ramsay[3,12], Lauren G Aoude[4,12], Victor Quesada[3], Zhihao Ding[1], Karen A Pooley[5], Antonia L Pritchard[4], Jessamy C Tiffen[1], Mia Petljak[1], Jane M Palmer[4], Judith Symmons[4], Peter Johansson[4], Mitchell S Stark[4], Michael G Gartside[4], Helen Snowden[2], Grant W Montgomery[6], Nicholas G Martin[7], Jimmy Z Liu[8], Jiyeon Choi[9], Matthew Makowski[9], Kevin M Brown[9], Alison M Dunning[10], Thomas M Keane[1], Carlos López-Otín[3], Nelleke A Gruis[11], Nicholas K Hayward[4,13], D Timothy Bishop[2,13], Julia A Newton-Bishop[2,13] & David J Adams[1,13]

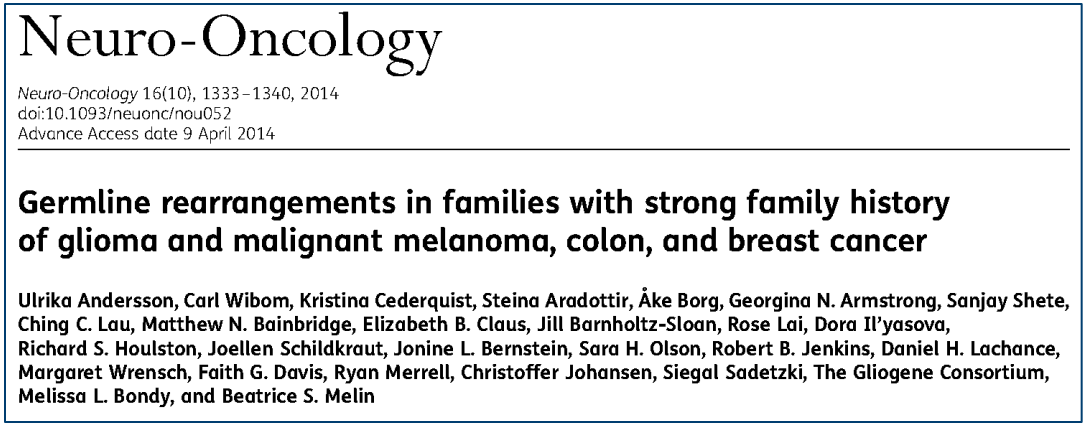


OXFORD

BRIEF COMMUNICATION

Germline Mutations in Shelterin Complex Genes Are Associated With Familial Glioma

Matthew N. Bainbridge, Georgina N. Armstrong, M. Monica Gramatges, Alison A. Bertuch, Shalini N. Jhangiani, Harsha Doddapaneni, Lora Lewis, Joseph Tombrello, Spyros Tsavachidis, Yanhong Liu, Ali Jalali, Sharon E. Plon, Ching C. Lau, Donald W. Parsons, Elizabeth B. Claus, Jill Barnholtz-Sloan, Dora Il'yasova, Joellen Schildkraut, Francis Ali-Osman, Siegal Sadetzki, Christoffer Johansen, Richard S. Houlston, Robert B. Jenkins, Daniel Lachance, Sara H. Olson, Jonine L. Bernstein, Ryan T. Merrell, Margaret R. Wrensch, Kyle M. Walsh, Faith G. Davis, Rose Lai, Sanjay Shete, Kenneth Aldape, Christopher I. Amos, Patricia A. Thompson, Donna M. Muzny, Richard A. Gibbs, Beatrice S. Melin, Melissa L. Bondy, The Gliogene Consortium



Neuro-Oncology

Neuro-Oncology 16(10), 1333–1340, 2014
doi:10.1093/neuonc/nou052
Advance Access date 9 April 2014

Germline rearrangements in families with strong family history of glioma and malignant melanoma, colon, and breast cancer

Ulrika Andersson, Carl Wibom, Kristina Cederquist, Steina Aradottir, Åke Borg, Georgina N. Armstrong, Sanjay Shete, Ching C. Lau, Matthew N. Bainbridge, Elizabeth B. Claus, Jill Barnholtz-Sloan, Rose Lai, Dora Il'yasova, Richard S. Houlston, Joellen Schildkraut, Jonine L. Bernstein, Sara H. Olson, Robert B. Jenkins, Daniel H. Lachance, Margaret Wrensch, Faith G. Davis, Ryan Merrell, Christoffer Johansen, Siegal Sadetzki, The Gliogene Consortium, Melissa L. Bondy, and Beatrice S. Melin

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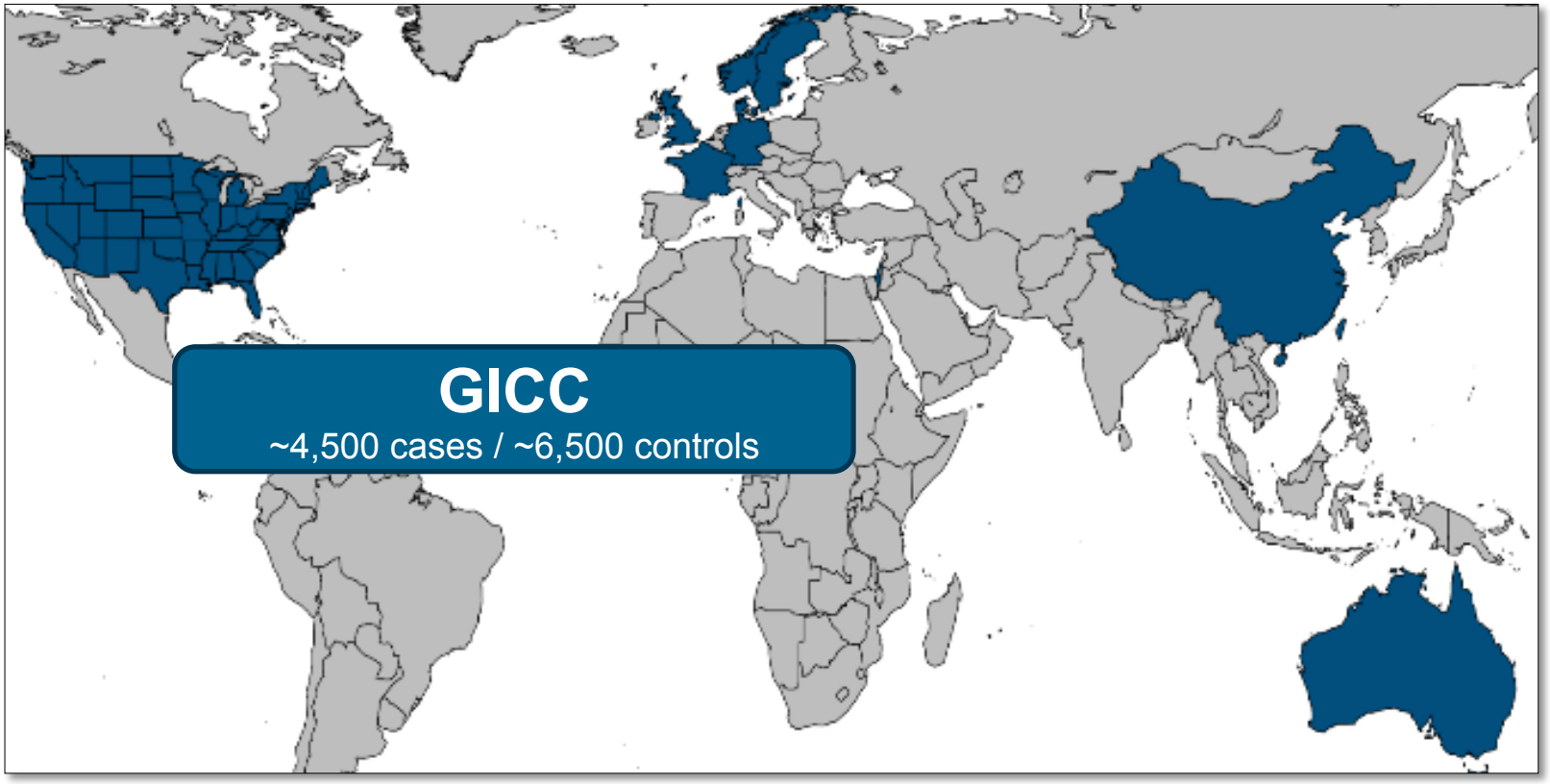
Gliogene International Case-Control (GICC) Study



- Largest glioma GWAS to date
  - Validation of previously discovered risk factor (4 previous glioma GWAS studied)
  - Discovery of new rare variants that may increase glioma risk

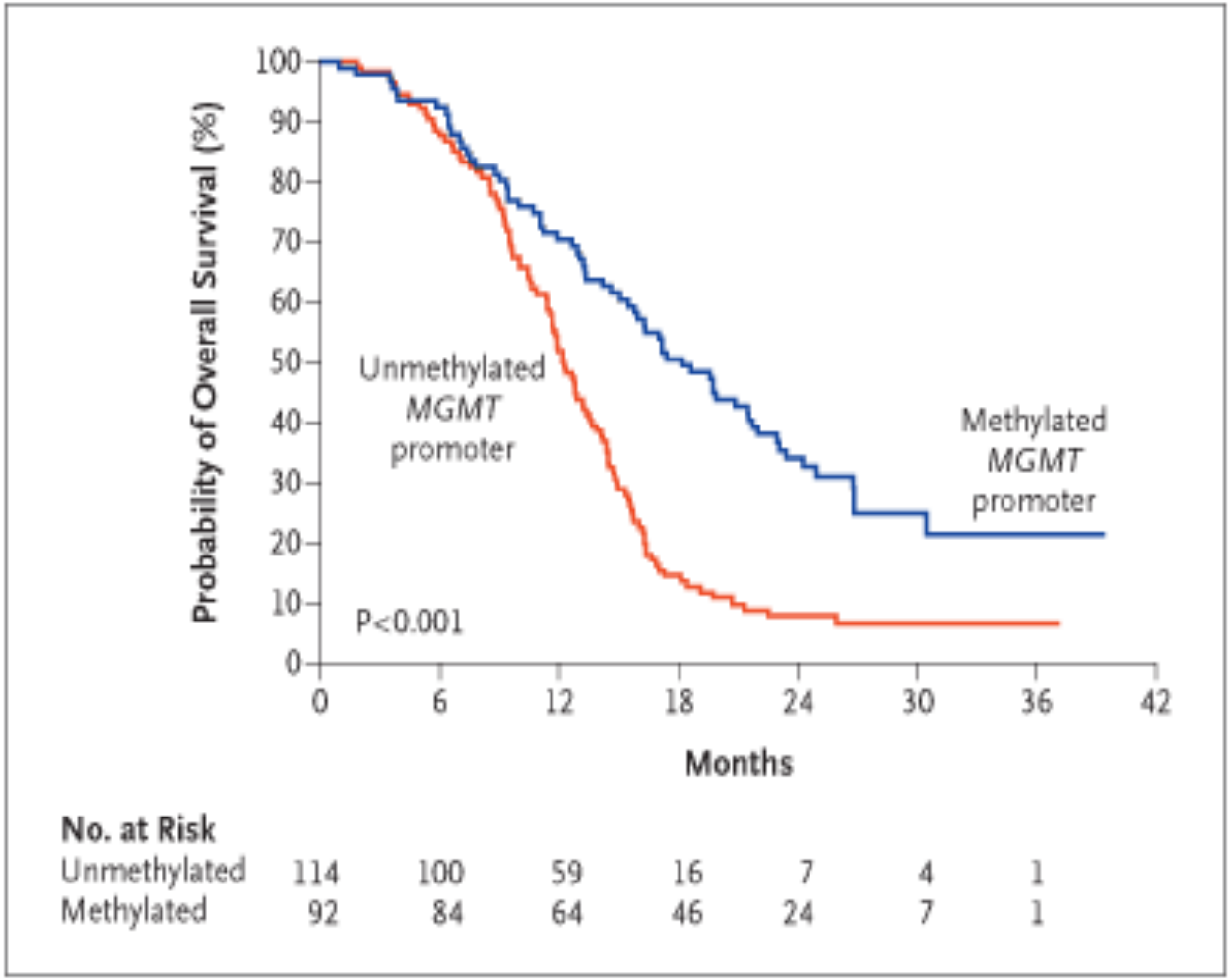
Prognostic Factors for BTs

- Karnofsky Performance Score (KPS)
- Age at diagnosis
- Extent of surgical resection
- Histological Type of Tumor

- Biomarkers??

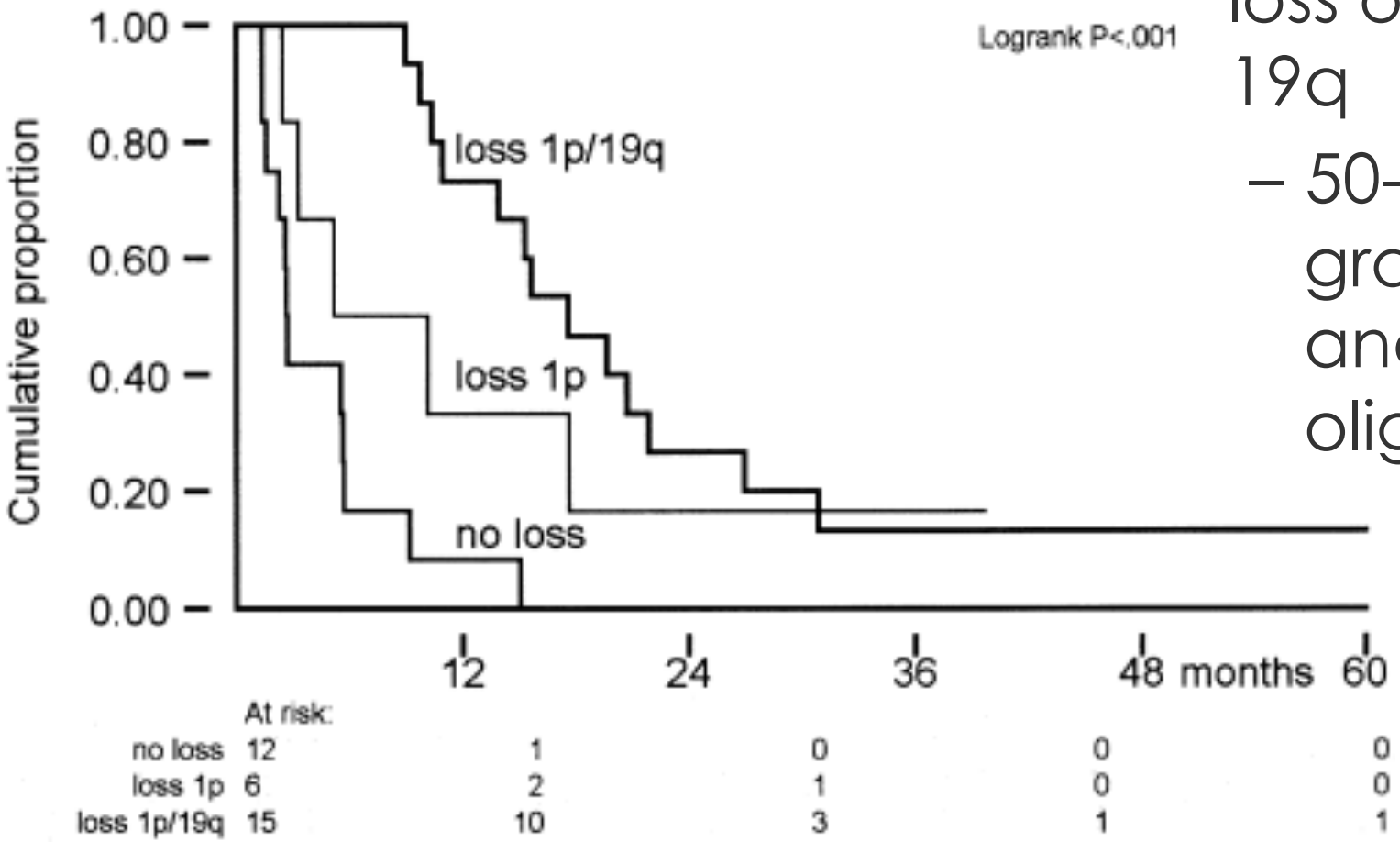
Genetics and Prognosis: Methylation of MGMT

- Hypermethylation at MGMT – responsive to alkylating agents (i.e. Temozolomide)
- More responsive to both chemo and radiation if methylated
  - ❖Hegi et al., NEJM 2005



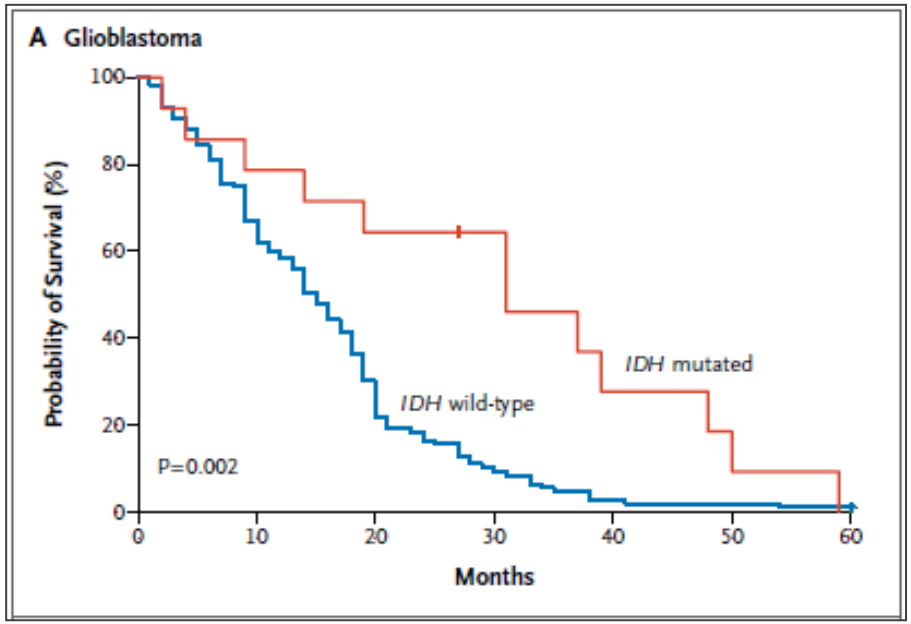
Genetics and Prognosis: Oligos and 1p/19q loss

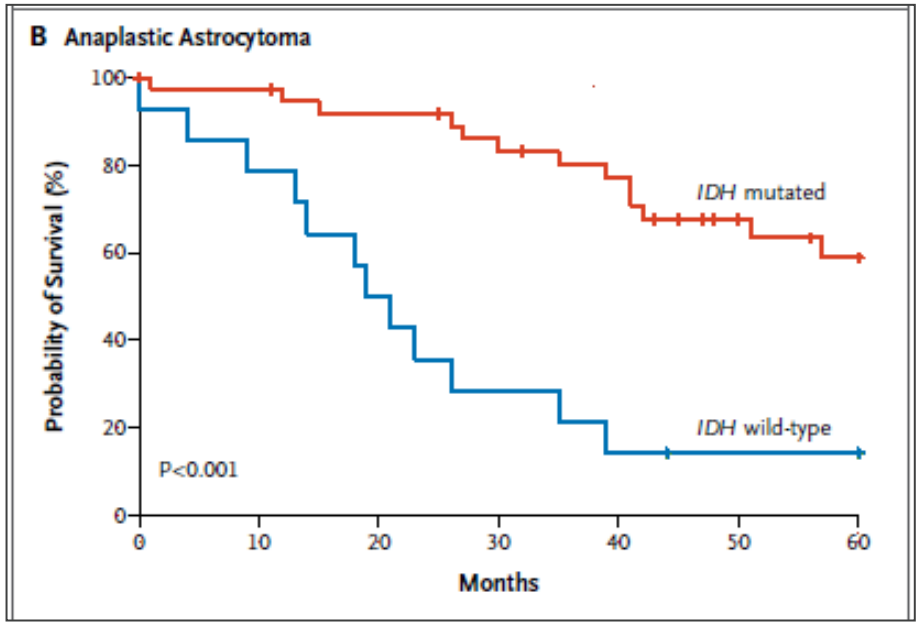
- Concurrent loss of 1p and 19q
  - 50-70% of grade III anaplastic oligos



Van den Bent et al, Cancer 2003

IDH1/2 mutations – survival advantage!





What have we learned about gliomas from The Cancer Genome Atlas (TCGA)?

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TCGA: "No Platform Left Behind"

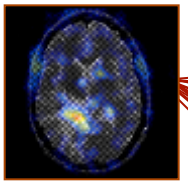
25* forms of cancer

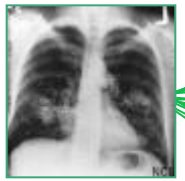
glioblastoma multiforme (brain)

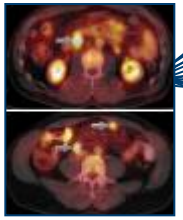
squamous carcinoma (lung)

serous cystadenocarcinoma (ovarian)

Etc. Etc. Etc.







Biospecimen Core Resource with more than 150 Tissue Source Sites

6 Cancer Genomic Characterization Centers

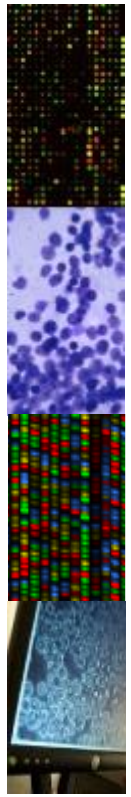
3 Genome Sequencing Centers

7 Genome Data Analysis Centers

Data Coordinating Center

Multiple data types

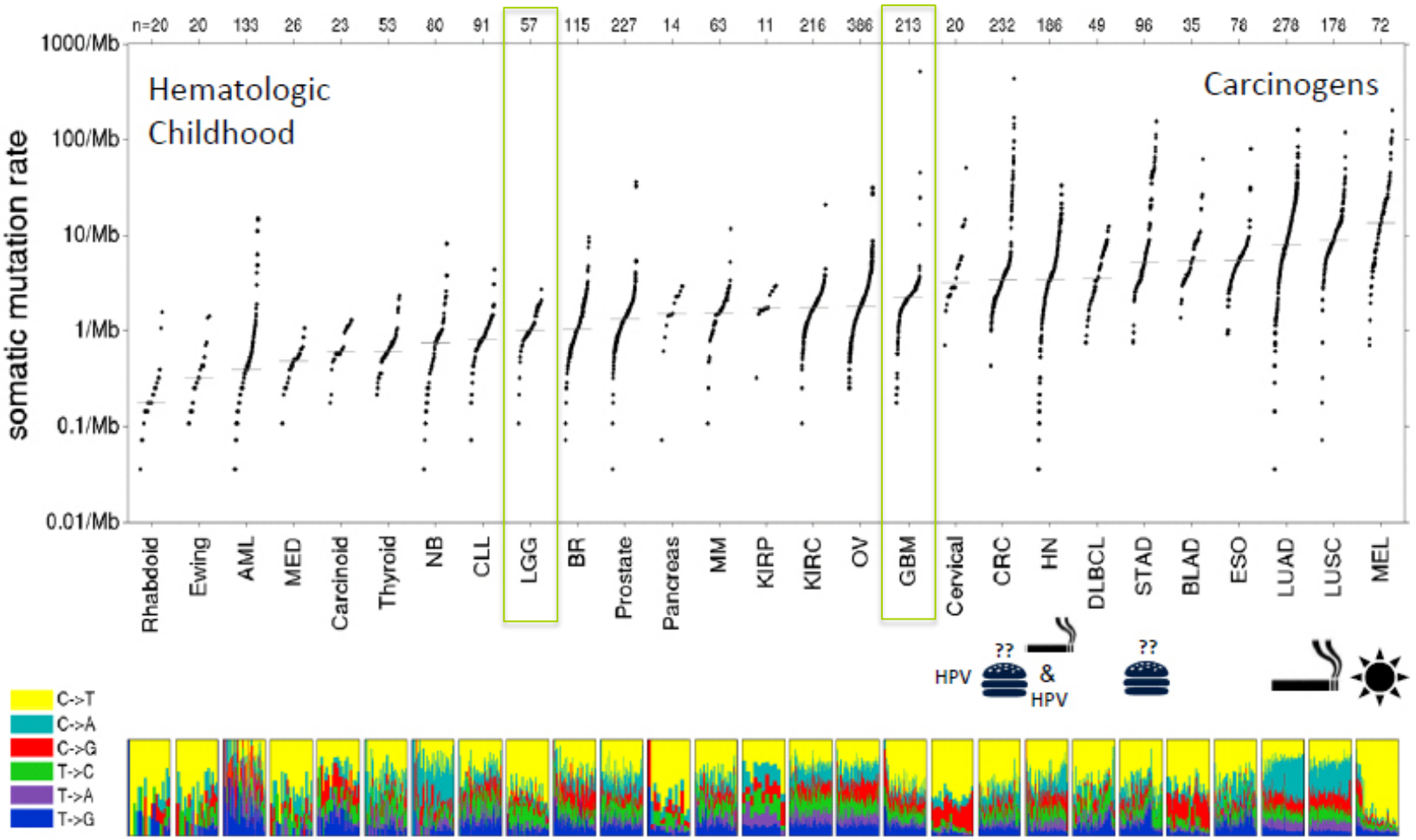
- Clinical diagnosis
- Treatment history
- Histologic diagnosis
- Pathologic report/ images
- Tissue anatomic site
- Surgical history
- Gene expression/RNA sequence
- Chromosomal copy number
- Loss of heterozygosity
- Methylation patterns
- miRNA expression
- DNA sequence
- RPPA (protein)
- Subset for Mass Spec



Cancer is a disease of the genome

- If we precisely characterize the cancer genome can we cure cancer??
  - Drivers
  - Passengers
  - Rapid evolution
    - Development of treatment resistance
    - Clonal evolution
  - Other components of biological process -- complex signaling

Mutational Landscape of Cancers

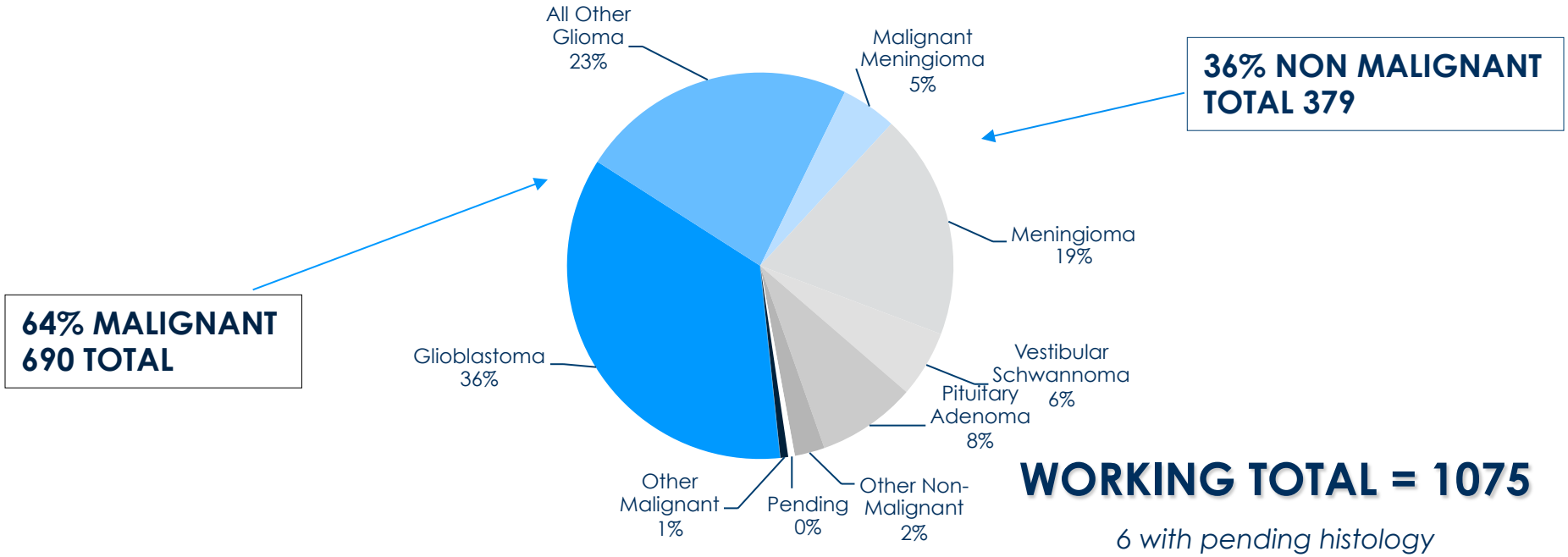


TCGA, 2014

Ohio Brain Tumor Study (OBTS) Statistics

- Accrual began at:
  - 9/07 University Hospitals Seidman Cancer Center
  - 7/08 University of Cincinnati
  - 9/08 Cleveland Clinic
  - 11/09 The James, Ohio State is a Comprehensive Cancer Center designated by the National Cancer Institute; NCI CCC

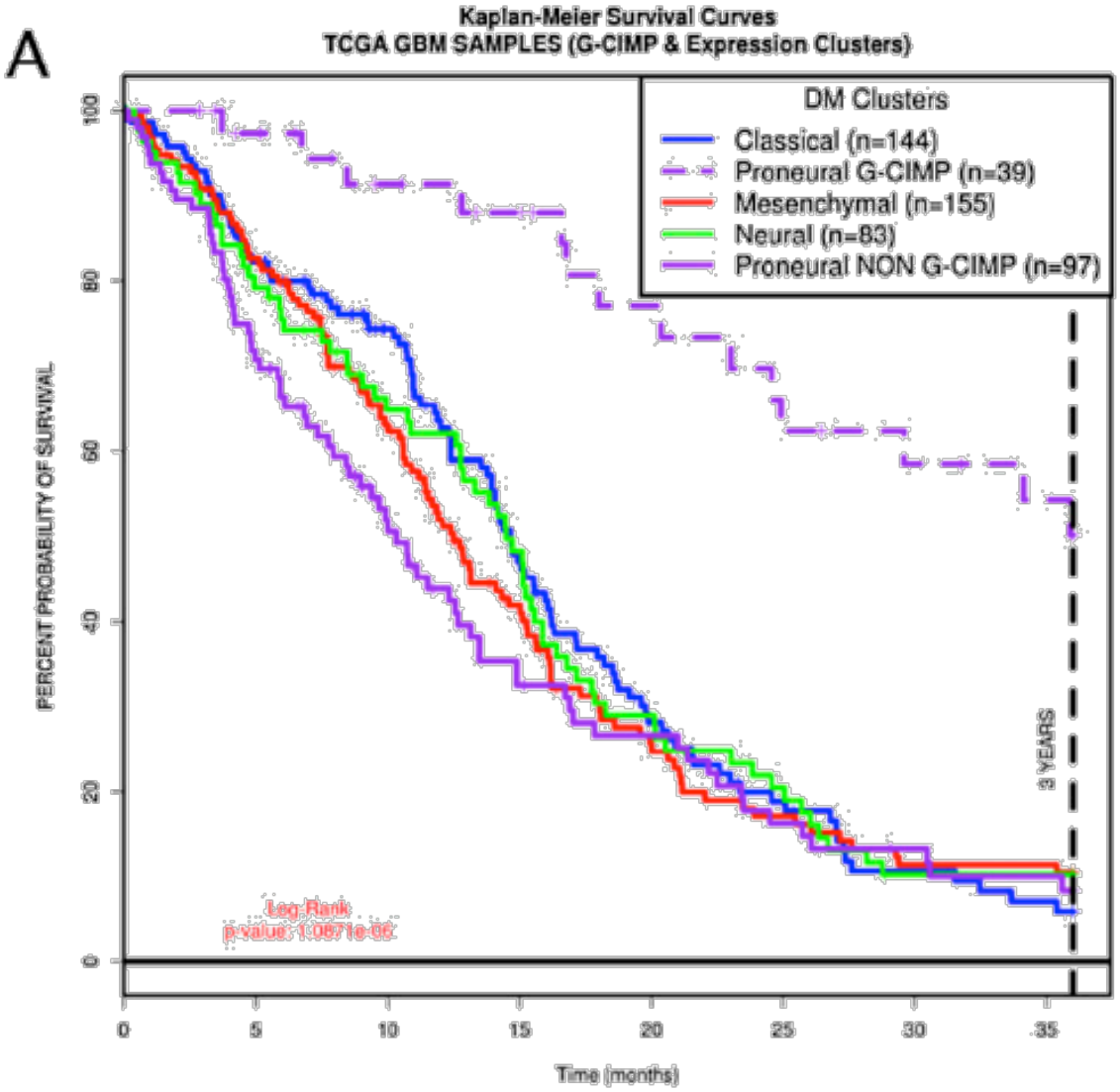
- Pre-treatment blood samples on ~75%
- Pre-treatment snap-frozen tumor tissue on ~60%
- Pre-treatment FFPE tumor tissue on ~80%
- Questionnaire on ~60%
- Biorepository has over 5000 tumor specimens related to these patients



WORKING TOTAL = 1075

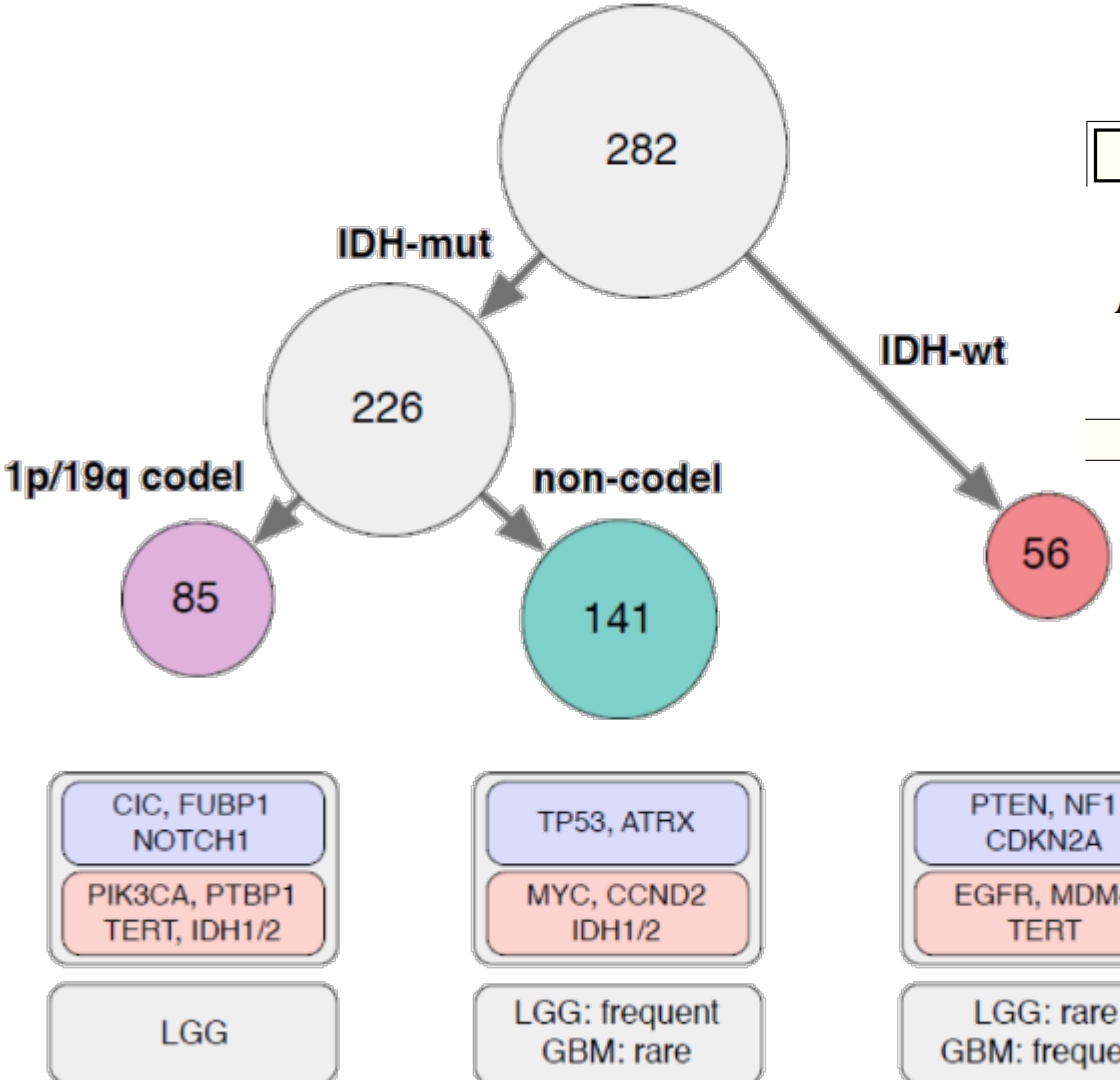
6 with pending histology

Molecular Subtypes and survival for GBM



Brennan et al, 2013
Verhaak et al, 2010
Noushmehr et al, 2010

LGG subtypes -- TCGA



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Comprehensive, Integrative Genomic Analysis of Diffuse Lower-Grade Gliomas

The Cancer Genome Atlas Research Network*

ABSTRACT

TCGA, NEJM, 2015

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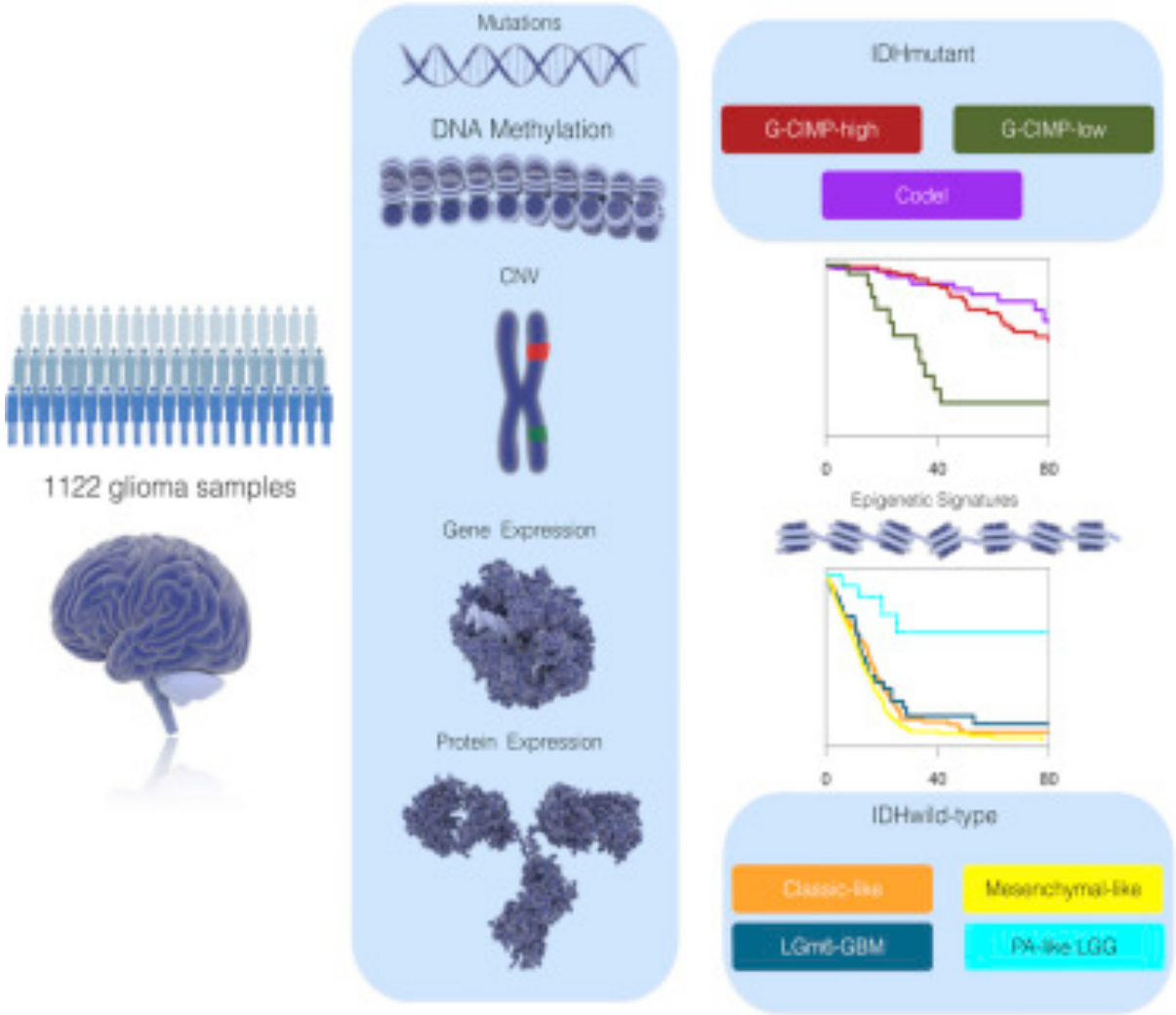
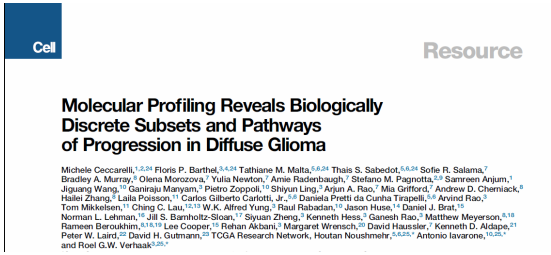
Further glioma subtyping -TCGA




Cell

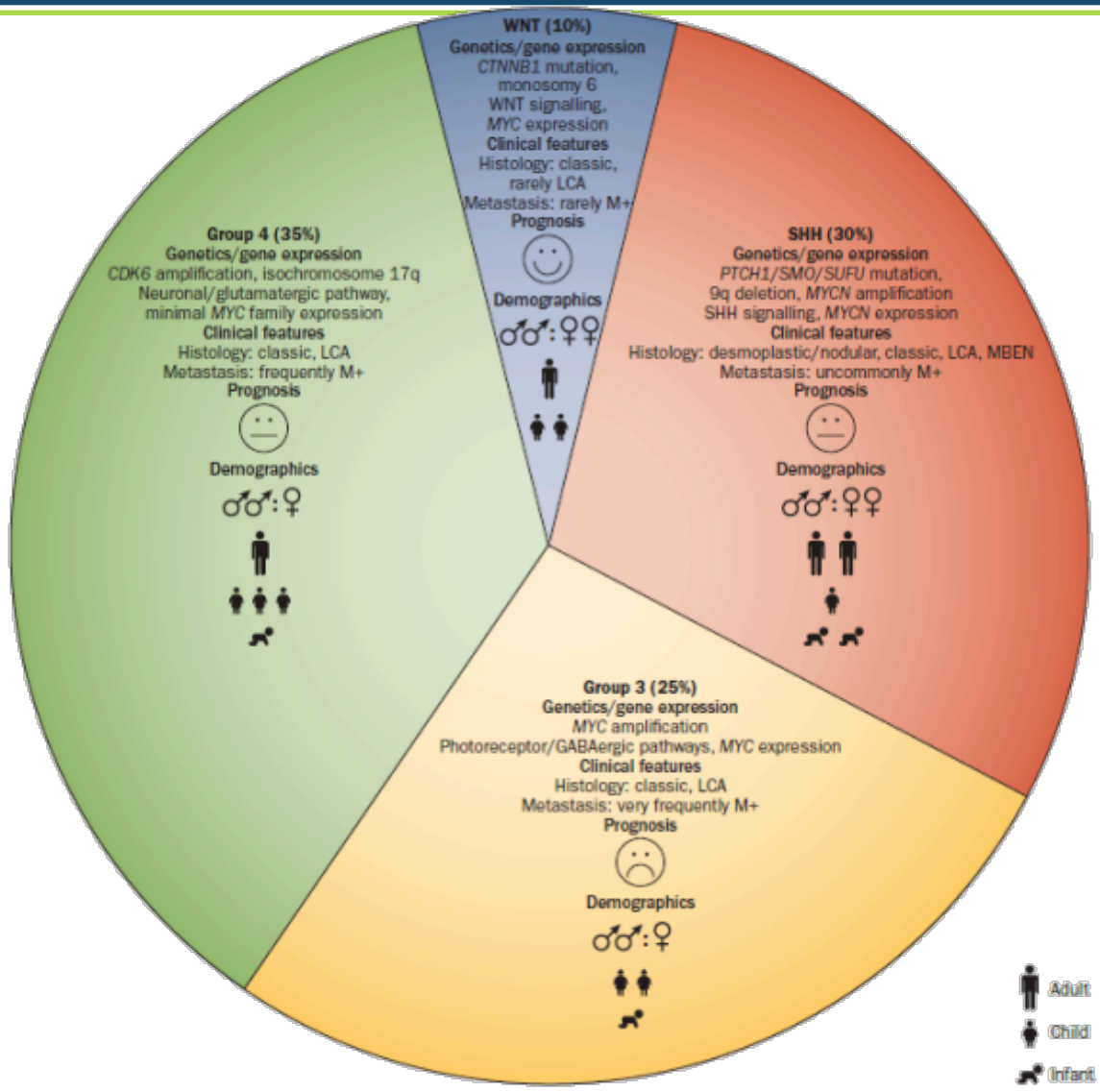
Resource

Molecular Profiling Reveals Biologically Discrete Subsets and Pathways of Progression in Diffuse Glioma

Michele Ceccarelli, Floris P. Barthel, Tathiane M. Malta, Thais S. Sabedot, Sofie R. Salama, Bradley A. Murray, Olena Morozova, Yulia Newton, Amie Radenbaugh, Stefano M. Pagnotta, Samreen Anjum, Jiguang Wang, Ganiraju Manyam, Pietro Zoppoli, Shiyun Ling, Arjun A. Rao, Mia Grifford, Andrew D. Cherniack, Hailei Zhang, Laila Poisson, Carlos Gilberto Carlotti, Jr., Daniela Pretti da Cunha Tirapelli, Arvind Rao, Tom Mikkelsen, Ching C. Lau, W.K. Alfred Yung, Raul Rabadan, Jason Huse, Daniel J. Brat, Norman L. Lehman, Jill S. Barnholtz-Sloan, Siyuan Zheng, Kenneth Hess, Ganesh Rao, Matthew Meyerson, Rameen Beroukhim, Lee Cooper, Rehan Akbani, Margaret Wrensch, David Haussler, Kenneth D. Aldape, Peter W. Laird, David H. Gutmann, TCGA Research Network, Houtan Noushmehr, Antonio Iavarone, and Roel G.W. Verhaak

Ceccerelli et al, Cell 2016

Medulloblastoma subtypes



Northcott et al, 2012

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Brain Tumor web resources

- Central Brain Tumor Registry of the United States – www.cbtrus.org
- Surveillance, Epidemiology and End Results Program (SEER) – http://seer.cancer.gov/statistics/summaries.html
- American Cancer Society Facts and Figures -- http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2013/index
- The Cancer Genome Atlas (TCGA) -- http://cancergenome.nih.gov/