Epidemiology of Adult Glioma

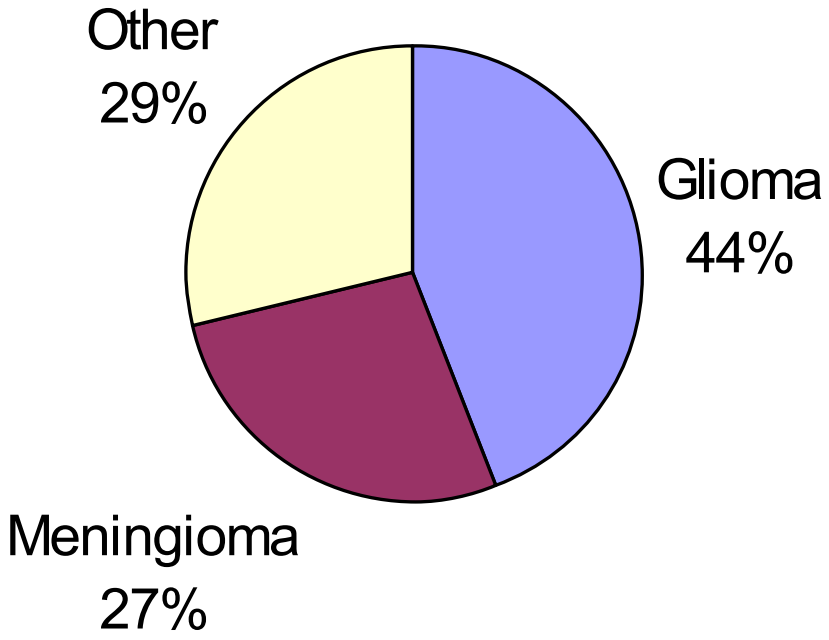
Joseph Wiemels, PhD

San Francisco, CA

August 2, 2017

UCSF
University of California
San Francisco

Proportion of Primary Brain Tumors by Histologic Type



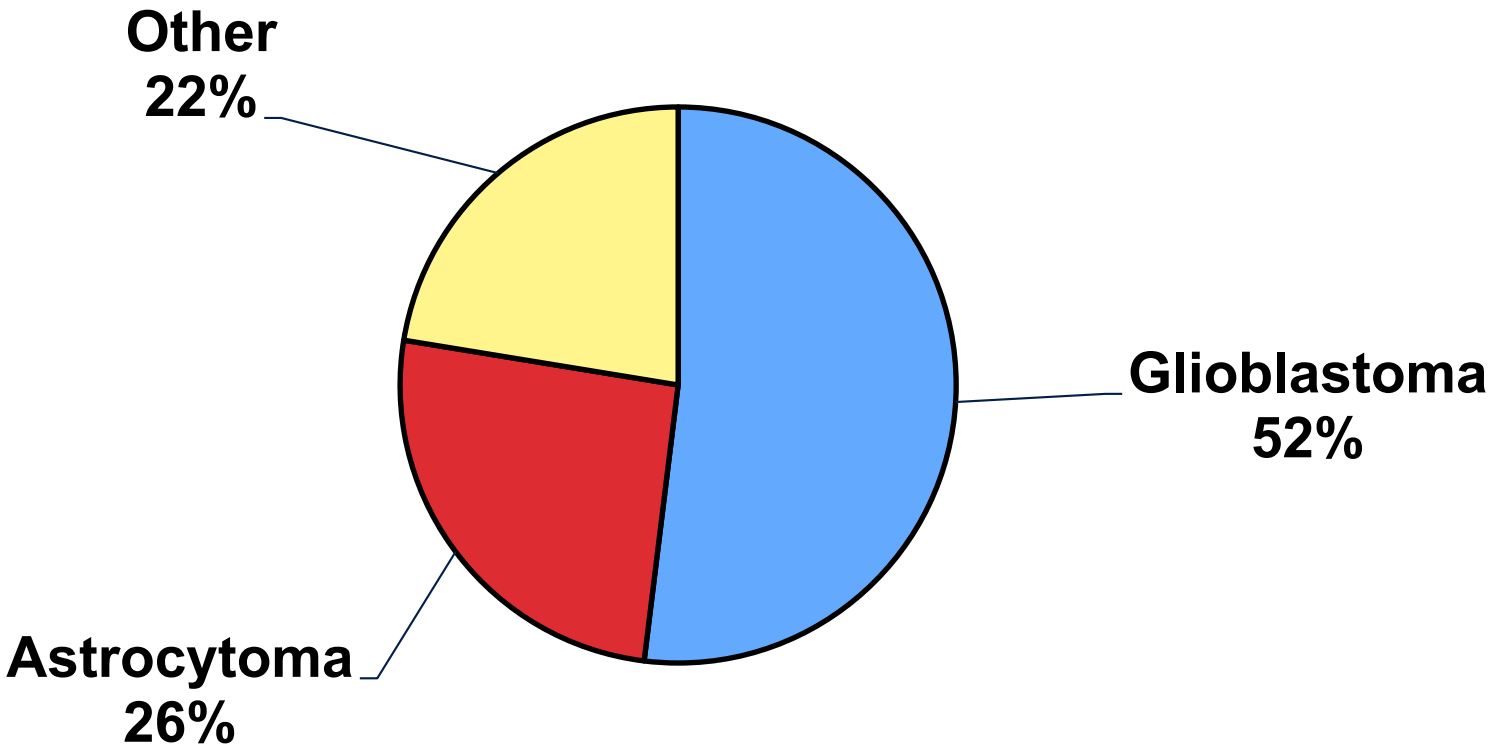
Total Number Cases for 2004 = 41,130

CBTRUS 2004-05

What is glioma?

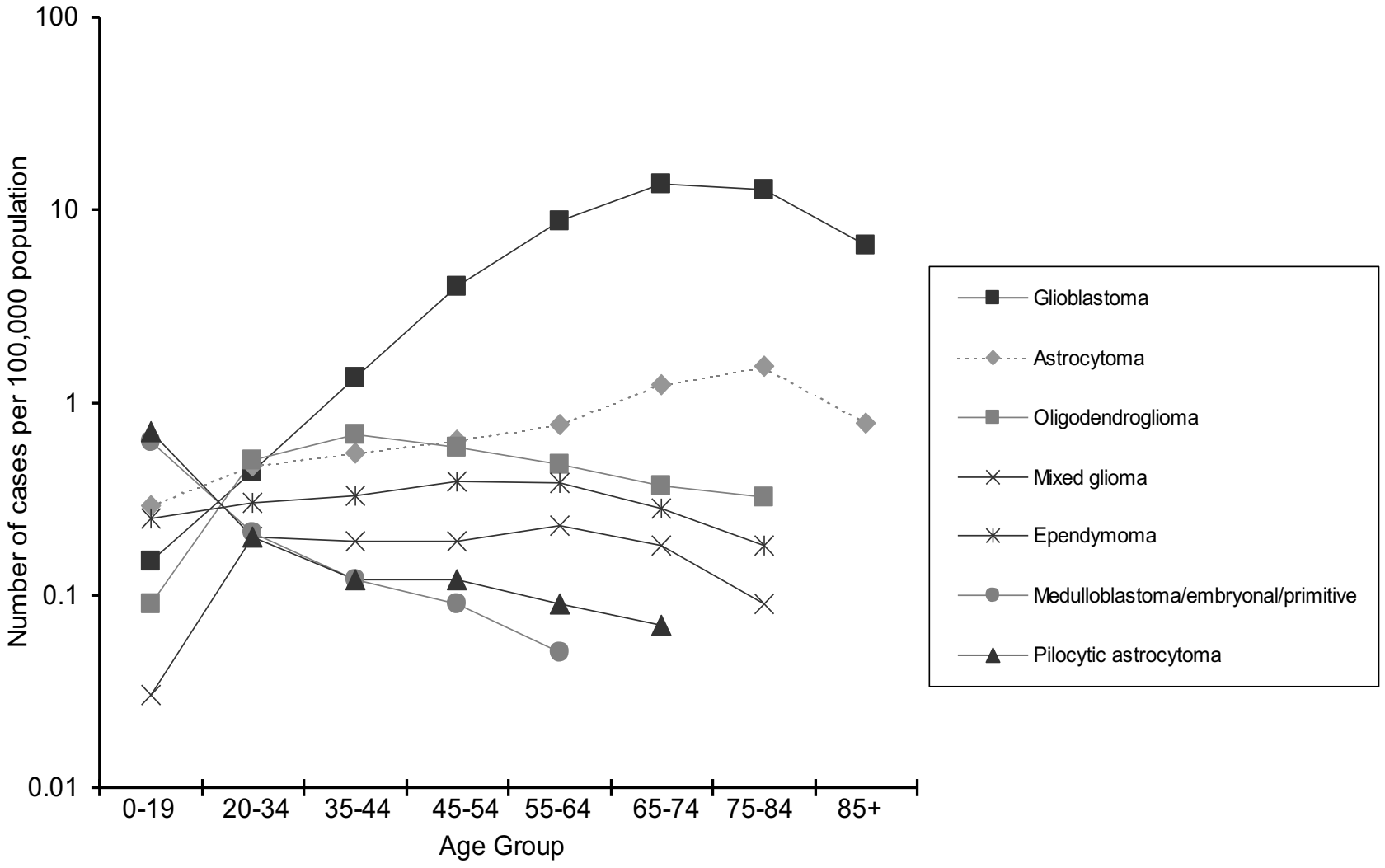
- Glioma refers to primary brain tumors that are thought to arise from glial tissue
- Nervous system composed of two primary cell types: neurons and glia (nerve glue)
- Main glial types are astrocytes, oligodendrocytes, ependyma
- Glioblastoma (aka astrocytoma, grade 4) is the most common (about 52% of gliomas)

Percentage of Gliomas by Histologic Type



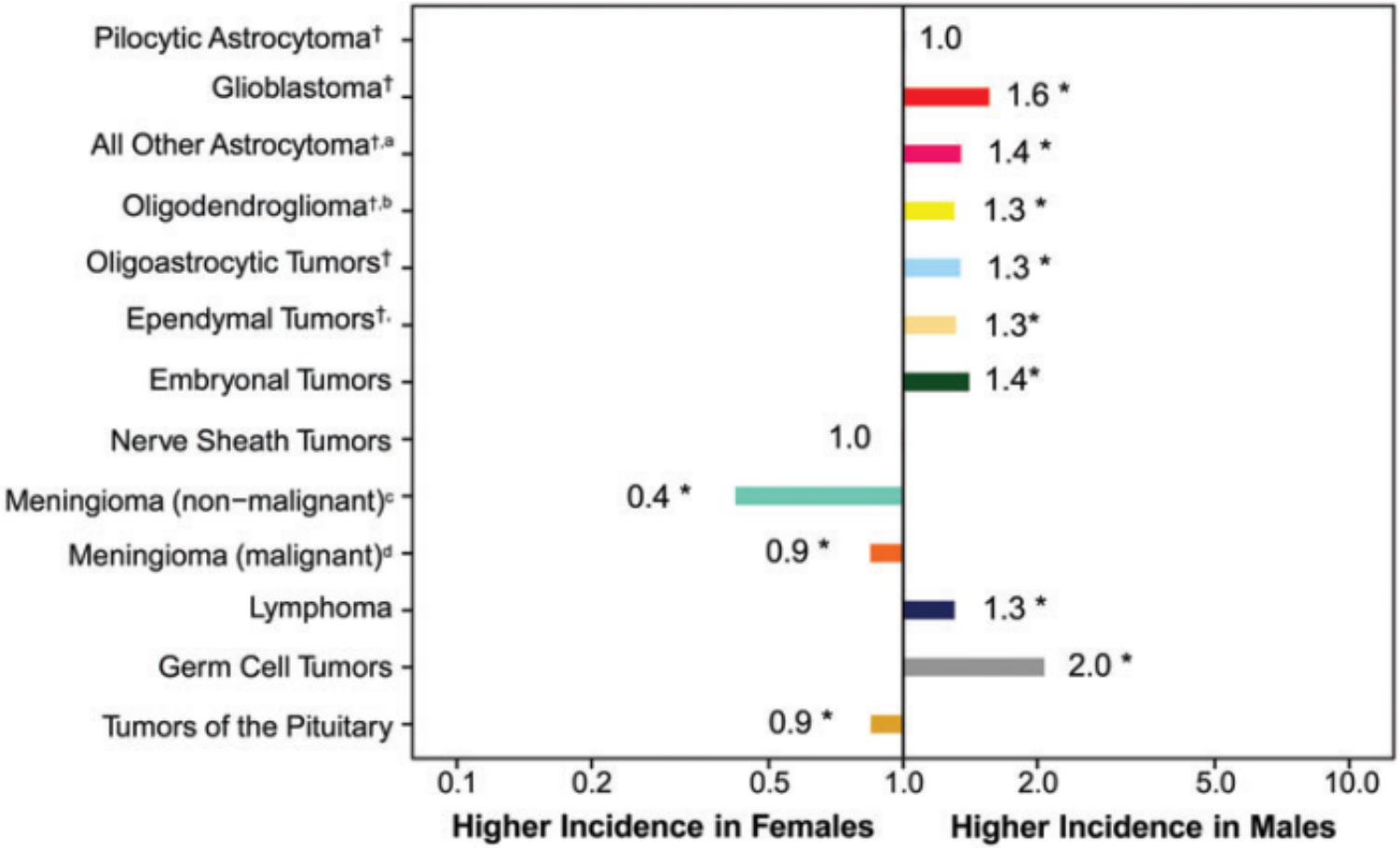
CBTRUS 2002-03

Glioma age distribution by histology



Source: CBTRUS

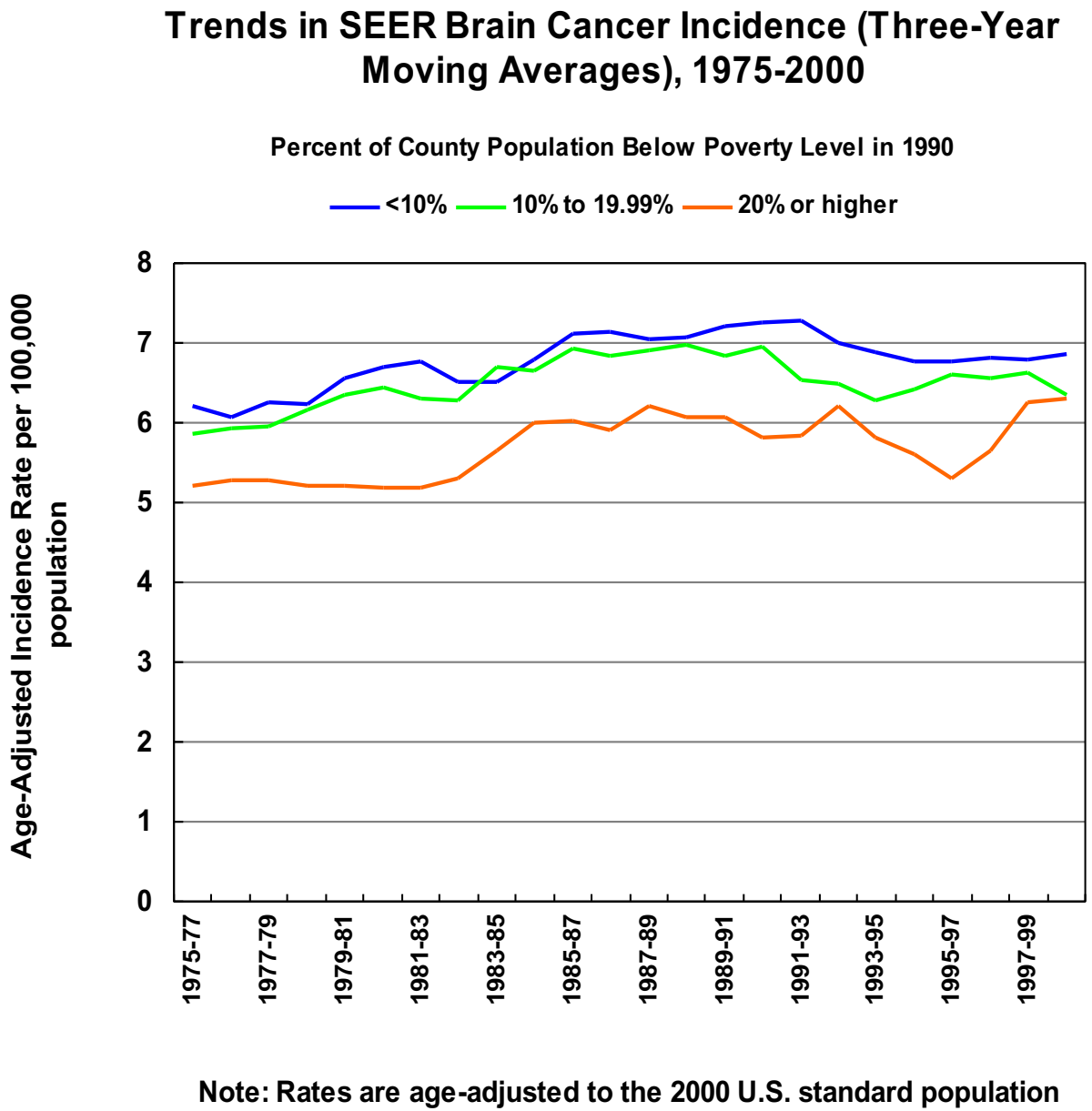
Gliomas are more common in men



** Incidence Rate is significantly different in males and females.*
† All or some of this histology are included in the CBTRUS definition of gliomas, including ICD-O-3 histology codes 9380-9384, 9391-9460, 9480.
a. ICD-O-3 Histology Codes: 9381, 9384, 9424, 9400, 9401, 9410, 9411, 9420. b. ICD-O-3 Histology Codes: 9450, 9451, 9460.
c. ICD-O-3 Histology Codes: 9530/0,9530/1, 9531/0, 9532/0, 9533/0, 9534/0, 9537/0, 9538/1, 9539/1. d. ICD-O-3 Histology Codes: 9530/3, 9538/3, 9539/3.

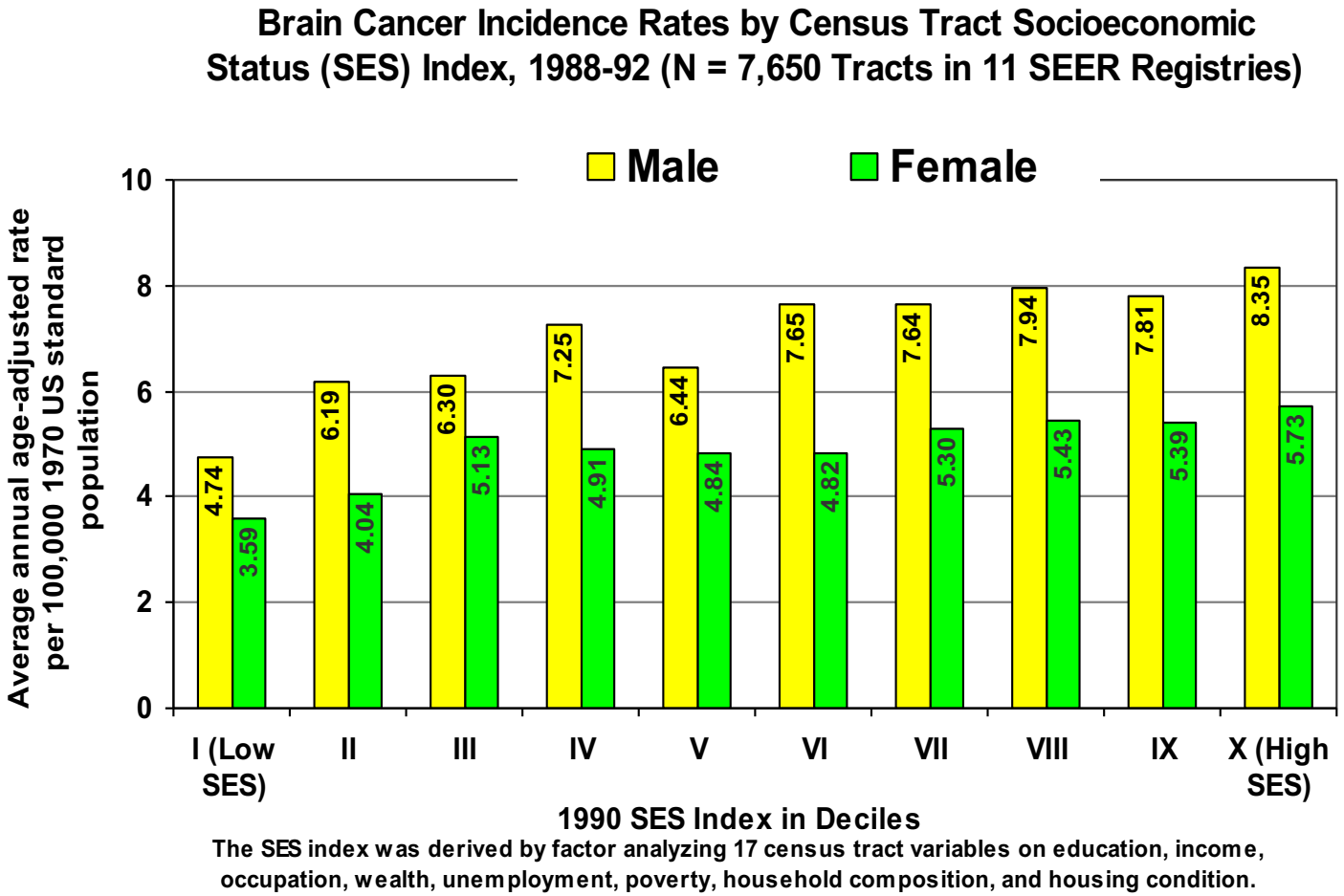
Fig. 12. Incidence Rate Ratios by Gender (Males:Females) for Selected CBTRUS Histology Groupings and Histology, CBTRUS Statistical Report: NPCR and SEER, 2007–2011.

Socioeconomic status



Gopal Singh, PhD
National Cancer Institute
Cancer Statistics Branch

Socioeconomic status



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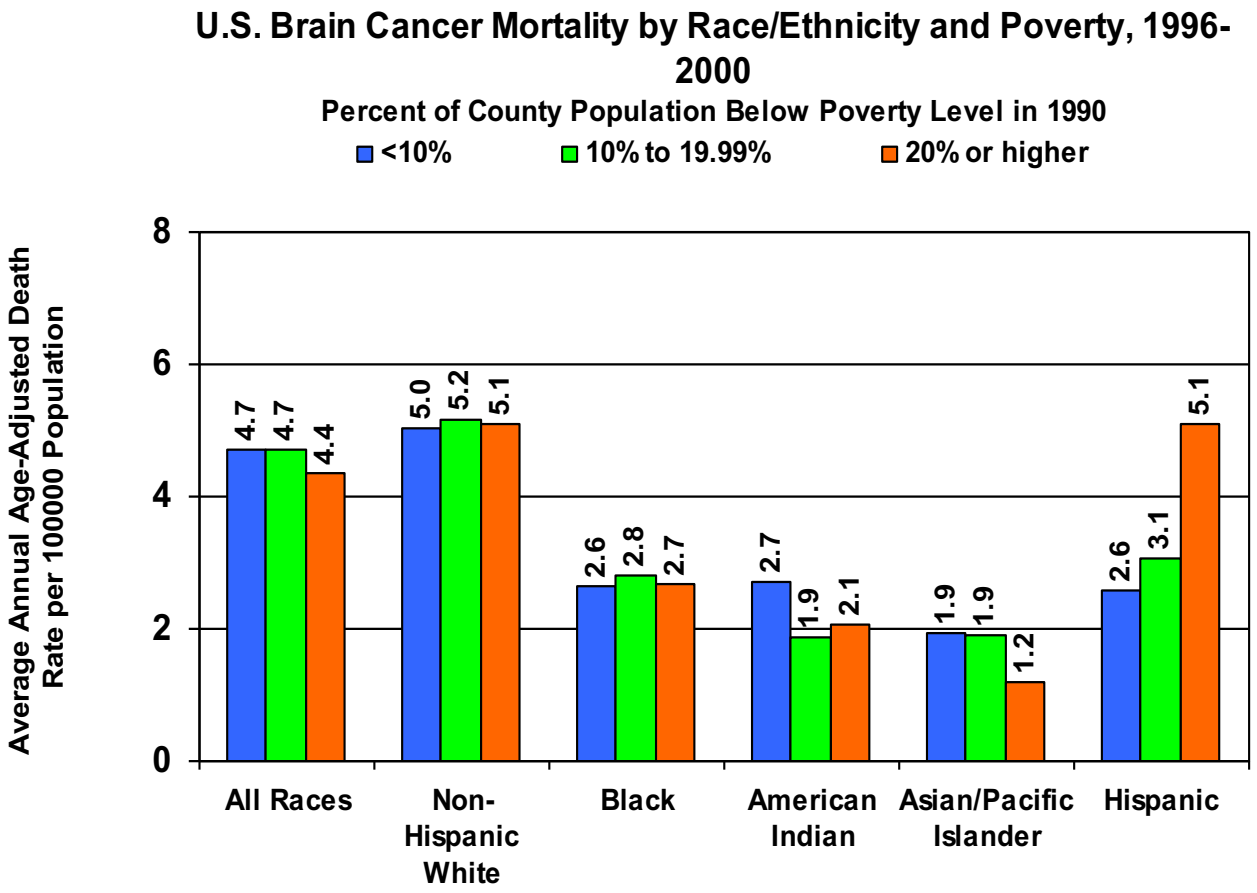
National Cancer Institute
Cancer Statistics Branch

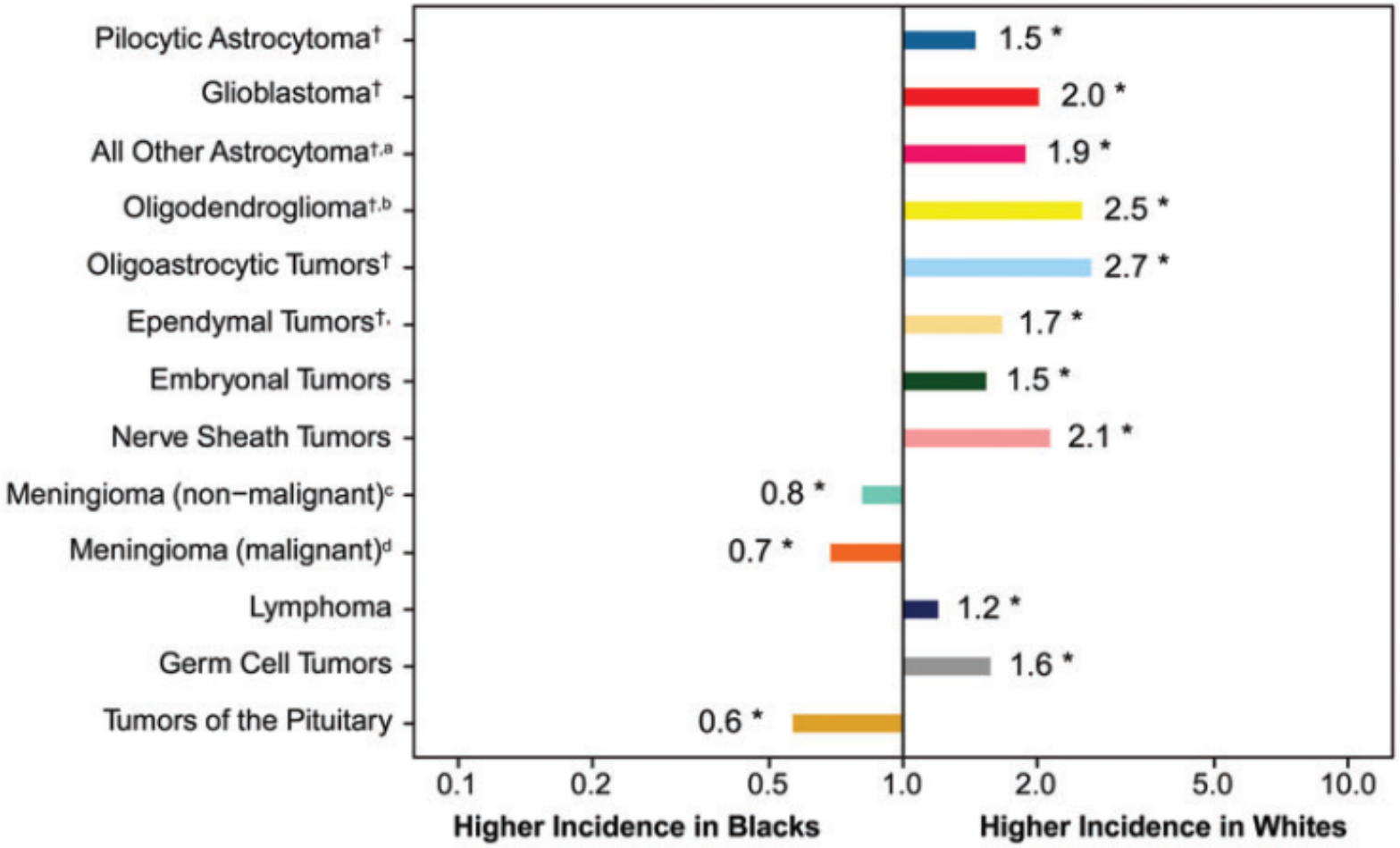
Race and ethnicity



Note: Rates are age-adjusted to the 2000 U.S. standard population. Rates for Hispanics and Non-Hispanic whites are based on 1997-2000 data.

Gopal Singh, PhD
National Cancer Institute
Cancer Statistics Branch

Gliomas are more common in whites



** Incidence Rate is significantly different in males and females.*
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Fig. 13. Incidence Rate Ratios by Race (Whites:Blacks) for Selected CBTRUS Histology Groupings and Histologies, CBTRUS Statistical Report: NPCR and SEER, 2007–2011.

Cancer in Gulf War Veterans

Are glioma rates higher?

Volume 10 committee states that the evidence continues to be inadequate/insufficient to determine whether deployed Gulf War veterans are at increased risk of developing any cancer, including lung cancer and brain cancer. The relative rarity of cancers such as brain cancer argues for larger studies with adequate statistical power. This may require pooling data where feasible and the use of a variety of data sources such as state cancer registries.

Gulf War and Health: Volume 10: Update of Health Effects of Serving in the Gulf War, 2016

Causes of Brain Tumors

Environment

Genetics

Evaluating Associations

- Is an association (or the absence of an association) between a disease and a factor real?

- If it's real, is it a causal association?

Association Caveats

- Chance (statistical significance and power)
- Bias
- Confounders
- Heterogeneity
- Real associations not necessarily causal

Strength of association; Consistency from study to study; Appropriate temporal relationship; Dose-response; Plausibility; Coherence; Experiment; Analogies; Specificity

Summary of Basic Epi of Gliomas

- Incidence increases with age up to a point and then declines
- About 50% more common in males than females
- More common in whites than non-whites
  - 2-3 fold excess in whites vs blacks
- Some geographic variation—4-5 fold difference between high and low risk areas
- Substantial heterogeneity of tumors between and within histologic categories

Challenges in Brain Tumor Epidemiology

- Relatively rare disease
  - Mainly rely on case-control studies (not cohort)
- Very poor survival
  - Proxy informants required in population based studies for substantial proportion of cases
  - Rapid case ascertainment
  - Hospital based studies
- Substantial disease heterogeneity
  - Uniform neuropathology review and meaningful tumor markers necessary

Additional Challenges in Brain Tumor Epidemiology among Veterans

- Long latency of disease…. 30 years plus
- Incomplete exposure information
- “healthy worker” effect
- Loss to follow up – registry data complete?

Review of Non-occupational Risk Factors For Adult Glioma

UCSF Indicates San Francisco Bay Area Glioma Study has published results on factor

Established Risk Factors	Association (size and direction)
High Dose Radiation	+++
Hereditary Syndromes	+++
Male vs Female Gender	+
White vs African American ethnicity	+
Increasing Age	+++
UCSF Epilepsy, seizures, convulsions (probably early symptom)	+

Probable Risk Factors	
UCSF Family history of brain tumors	+
Mutagen sensitivity	+
UCSF Allergies/Asthma/Elevated IgE	-
UCSF Chicken pox/anti-VZV IgG	-

Probably Not Risk Factors
UCSF Diagnostic radiation
UCSF Head injury
UCSF Residential power frequency EMF
UCSF Prior cancers
UCSF Filtered cigarette smoking
UCSF Alcohol consumption
Cell phone use

Too Few Studies to Assess Consistency	Association (size and direction)
Dietary intake:	
UCSF -Calcium (high vs low quartile)	-
UCSF -Cured foods	+
UCSF -Antioxidants	-
NSAIDs	-
Exogenous hormones/menstrual factor	?
Constitutive polymorphisms: (Associations observed for some histologic or molecular glioma subtypes or for some combinations of polymorphisms.)	
Carcinogen/oxidative metabolism:	
UCSF -Glutathione transferases	
-CYP2E1	
DNA repair:	
UCSF -ERCC1, ERCC2	
UCSF -MGMT	
-XRCC7	
Immune function:	
-Polymorphisms positively associated with asthma risk: IL4Ralpha, IL13	
UCSF -HLA B*13, B*07-Cw*07 (more common in whites)	
Other:	
-GLTSCR1 (same region as ERCC1 and ERCC2)	

+++	relative risk>3
+	1<relative risk <3
-	0.3<relative risk <1

Occupational causes of brain cancers

Petrochemical

Electrical and electronics workers

Agrobusiness

Reduction of occupational exposures has not reduced the risk of brain cancers at the population level.

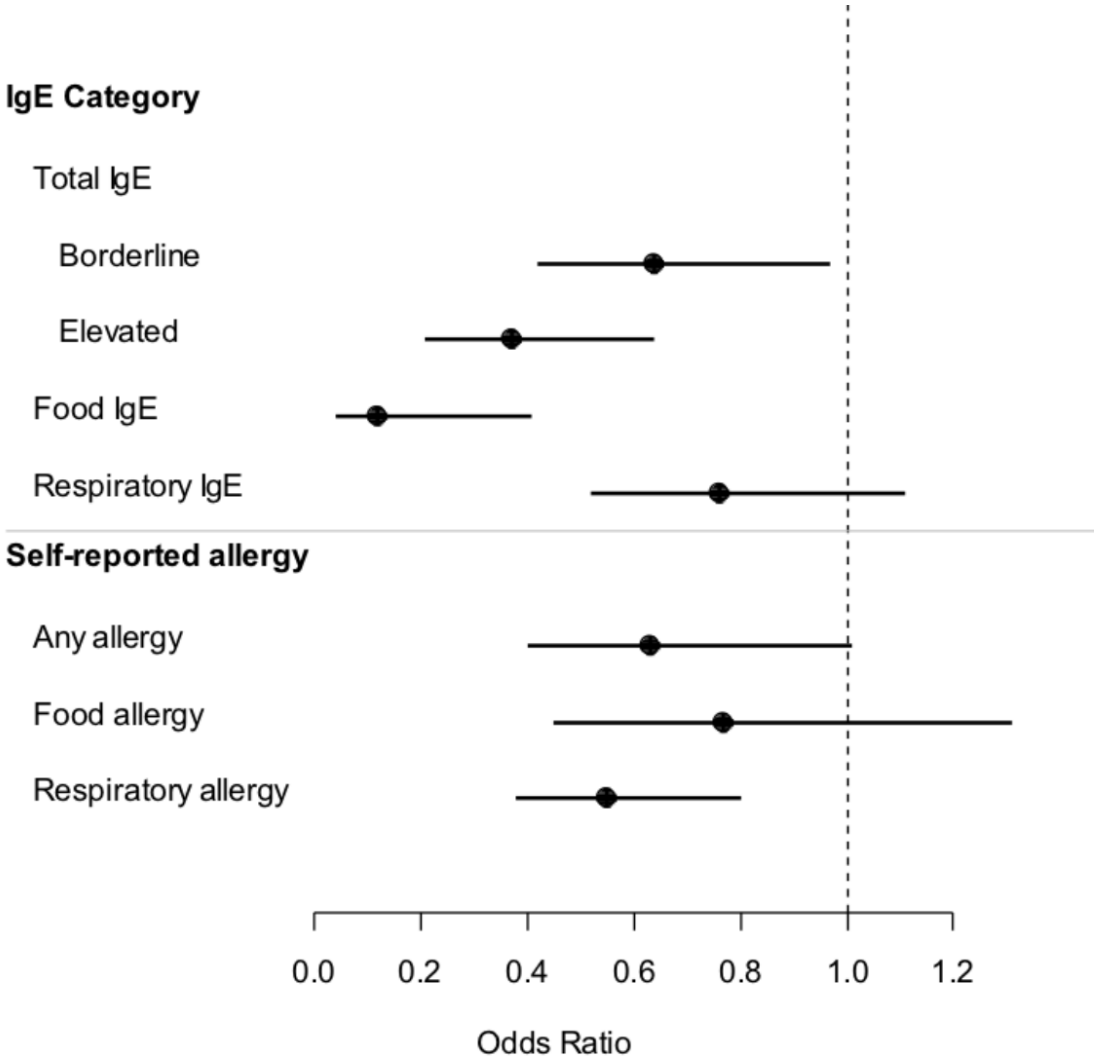
Immunological Associations

Allergies

Viruses:

- Cytomegalovirus
- Varicella (chicken pox)

Allergies



Brain cases exhibit *fewer* allergies compared withy healthy controls

Varicella (chicken pox)

	Cases vs. controls		Glioblastoma cases vs. controls	
	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval
Model A* (odds ratios for risk of glioma adjusted by age, ethnicity, and gender by immunoglobulin G antibodies)				
Varicella-zoster virus, continuous†	0.49	0.32, 0.75	0.46	0.28, 0.75
Varicella-zoster virus, quartiles‡				
1st	1.00		1.00	
2nd	0.61	0.37, 1.00	0.41	0.22, 0.76
3rd	0.66	0.40, 1.10	0.63	0.36, 1.10
4th	0.41	0.24, 0.70	0.31	0.16, 0.60
Herpes simplex virus	1.24	0.80, 1.91	1.34	0.77, 2.31
Cytomegalovirus	1.25	0.86, 1.84	1.27	0.79, 2.03
Epstein-Barr virus	0.82	0.40, 1.67	0.81	0.35, 1.88

Comparison of antibody levels against varicella in glioma cases compared to healthy controls

Cytomegalovirus

Neuro-Oncology 14(3):246–255, 2012.
doi:10.1093/neuonc/nor227
Advance Access publication February 8, 2012

NEURO-ONCOLOGY

Consensus on the role of human cytomegalovirus in glioblastoma

Kristine Dziurzynski, Susan M. Chang, Amy B. Heimberger, Robert F. Kalejta, Stuart R. McGregor Dallas, Martine Smit, Liliana Soroceanu, and Charles S. Cobbs, the HCMV and Gliomas Symposium†

Department of Neurosurgery, The University of Texas MD Anderson Cancer Center, Houston, Texas (K.D., A.B.H.); Neurological Surgery, the University of California at San Francisco, San Francisco, California (S.M.C., C.S.C.); Institute for Molecular Virology and McArdle Laboratory for Cancer Research, the University of Wisconsin-Madison, Madison, Wisconsin (R.F.K.); Molecular Biology, Lewis Thomas Laboratory, Princeton University, Princeton, New Jersey (S.R.M.D.); Department of Medicinal Chemistry, Faculty of Sciences, VU University Amsterdam, The Netherlands (M.J.S.); and California Pacific Medical Center Research Institute, San Francisco, California (C.S.C., L.S.)

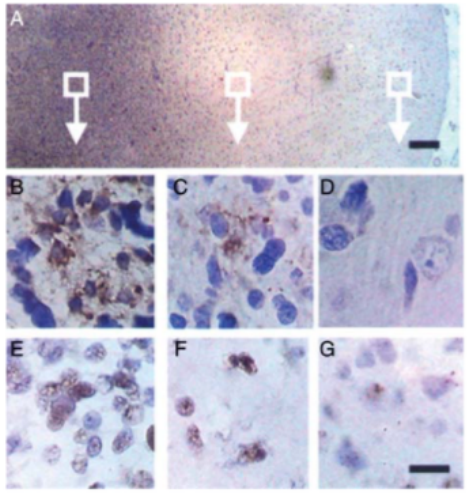


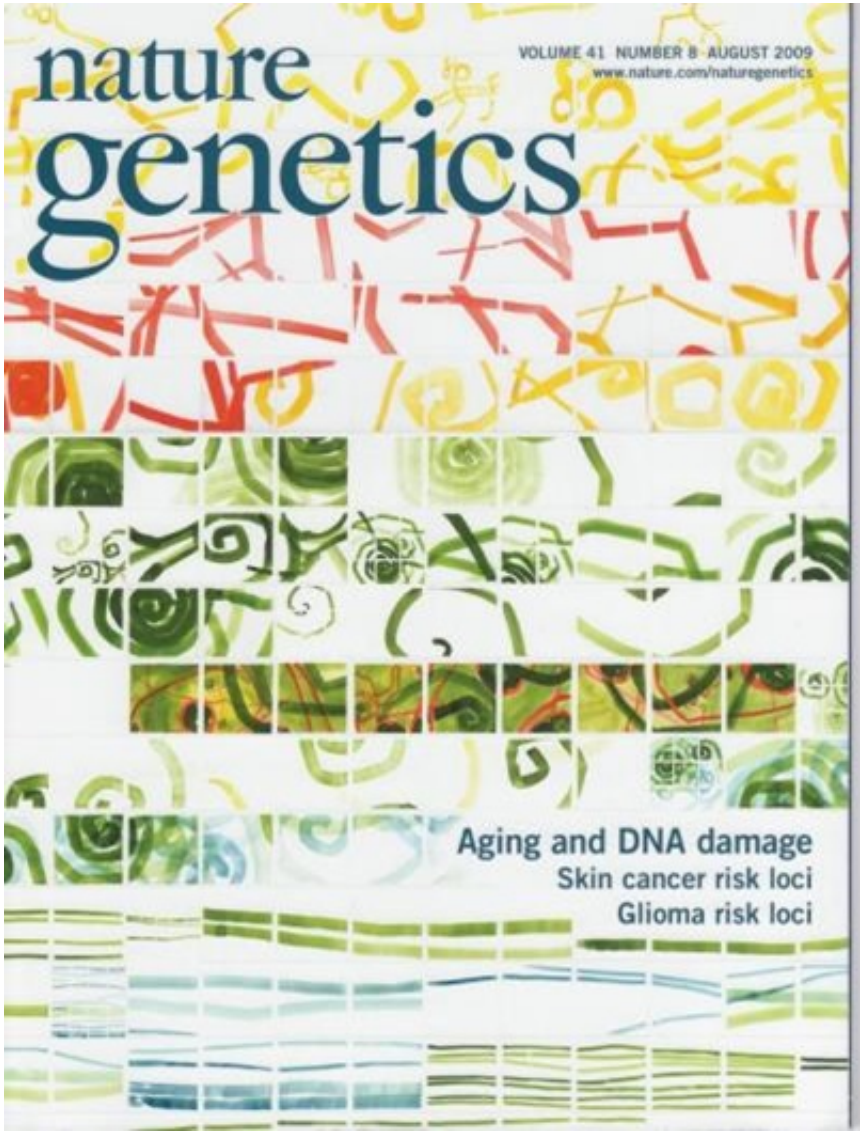
Fig. 1. Correlation of patterns of immunohistochemical localization of human cytomegalovirus (HCMV) immediate early 1 (IE1) protein with in situ hybridization for HCMV DNA in a glioblastoma (GBM) that invades normal brain. (A) Low-power view of anti-IE1 immunostain demonstrates GBM invading normal brain cortex (cortical surface at far right; bar, 200 μm). (B–D) Boxed areas in (A) at higher power demonstrate IE1 immunoreactivity moving from an area of frank tumor (B) to an area of invading tumor (C) to an area of normal brain (D). Detection of HCMV DNA by in situ hybridization using an HCMV total genome probe (in an adjacent section and similar regions of the same tumor in B–D) reveals a similar pattern, moving from malignant (E) to invasive (F) to normal (G) brain. Bar, 10 μm.

In summary, existing evidence supports an oncomodulatory role for HCMV in malignant gliomas, but future studies need to focus on determining the role of HCMV as a glioma-initiating event.

UCSF Adult Glioma Study (1991-present) Contributions to Glioma Epidemiology Margaret Wrensch and John Wiencke, Co-PIs

- Discovery of inherited risk factors for glioma
- Delineation of tumor markers of distinct glioma subtypes
- Determining mechanisms of risk loci for glioma subtypes
- Determination and clarification of biologic basis of immunologic risk factors for glioma
- Discovery of new inherited, immunologic and somatic prognostic or predictive factors in glioma

Glioma GWAS discover **8 risk regions**



UCSF AGS Glioma GWAS

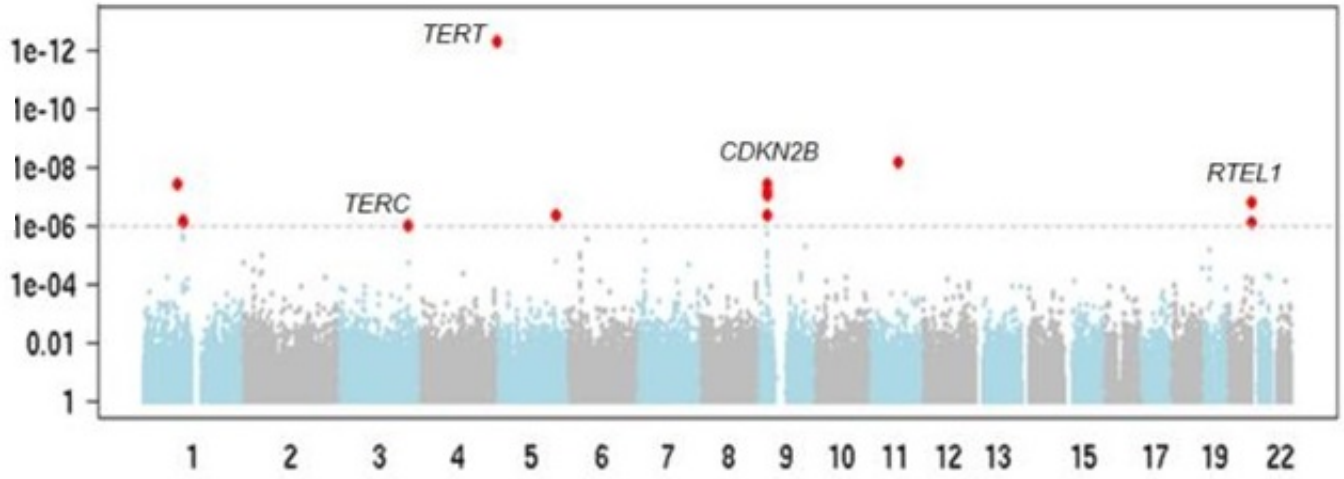
Variants in the *CDKN2B* and *RTEL1* regions are associated with high-grade glioma susceptibility

Margaret Wrensch[1,2,12], Robert B Jenkins[3,12], Jeffrey S Chang[4,12], Ru-Fang Yeh[4,12], Yuanyuan Xiao[4], Paul A Decker[5], Karla V Ballman[5], Mitchel Berger[1], Jan C Buckner[6], Susan Chang[1], Caterina Giannini[3], Chandralekha Halder[3], Thomas M Kollmeyer[3], Matthew L Kosel[3], Daniel H LaChance[7], Lucie McCoy[1], Brian P O'Neill[7], Joe Patoka[1], Alexander R Pico[8], Michael Prados[1], Charles Quesenberry[9], Terri Rice[1], Amanda L Rynearson[3], Ivan Smirnov[1], Tarik Tihan[10], Joe Wiemels[2,4], Ping Yang[11,13] & John K Wiencke[1,2,13]

A low-frequency variant at 8q24.21 is strongly associated with risk of oligodendroglial tumors and astrocytomas with *IDH1* or *IDH2* mutation

Robert B Jenkins[1,12], Yuanyuan Xiao[2,11], Hugues Sicotte[3,11], Paul A Decker[3,11], Thomas M Kollmeyer[1,11], Helen M Hansen[4,11], Matthew L Kosel[3,11], Shichun Zheng[4], Kyle M Walsh[4,5], Terri Rice[4], Paige Bracci[2], Lucie S McCoy[4], Ivan Smirnov[4], Joseph S Patoka[4], George Hsuang[4], Joe L Wiemels[2,6], Tarik Tihan[7], Alexander R Pico[8], Michael D Prados[4], Susan M Chang[4], Mitchel S Berger[4], Alissa A Caron[1], Stephanie R Fink[1], Chandralekha Halder[1], Amanda L Rynearson[1], Brooke L Fridley[3], Jan C Buckner[9], Brian P O'Neill[10], Caterina Giannini[3], Daniel H Lachance[1,10], John K Wiencke[4,6,12], Jeanette E Eckel-Passow[3,12] &

nature genetics



Variants near *TERT* and *TERC* influencing telomere length are associated with high-grade glioma risk

Kyle M Walsh[1,2], Veryan Codd[3,4], Ivan V Smirnov[5], Terri Rice[1], Paul A Decker[6], Helen M Hansen[1], Thomas Kollmeyer[7], Matthew L Kosel[6], Annette M Molinaro[5], Lucie S McCoy[1], Paige M Bracci[8], Belinda S Cabriga[1], Melike Pekmezci[9], Shichun Zheng[1], Joseph L Wiemels[1,8,10], Alexander R Pico[1,11], Tarik Tihan[9], Mitchell S Berger[3], Susan M Chang[3], Michael D Prados[3], Daniel H Lachance[12], Brian Patrick O'Neill[12], Hugues Sicotte[6], Jeanette E Eckel-Passow[6], ENGAGE Consortium Telomere Group[13], Pim van der Harst[14,15], John K Wiencke[1,10], Nilesh J Samani[3,4], Robert B Jenkins[7] & Margaret R Wrensch[1,10]

A germline variant in the *TP53* polyadenylation signal confers cancer susceptibility

Glioma Risk Variants

Chromosome region	Genes	Odds Ratios	Year discovered
3q26	TERC	1.3	2014
5p15	TERT	1.5	2009
7p11	EGFR	1.2	2011
8q24	CCDC26	1.4/**6.3**	2009/2012
9p21	CDKN2B/ANRIL	1.4	2009
11q23	PHLDB1	1.2	2009
17p13	TP53	2.4	2011
20q13	RTEL1	1.5	2009

Blue highlights SNPs with known/suspected function: TERC and TERT SNPs associated with longer telomeres; base pair substitution in polyadenylation site impairs processing of TP53 mRNA.

Lifetime risk of oligodendroglial tumors and IDH mutated astrocytomas (grades II-IV) associated with rs55705857

- **Overall** lifetime risk is ~**1.2** per thousand
- **Having one G** variant in rs55705857 confers a lifetime risk of ~**7.5** per thousand
- **Having two G** variants in rs55705857 confers a lifetime risk of ~**27** per thousand

nature genetics

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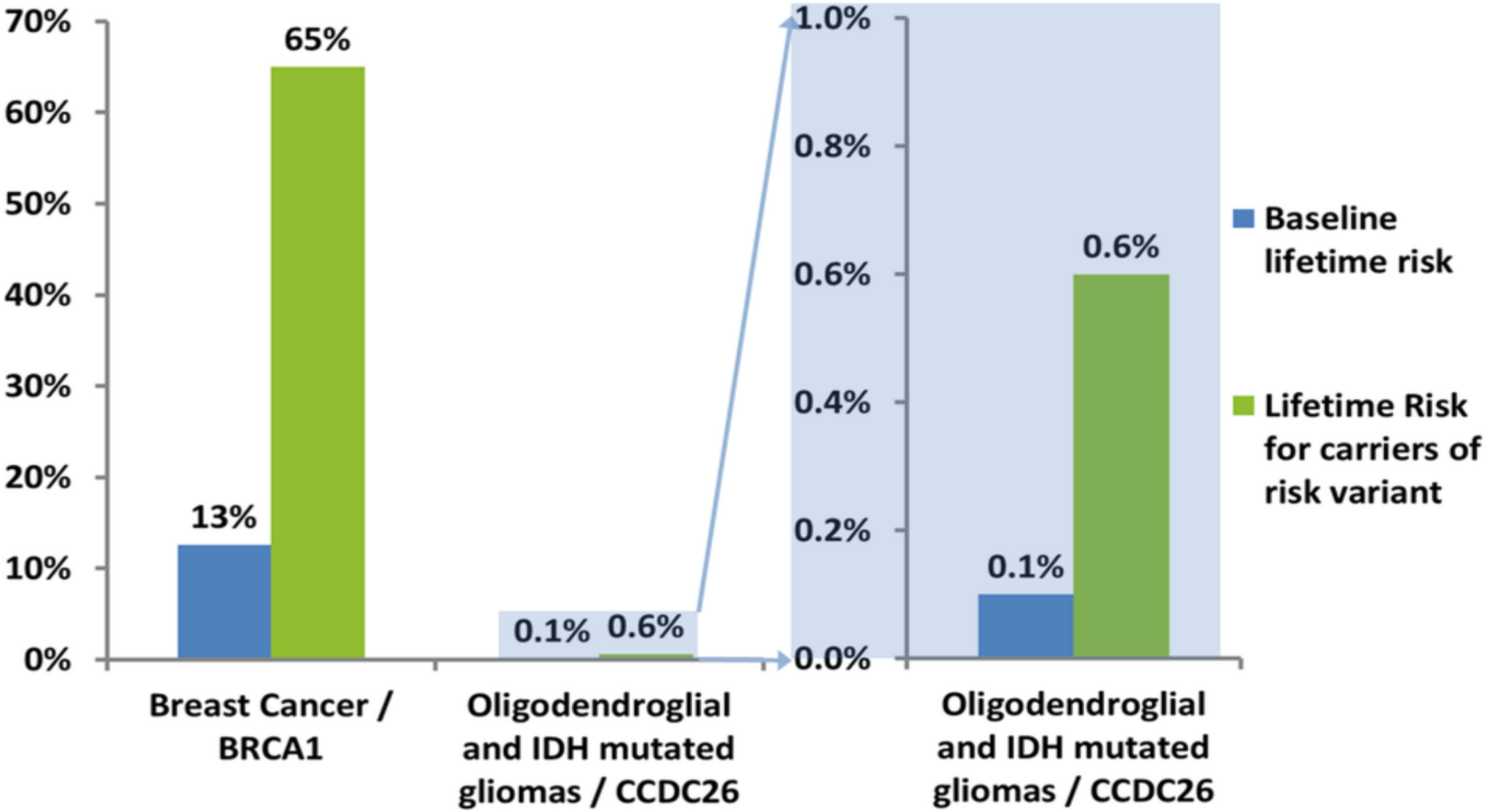
Implications

This is the first identification of a **strong genetic risk factor** for these tumor types.

No environmental risk factors have been found for these tumors. Although this type of tumor can occur in people who have had radiation treatment for other brain tumors, very few people who get these tumors have had such prior radiation.

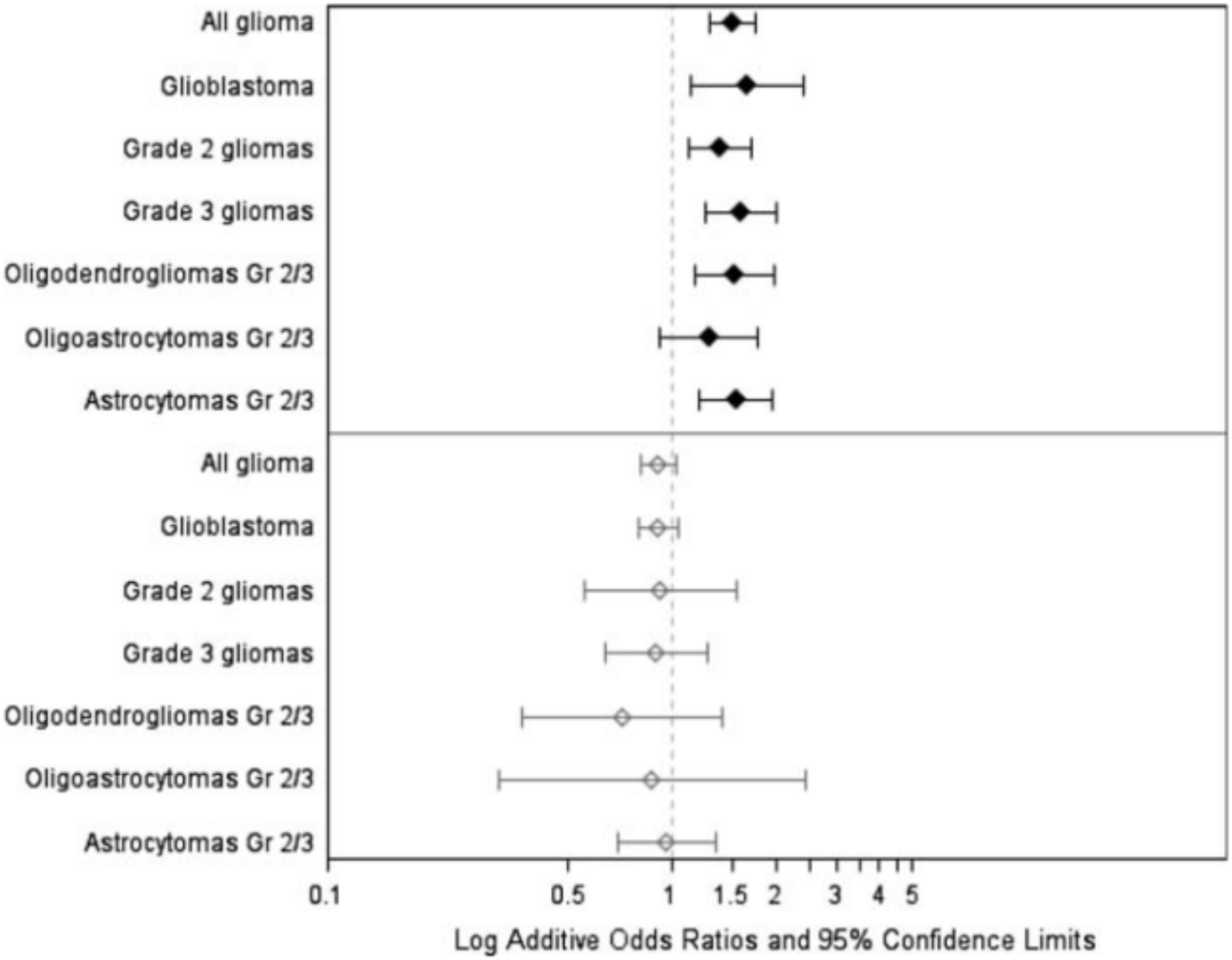
Understanding what this and other inherited variants do will provide insight into the **mechanisms of gliomagenesis** and thereby provide potential **new targets** for **intervention** and **treatments**.

Comparison of lifetime risk for BRCA1 and breast cancer and for rs55705857 and oligodendroglial/IDH mutated gliomas



Understanding Inherited Risk of Glioma; Rice et al. Neuro-onc Practice 2016

The 11q23 risk variant is only associated with IDH+ gliomas regardless of grade or type



Rice et al. Neuro-oncology 2013; using **1102** cases and **5299** controls from AGS, Mayo clinic and iControls

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Glioma Groups Based on 1p/19q, *IDH*, and *TERT* Promoter Mutations in Tumors

Jeanette E. Eckel-Passow, Ph.D., Daniel H. Lachance, M.D., Annette M. Molinaro, Ph.D., Kyle M. Walsh, Ph.D., Paul A. Decker, M.S., Hugues Sicotte, Ph.D., Melike Pekmezci, M.D., Terri Rice, M.P.H., Matt L. Kosel, B.S., Ivan V. Smirnov, Ph.D., Gobinda Sarkar, Ph.D., Alissa A. Caron, B.S., Thomas M. Kollmeyer, M.S., Corinne E. Praska, Anisha R. Chada, B.A., Chandralekha Halder, B.S., Helen M. Hansen, B.A., Lucie S. McCoy, M.P.H., Paige M. Bracci, Ph.D., Roxanne Marshall, B.S., Shichun Zheng, Ph.D., Gerald F. Reis, M.D., Ph.D., Alexander R. Pico, Ph.D., Brian P. O'Neill, M.D., Jan C. Buckner, M.D., Caterina Giannini, M.D., Ph.D., Jason T. Huse, M.D., Ph.D., Arie Perry, M.D., Tarik Tihan, M.D., Ph.D., Mitchell S. Berger, M.D., Susan M. Chang, M.D., Michael D. Prados, M.D., Joseph Wiemels, Ph.D., John K. Wiencke, Ph.D., Margaret R. Wrensch, Ph.D., and Robert B. Jenkins, M.D., Ph.D.

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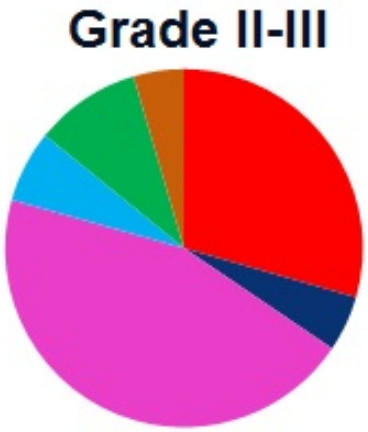
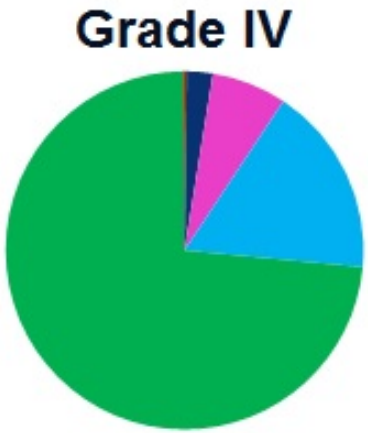
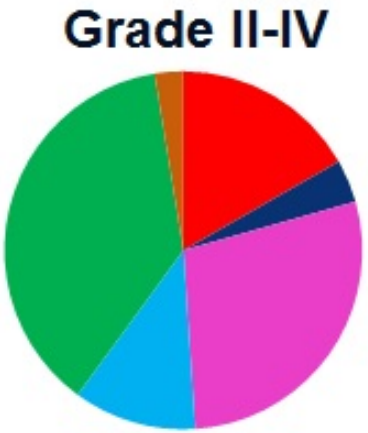
DOI: 10.1056/NEJMoa1407279

Improving glioma classification using 3 tumor markers: TERT mutation, IDH mutation, 1p/19q deletion





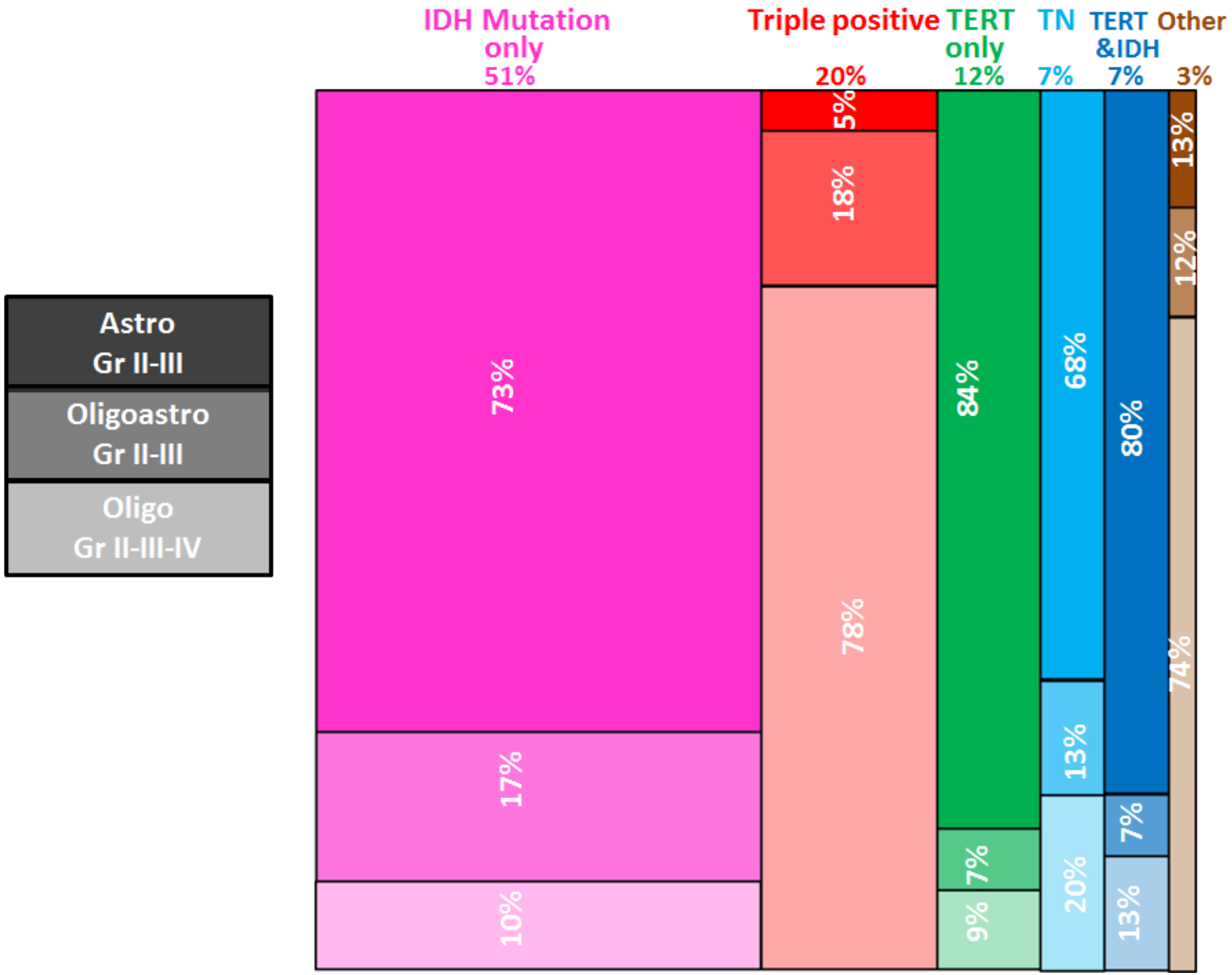


KEY

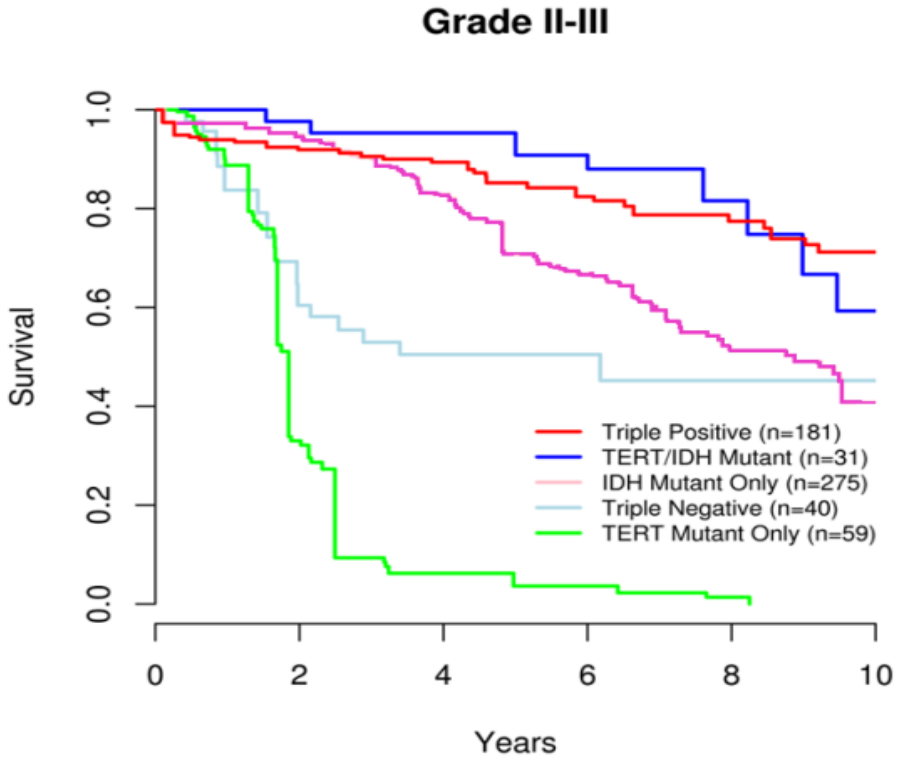
Bar	TERT mutant	IDH mutant	1p/19q codel	Aliases
	X	X	X	Triple Positive
	X	X		TERT & IDH Mutant
		X		IDH Mutant Only
				Triple Negative
	X			TERT Mutant Only
		(other combinations)		Other Patterns

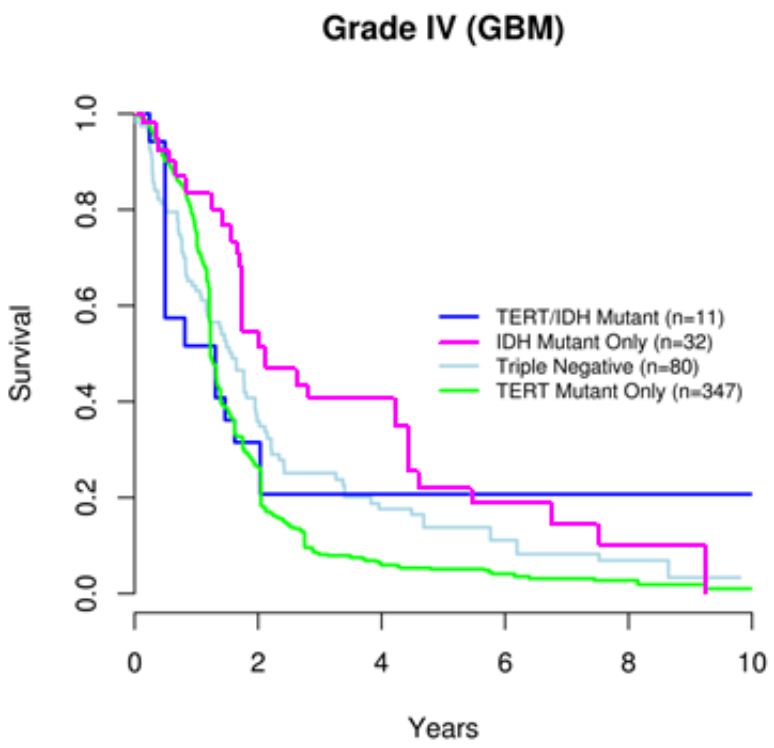
Data from Eckel-Passow et al. NEJM 2015

Histological distribution of GrII/III gliomas by molecular subgroups

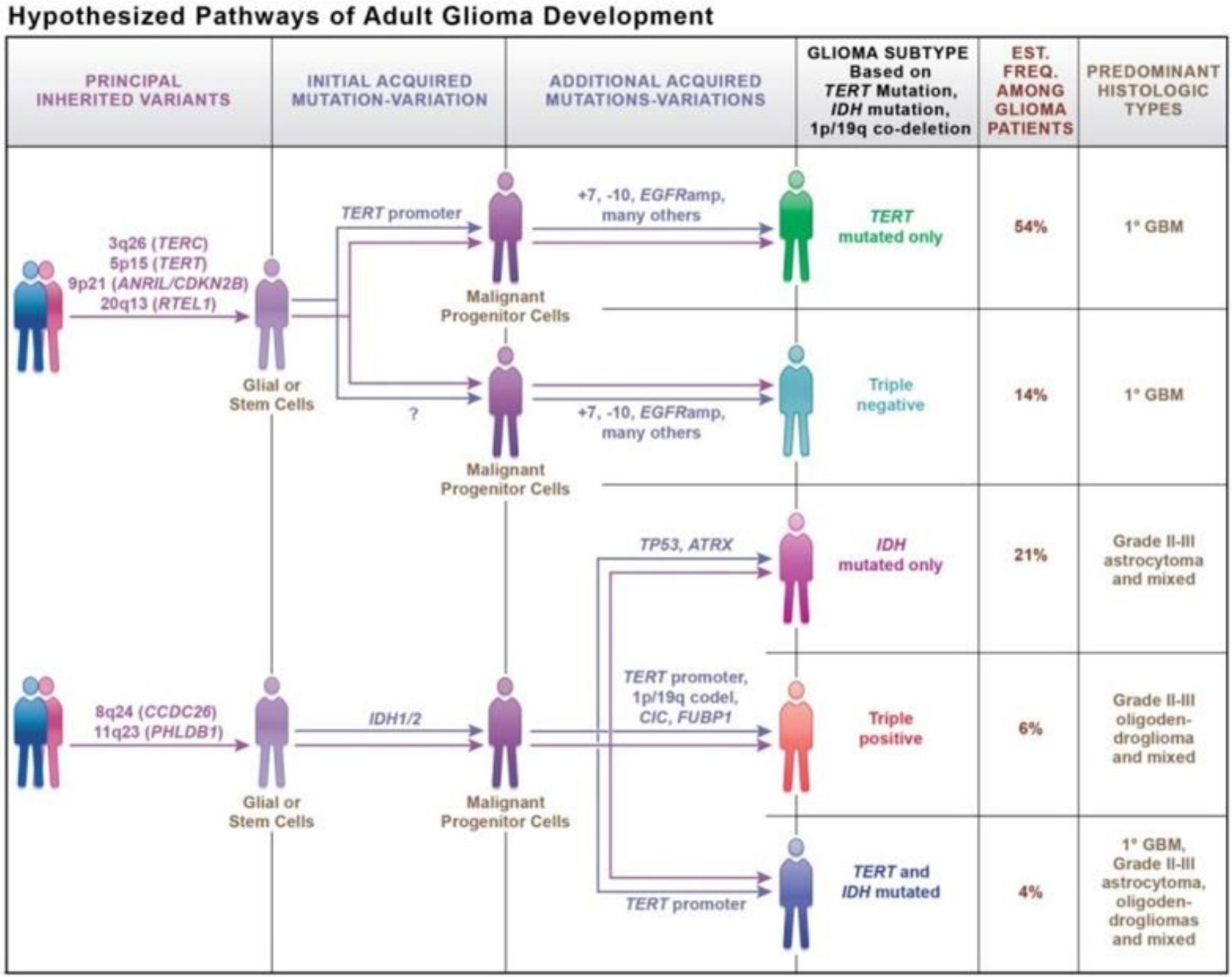


Age adjusted survival by molecular groups in GrII-III and GrIV gliomas



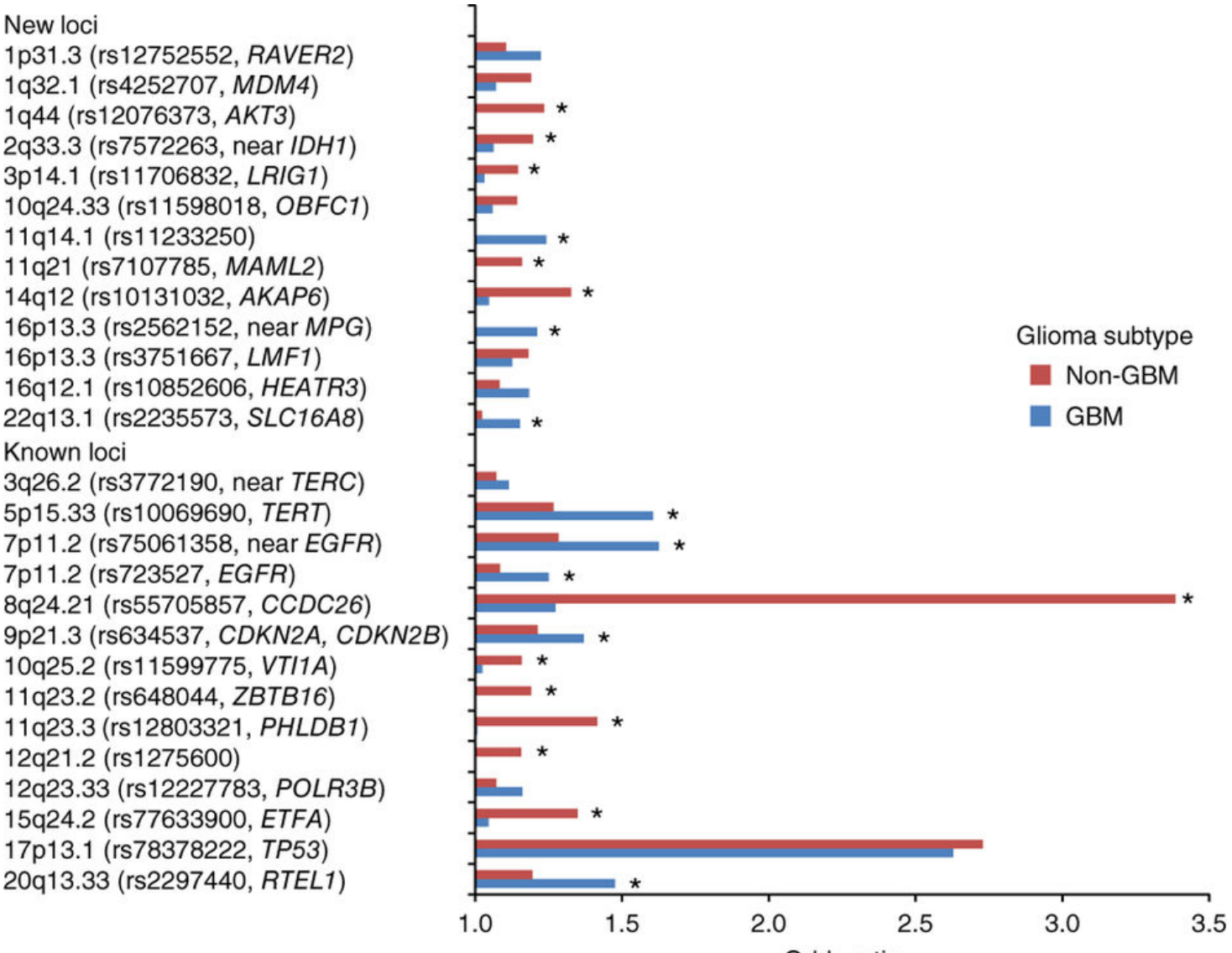


Survival by moelcular group is significant and independent of age, histology and grade in those with GrII-III glioma.



Understanding Inherited Risk of Glioma; Rice et al. Neuro-onc Practice 2016

Inborn genetic risk and glioma



Melin, Nat Genet 2017

Review of Non-occupational **Risk Factors** for **Glioma after GWAS**

	Established Risk Factors	Association
	High Dose Radiation	+++
	Hereditary Syndromes	+++
	Male vs Female Gender	+
	White vs African American ethnicity	+
	Increasing Age	+++
UCSF	Epilepsy, seizures, convulsions (probably early symptom)	+
UCSF	Inherited variants in **RTEL1, TERT, TERC, EGFR, TP53, 9p21, 8q24, and 11q23**	+
UCSF	**G allele in rs55705857**	+++

+++	relative risk>3
+	1<relative risk <3
-	0.3<relative risk <1

Ongoing topics in adult glioma epidemiology

- Discover inherited risk factors for glioma
- Delineate tumor markers of distinct glioma subtypes
- Define risk loci for glioma subtypes and how they help to understand networks and pathways involved in gliomagenesis
- Determine and understand biologic basis of immunologic and viral risk factors for glioma
- Discover new inherited, immunologic and somatic prognostic or predictive factors in glioma

Large epidemiologic studies are helpful for genetic studies but somewhat disappointing for environmental risk factors

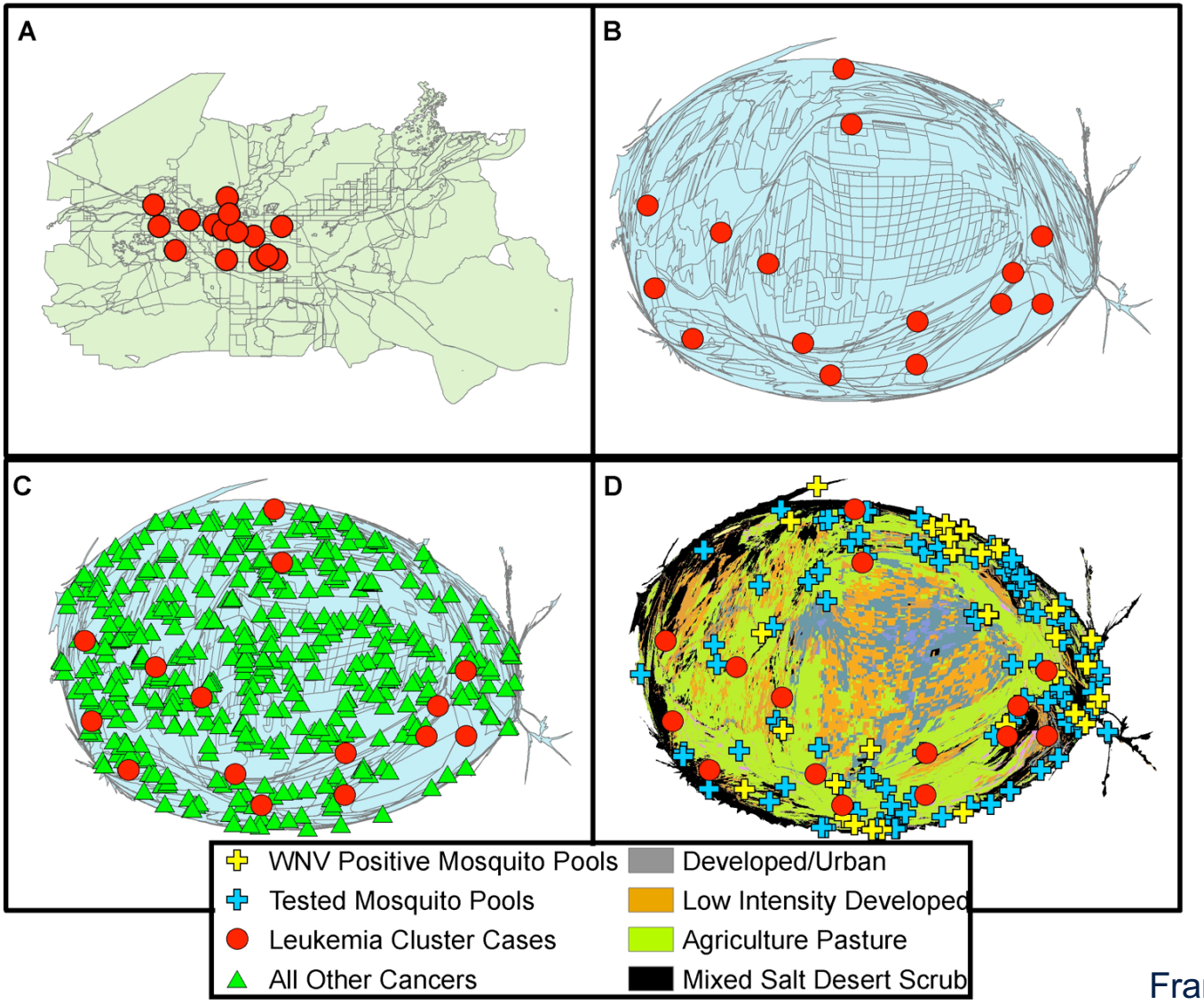
A role for cancer cluster investigation?

- Example: Fallon Nevada
    - 16 leukemia cases in a town of 8000 over 3 years

Fallon, Nevada leukemia cluster

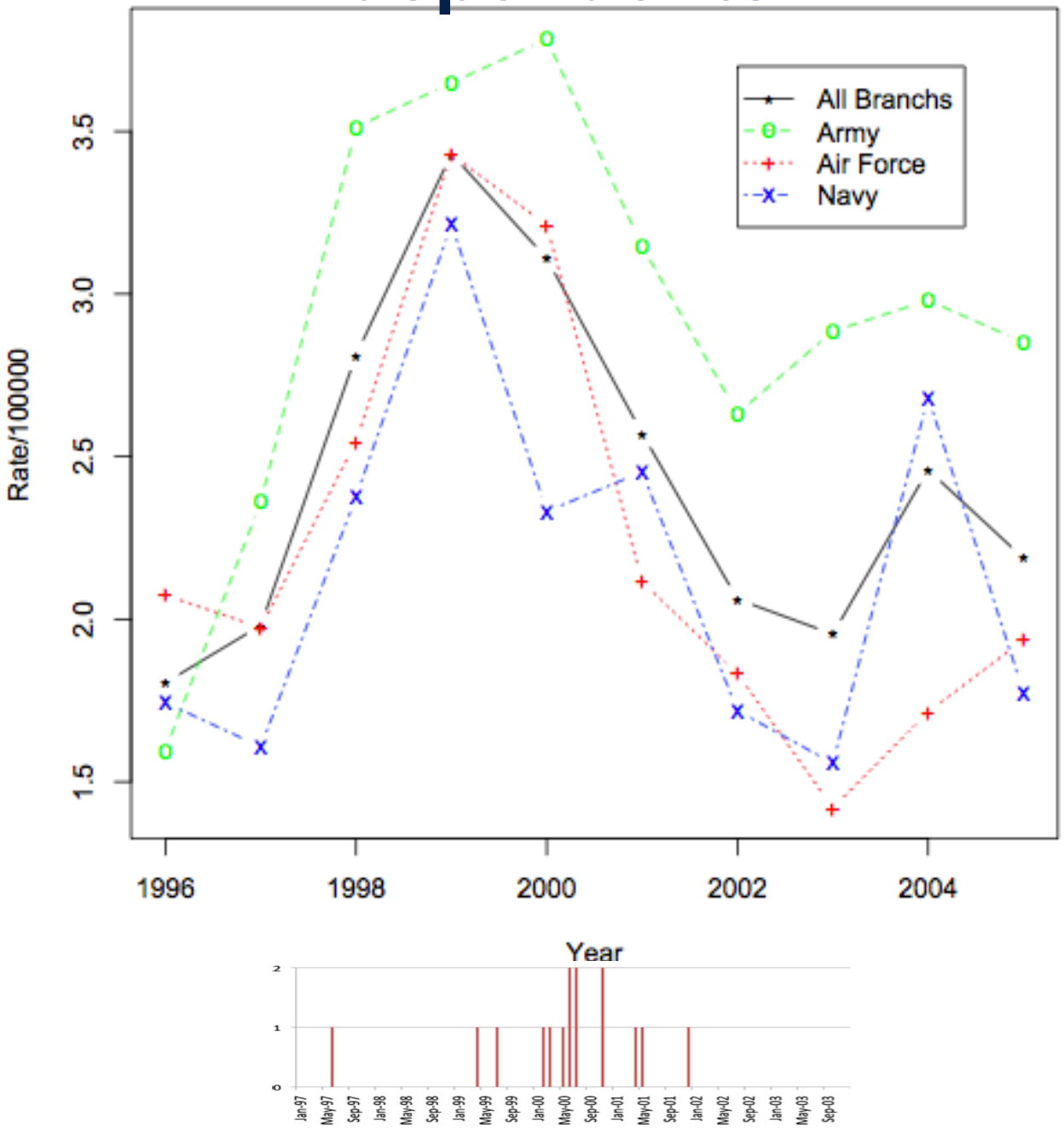
16 leukemia cases within 3 years 1/22,000 chance occurrence

Figure 2



Francis, et al 2011

Leukemia Incidence in military dependents



Francis, et al 2011

Brain cancer clusters?

Mortality in US Army Gulf War Veterans Exposed to 1991 Khamisiyah Chemical Munitions Destruction

Tim A. Bullman, MA, Clare M. Mahan, PhD, Han K. Kang, DrPH, William F. Page, PhD

TABLE 3—Cause-Specific Mortality Risks Among US Army Gulf War Veterans Exposed at Khamisiyah, Iraq, in 1991 Stratified by Number of Days Exposed Compared With Unexposed Gulf War Veterans

Underlying Cause of Death *(ICD-9)*	1 Day Exposure (n = 86 167) No. (Rate[a])	≥2-Day Exposure (n = 14 320) No. (Rate[a])	All Nonexposed (n = 224 980) No. (Rate[a])	1-Day Exposure, RR[b] (95% CI)	≥2-Day Exposure, RR[b] (95% CI)
All causes	1020 (12.34)	159 (11.51)	2696 (12.47)	0.97 (0.90, 1.04)	0.96 (0.82, 1.13)
All diseases (001–799)	427 (5.17)	69 (5.00)	1093 (5.05)	0.95 (0.85, 1.06)	1.06 (0.83, 1.36)
Infectious and parasitic disease (001–139)	24 (0.29)	5 (0.36)	56 (0.26)	1.11 (0.69, 1.80)	1.49 (0.59, 3.74)
Malignant neoplasm (140–208)	156 (1.89)	28 (2.03)	391 (1.81)	0.94 (0.78, 1.13)	1.25 (0.85, 1.84)
Brain cancer (191, 192)	19 (0.23)	6 (0.43)	27 (0.12)	1.72 (0.95, 3.10)	3.26 (1.33, 7.96)
Disease of circulatory system (390–459)	147 (1.78)	23 (1.67)	407 (1.88)	0.88 (0.73, 1.07)	0.94 (0.61, 1.43)
Disease of respiratory system (469–519)	18 (0.22)	4 (0.29)	45 (0.21)	0.97 (0.56, 1.67)	1.58 (0.56, 4.42)
Disease of digestive system (520–579)	21 (0.25)	3 (0.22)	46 (0.21)	1.11 (0.66, 1.87)	1.02 (0.32, 3.31)
All external causes (E900–E989)	550 (6.65)	87 (6.30)	1460 (6.75)	1.01 (0.92, 1.12)	0.95 (0.77, 1.18)
All accidents (799–E929)	308 (3.73)	40 (2.90)	807 (3.73)	1.02 (0.89, 1.16)	0.79 (0.58, 1.09)
Motor vehicle accident (E810–E929)	213 (2.58)	26 (1.88)	546 (2.52)	1.04 (0.89, 1.22)	0.77 (0.52, 1.15)
Suicide (E950–E959)	142 (1.72)	32 (2.32)	386 (1.78)	1.00 (0.83, 1.21)	1.29 (0.90, 1.86)

Note. ICD-9 = International Classification of Diseases, Ninth Revision; RR = adjusted relative risk; CI = 95% confidence interval. Exposure is to nerve gas as a result of demolition of weapons at Khamisiyah, Iraq. Exposure is based on the 2000 exposure model developed by the US Department of Defense.

[a]Crude death rates per 10 000 person-years at risk.

[b]Estimates of relative risk were derived from a proportional hazards multivariate model, with adjustment for age at entry to follow-up, race, sex, rank, and unit component.

Brain cancer

Gulf War and Brain Cancer

The relative rarity of cancers such as brain cancer argues for larger studies with adequate statistical power. This may require pooling data where feasible and the use of a variety of data sources such as state cancer registries. *Gulf War and Health, Vol 10*

Also, creative examination of highly exposed subpopulations may reveal new associations

San Francisco Bay Area Adult Glioma Study: 1991-2016 and Adult Glioma Survival Study: 2002-2018

Accrual to date: ~3000 people with glioma; ~2000 controls

Collaborators have included scientists and students from:

UCSF (Wrensch, Wiencke, Co-PIs)
Brown
Duke University
Harvard
Kaiser Division of Research
KUMC
Mayo Clinic (Robert Jenkins, MD, PhD)
MD Anderson
Moffitt Cancer Center (Kathy Egan, PhD)
New York Health Dept
Northern California Cancer Center
Stanford University
Texas A&M
University of Alabama
University of Colorado HSC
University of Southern California
University of North Carolina
University of Washington
Wayne State

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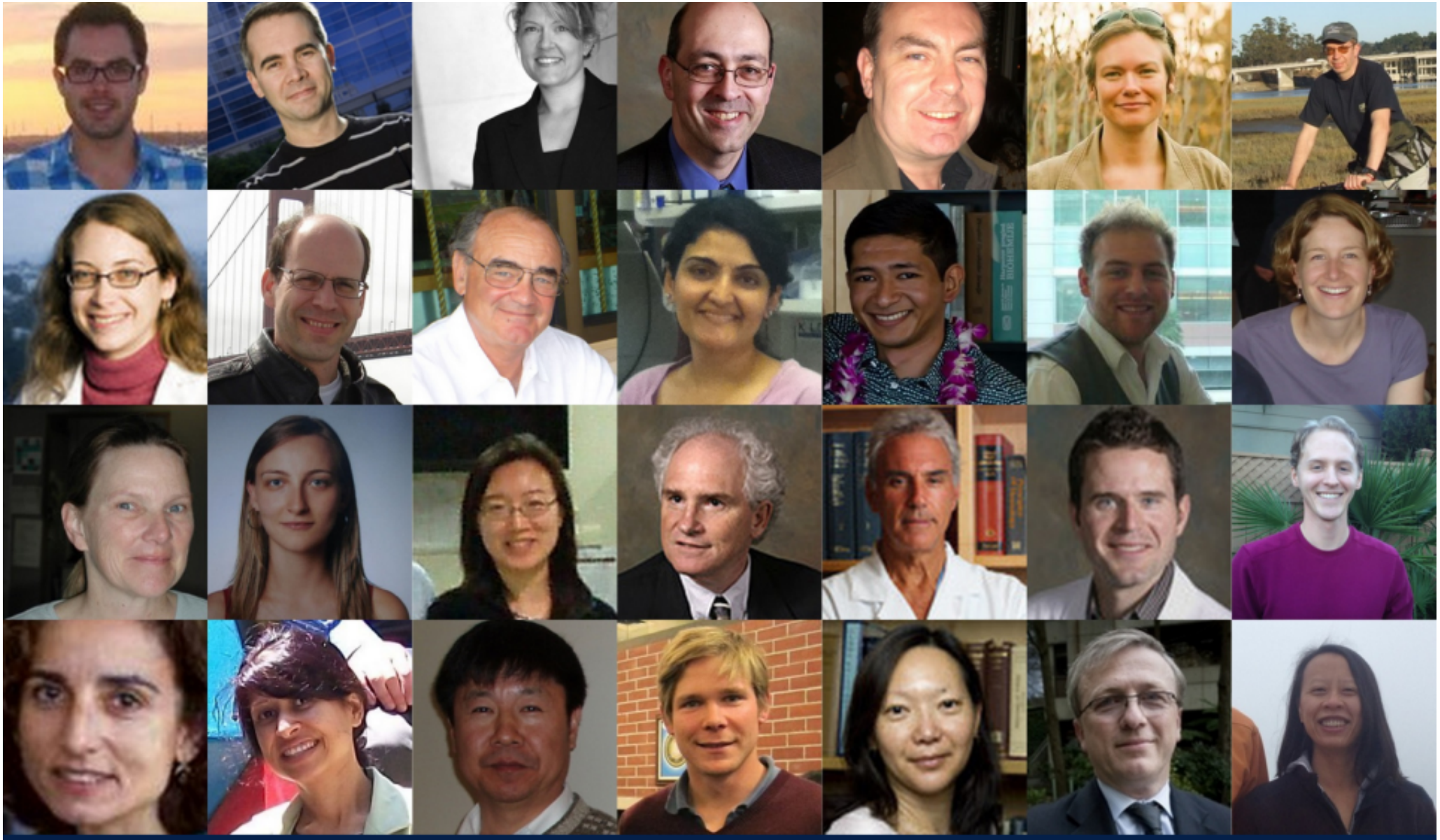
Loglio collective
National Institute of Environmental Health Sciences
Accelerate Brain Cancer Cure
Brain Tumor Society
National Brain Tumor Foundation
American Cancer Society
Families and Friends of John Berardi, Helen Glaser, and Elvera Olsen



UCSF Adult Glioma Study and Neuro-oncology Clinic

Adam De Smith, PhD, Alex Pico, PhD, Annette Molinaro, PhD, Arie Perry, MD, Ed Elhauge, MPH, Helen Hansen, Ivan Smirnov, PhD, Jennifer Clarke, MD, Joe Wiemels, PhD, John Wiencke, Juhi Ojha, PhD, Julio Gonzalez, Kyle Walsh, PhD, Lucie McCoy, MPH, Margaret Wrensch, PhD, Melike Pekmezci, MD, Mi Zhou, MD, Michael Prados, MD, Mitchel Berger, MD, Nicholas Butowski, MD, Nils Madsen Paige Bracci, PhD, Ritu Roy, PhD, Shichun Zheng, MD, Steve Francis, PhD, Susan Chang, MD, Tarik Tihan, MD, Terri Rice, MPH

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